

# DRUG INFORMATION BULLETIN

Vol 1: Medicines Control Authority of Zimbabwe March 2015

## Pilot phase of Targeted Spontaneous Reporting (TSR) of Anti-retrovirals and Anti-tuberculosis

Nyambayo P P<sup>1</sup>; Gavi S<sup>2</sup>Mahlangu GN<sup>1</sup>; Khoza S<sup>1</sup>; Masuka J<sup>1</sup>; Manyuchi P<sup>1</sup>

<sup>1</sup>Medicines Control Authority of Zimbabwe (MCAZ)

<sup>2</sup>College of Health Sciences - University of Zimbabwe (CHS-UZ)

### Abstract

**Background:** Adverse drug reaction monitoring is essential in achieving the goals of anti-retroviral (ARV) and anti-tuberculosis (anti-TB) treatment, and is an important element in promoting rational medicine use principles and promoting patient safety.

**Objectives:** The pilot phase of the Targeted Spontaneous Reporting (TSR) system for monitoring adverse drug reactions pilot phase research was carried out to strengthen pharmacovigilance activities in the National ART and TB programmes in Zimbabwe; and to understand and characterize adverse drug reactions (ADRs) or individual case safety reports (ICSRs) due to ARV and anti-TB medicines.

**Methods: Targeted Spontaneous Reporting (TSR)** refers to the reporting of adverse events by spontaneous reporting from a known cohort of patients on a particular medicine or group of medicines. The Medicines Control Authority of Zimbabwe (MCAZ,) in collaboration with the Ministry of Health and Child Care (MoHCC) conducted a pilot phase of TSR of ARVs and Anti-TBs in public and selected private health institutions since October 2012 to September 2013.

**Results:** The age range of participants in the study was 0.9-76 years with a median of 38 years. Most of the reports described at least one ADR (83%) and a few reported more than one (2 ADRs=11% and 3 ADRs=6%). The majority of ADRs reported were mainly cutaneous in nature (44%), followed by CNS (27%), metabolic (11%) in nature. Patients on Efavirenz had a lower odds of cutaneous reactions compared to those on Nevirapine containing regimens (OR=0.07, p-value<0.0005); while those on Efavirenz had a higher odds of CNS type of reactions compared to those on NVP (OR=6.0; p-value<0.0005). The same trend was seen with gastrointestinal reactions which were more frequent in those on Efavirenz containing

### In this issue

1. Pilot phase of Targeted Spontaneous Reporting (TSR) of Anti-retrovirals and Anti Tuberculosis
2. Targeted Spontaneous Reporting of All essential medicines including Anti TBs and ARVs – Scale up Main Phase.
3. Functions of the Zimbabwe National Pharmacovigilance Centre
4. Praziquantel and Albendazole Mass Drug Administration Programme
5. TSR Monitoring of Praziquantel and Albendazole
6. Recent Changes in Category of Distribution of Medicines in Zimbabwe
7. Access Programme for Safe, Quality and Efficacious Veterinary Medicines in Zimbabwe
8. Adverse Drug Reaction Monitoring

regimens (OR=3.3, p-value=0.03). Gender as a demographic variable showed an association with development of cutaneous reactions (OR=2.3, p-value=0.001) and metabolic reactions (OR = 0.4, p-value=0.01). Rash seems to have an association with gender in this population (OR=2.7; p-value<0.0005); females had a lower odds of peripheral neuropathy compared to males (OR=0.6, p-value=0.04). A total of 120 individual case safety reports (ICSRs) associated with tenofovir were also received and all ICSR were analyzed for causality assessment and uploaded onto the Vigiflow database.

**Conclusion:** Pharmacovigilance activities need to be strengthened and included as part of clinical care especially for patients on ART and anti-TB treatment including essential medicines. The TSR pilot phase demonstrated significant increase in ADR reporting and was considered a relatively feasible cost effective method hence TSR was scaled up to the main phase program. Further in depth analysis of ICSR of medicines reported such as tenofovir and / or efavirenz in combination with other anti-retrovirals is required.

## Targeted Spontaneous Reporting of All essential medicines including Anti TBs and ARVs – Scale up Main Phase.

### Introduction

The advent of HIV/AIDS as a chronic infectious disease revolutionized the medical field by ‘forcing’ improved research methods as well as data collection tools to detect transmission of diseases and their management epidemiologically. The emergence of previously neglected diseases is providing new challenges in disease management because a lot of emphasis has been put in managing infectious diseases in developing countries which had the highest mortality rates. Chronic non-infectious diseases like hypertension, diabetes are on the rise, and most people have more than one disease condition at the same time.

While treatment options are available in abundance, expected therapeutic outcomes can be compromised by adverse drug reactions. Pharmacovigilance activities are a necessary component in managing patients, enabling prevention or treatment of adverse reactions. In Zimbabwe, an essential drugs list (EDLIZ) was developed by the Ministry of Health and Child Care (MoHCC) National Medicines and Therapeutics Committee to guide management of most common disease conditions using established treatment guides. Recent ADR experiences in the 2013 mass treatment and prophylaxis program using praziquantel and albendazole have shown the need for stronger pharmacovigilance activities with all commonly used medicines in Zimbabwe. Studies have shown that long term therapeutic outcomes to chronic diseases like HIV can be compromised by adverse drug reactions due to the drugs used.<sup>1, 2</sup> Understanding adverse drug reactions of the antiretroviral drugs is essential to optimizing therapeutic outcomes in patients.<sup>1</sup> In a large follow-up study done in Nigeria to monitor ADRs in patients taking them, the majority of ADRs due to ARVs occurred during the first six months of treatment.<sup>3</sup> This study showed that intensive monitoring of patients during initial stages of treatment could help patients achieve long term treatment goals. Other studies have demonstrated the importance of ADR monitoring in patients taking ARVs as a way of improving therapeutic outcomes.<sup>3-5</sup>

In a cohort study by Dormann et al., effective monitoring of adverse drug reactions reduced the length of stay and costs associated with adverse reactions.<sup>6</sup> The major challenge that remains in Zimbabwe due

to lack of electronic patient records is the actual identification of the adverse reactions and how they can be minimised. Reporting of adverse drug reactions may also be influenced by age of patients due to inability to understand disease manifestations and treatment in elderly and young patients.<sup>7</sup> Occurrence of ADRs in other patients with non-infectious chronic diseases like cardiovascular conditions can cause serious fatalities as it complicates drug therapy for those patients.<sup>8</sup> In a large meta-analysis study done in the USA, fatal ADRs occurred frequently in hospitalized patients and this has an increased cost in clinical management of patients.<sup>9</sup>

The MCAZ as the national centre of pharmacovigilance conducted Cohort Event Monitoring (CEM) of Artemisinin Combination Therapies (ACTs) from 2008-2012 and the results are being analysed for publication.<sup>11</sup> The MCAZ also conducted targeted spontaneous reporting of the H1N1 vaccine in 2010-2011 and the data is being analysed for publication.<sup>11</sup> This data will assist in clinical management of patients, guiding policy, and promote patient safety.

### **Objectives:**

- i. To use the TSR system in pharmacovigilance of essential drugs mainly anti-retrovirals, anti-tuberculosis, anti-asthmatics, anti-diabetes, anti-hypertensives anti-malarials and vaccines.
- ii. To strengthen pharmacovigilance activities in Zimbabwe.
- iii. Estimate prevalence of adverse drug reactions associated with use of essential drugs in Zimbabwe.
- iv. To characterize known and unknown adverse reactions from essential medicines mainly anti-retrovirals, anti-tuberculosis, anti-asthmatics, anti-diabetes, anti-hypertensives and anti-malarials.
- v. To assess the feasibility and impact of TSR on pharmacovigilance system in Zimbabwe
- vi. To identify potential regional (sentinel) pharmacovigilance centres to work with the MCAZ National Pharmacovigilance Centre.
- vii. To integrate pharmacovigilance into public health programs

### **Methods**

The MCAZ, in collaboration with the Ministry of Health and Child Care (MoHCC) Directorate of Pharmacy Services (DPS) and AIDS and TB Departments are responsible for coordinating the program, training of sites, and collection of reports and data analysis.

### **Selection of sites**

All public health care centres in Zimbabwe will be introduced to and trained on pharmacovigilance activities (Targeted Spontaneous Reporting of Essential Medicines).<sup>10</sup> This scale up phase will involve intensive training of all provinces until all public health care centres in the country have been trained. Sites that were involved in the pilot phase (TSR of anti-TB and ARVs) will also be re-trained and re-trained in the TSR main phase.

### **Target Population**

Patients in the public and private health institutions receiving medical care using essential medicines including Anti – TBs and ARVs.

## Data management and analysis

The MCAZ Pharmacovigilance and Clinical Trials (PVCT) Committee will analyse the data for causality assessment. The data will be entered into Vigiflow database (WHO recommended database), analysed and then published.

## Monitoring and Evaluation

Quarterly monitoring and evaluation supportive visits to the sites will be carried out to provinces for feedback and collection of completed ADR forms. This will help in identifying the training needs of the staff at the sites, challenges being faced, and give an opportunity for training and re-training exercises to be done. The number of reports received and the quality of the reports will be monitored using the WHO-UMC VigiGrade Completeness score.

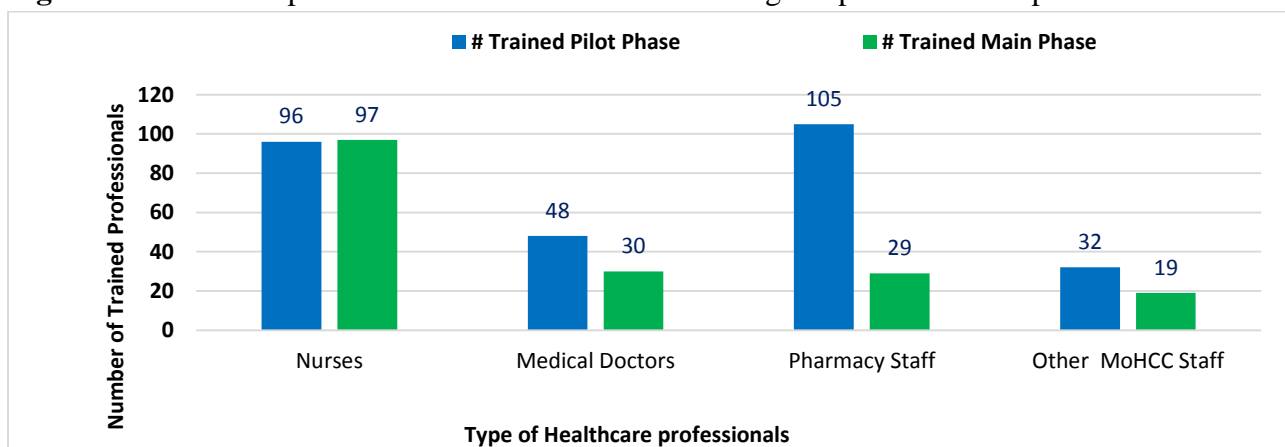
## Results dissemination

The results will also be presented to the MoHCC - DPS, AIDS and TB Division including all MoHCC essential drug programs in all the provinces countrywide, Pharmacovigilance and Clinical Trials Committee, National HIV/TB forum, MoHCC, project sites, and healthcare professional societies. A scientific article will also be published in a peer reviewed Journal.

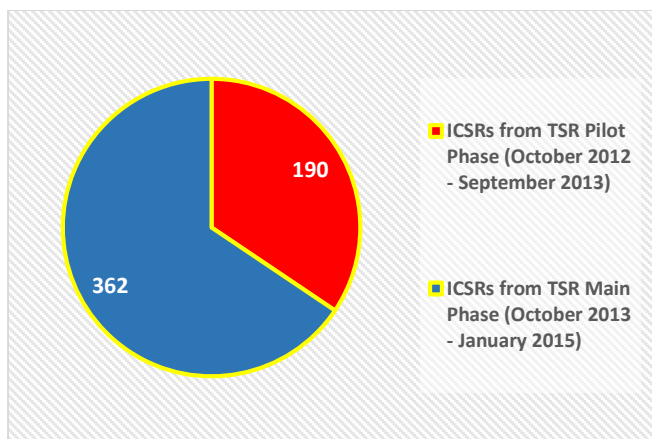
## Key stakeholders

The MCAZ Pharmacovigilance and Clinical Trials (PVCT) Division is the national pharmacovigilance centre and will conduct the project in collaboration with the MoHCC AIDS and TB Departments, National ART Programme, National PMTCT Programme, National TB Programme, Directorate of Pharmacy Services, and National Drugs and Therapeutics Policy Advisory Committee. These programmes are under the Ministry of Health and Child Care (MoHCC). Other stake holders who will be informed about the project for their support and good will are all public health programs and the healthcare professional societies such as Pharmaceutical Society of Zimbabwe (PSZ), Nurses Association of Zimbabwe (NAZ), Pharmacy Technicians Association (PTA), Zimbabwe Medical Association (ZiMA), the University of Zimbabwe Department of Clinical Pharmacology and Department of Pharmacy, Drugs and Toxicology Information Services (DaTIS) and the Medical Research Council of Zimbabwe (MRCZ).

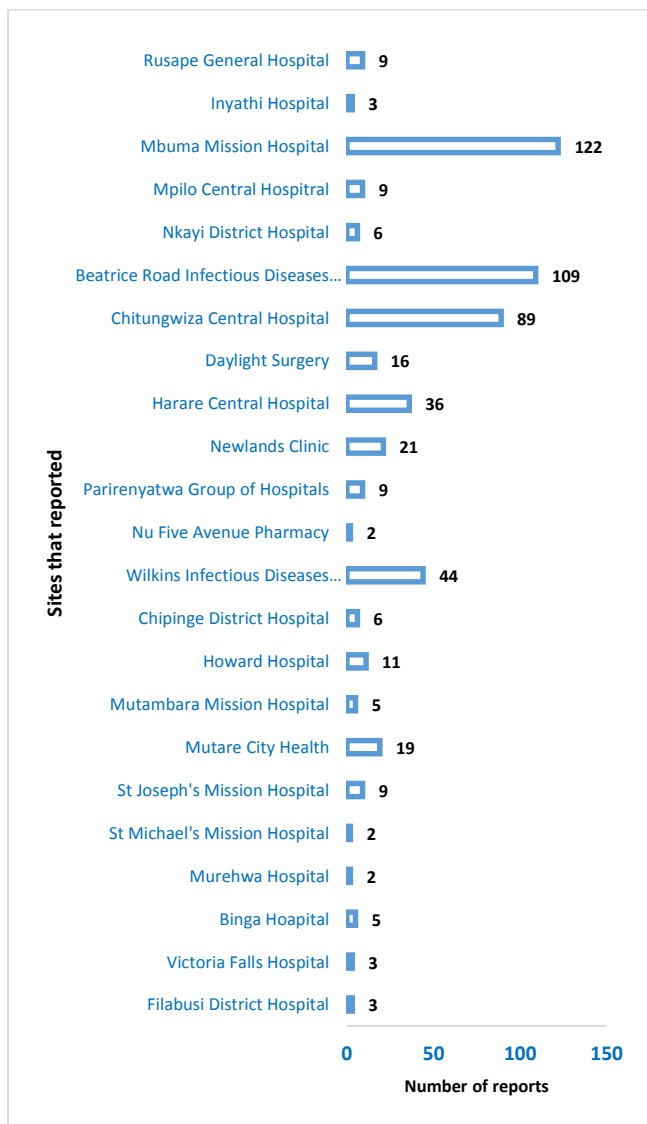
**Figure 1:** Healthcare professionals trained for the TSR Program pilot and main phase



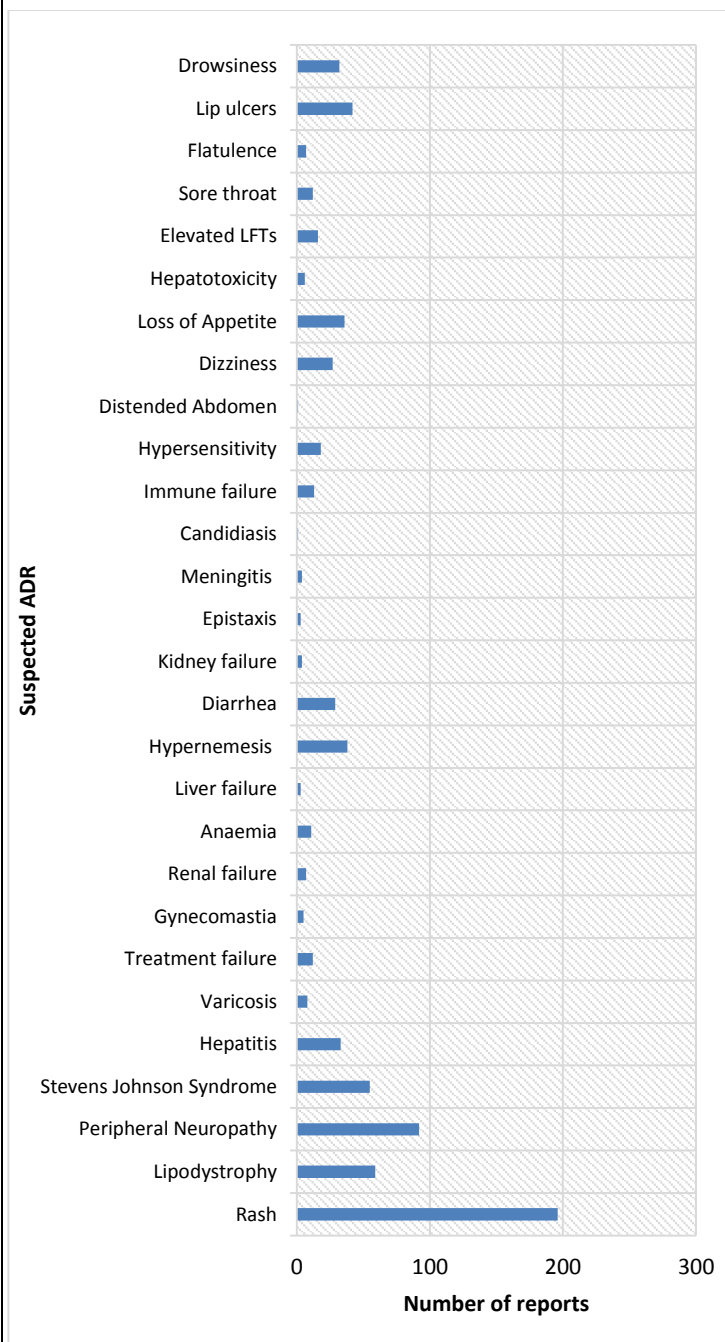
**Figure 2:** Number of ICSRs received from the TSR Pilot and Main phase



**Figure 3:** Total number of reports received in the TSR Program to date and the sites that reported



**Figure 4:** ADR Profile – Most Commonly reported ADRs in the TSR Program pilot and main phase.



### Functions of the Zimbabwe National Pharmacovigilance Centre

The MCAZ Pharmacovigilance and Clinical Trials (PVCT) is the Zimbabwe national pharmacovigilance. Zimbabwe through the MCAZ has been a participating country in the WHO international drug monitoring program

since 1998. The functions of a national pharmacovigilance system are numerous and varied. Through consultation between WHO, the WHO Advisory Committee on the Safety of Medicinal Products (ACSoMP and the Global Fund, the minimum

Functions of the Zimbabwe national pharmacovigilance system have been defined as follows:

- a. To promote pharmacovigilance in the country, collect and manage ADR reports as well as reports of medication errors and suspected counterfeit/substandard drugs.
- b. To collaborate and harmonize with other ADR collection activities within the country (such as public and health programs, national disease control programmes, poison control centres, etc.) and international ADR monitoring programmes.
- c. To identify signals of drug safety such as unknown or poorly characterized adverse events in relation to a drug.
- d. To undertake assessment of risk and options for risk management.
- e. To identify if there are quality problems in medicines resulting in ADRs and more generally, support the identification of medicine quality issues.
- f. To provide effective communication on aspects related to drug safety, including dispelling unfounded rumors of toxicity attributed to medicines and/or vaccines.
- g. To apply information from pharmacovigilance for the benefit of public health programmes, individual patients and national medicines policies and treatment guidelines.
- h. To encourage conduct of drug utilization studies.
- i. To be an active participating member of the WHO International Drug Monitoring Programme WHO Collaborating Centres for Pharmacovigilance, the WHO Uppsala Monitoring Centre (UMC) in Uppsala, Sweden. The WHO headquarters is responsible for all policy issues relating to the WHO Drug Monitoring Programme whilst the WHO-UMC focuses on technical issues and the day to day running of the WHO Programme.
- j. Reporting ADRs, SAEs, AEFIs known as Individual Case Safety Reports (ICSRs) to the WHO drug safety databases such as Vigiflow, Cemflow, Paniflow, Vigibase and Vigilyze and sharing of safety data for analysis and signal detection.
- k. Collaborate with regional centres of excellence such as the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Accra Ghana and the WHO Collaborating Centre for Pharmacovigilance in Rabat, Morocco.

## **Praziquantel and Albendazole Mass Drug Administration Programme**

Following the government's mass bilharzia immunisation country-wide in November 2013, there were a few serious adverse events (SAE's) which were attributed to the drugs, praziquantel and albendazole, by some members of the public. For the few fatal cases there were no post mortems done on the deceased to confirm whether it was the drugs used in the immunisation or the disease itself or other disease conditions.

Also, the drugs used in the mass immunisation (praziquantel and albendazole) are considered relatively safe and well tolerated drugs and are also on the WHO Model List of Essential Medicines. The drugs are

registered with MCAZ. However the known side effects of the medicines are listed below, including indicators, dosage and administration, drug interactions and warnings. Praziquantel and Albendazole should be administered after food or a drink of mahewu.

### **Praziquantel**

Praziquantel is an anthelmintic. It is effective against flatworms and well absorbed from the GIT. It has got a therapeutic effect on patients with schistosomiasis, in whom, within six months of praziquantel dose, up to 90% of damage to internal organs due to schistosomiasis infection can be reversed.

#### *Indications*

Used to treat diseases in humans, mammals and fish that are caused by infection with several types of internal/gastrointestinal and external parasites including the following:

- Salmon poisoning disease
- Hydatid disease caused by infection of various organs with larval stages of tapeworms of the genus *Echinococcus*.
- Cysticercosis, caused by infection of the brain and/or muscles with the eggs and larvae of the pork tapeworm *Taenia solium* (less effective than albendazole in treatment of neurocysticercosis).
- Schistosomiasis caused by trematodes of the genus *Schistosoma* (Praziquantel is the primary drug and is usually effective as a single dose).
- Clonorchiasis caused by the Chinese liver fluke *Chlonorchis sinensis*.
- Paragonimiasis caused by infection with lung flukes, mostly of the species *Paragonimus Westermani*.
- Fasciolopsiasis caused by intestinal fluke *Fasciolopsis buski*.
- *Diplozoon paradoxum* and other Trematoda infections.

WHO includes it on its list of Model List of Essential Medicines.

#### *Dosage and administration*

Schistosomiasis 20mg/Kg per oral every 4-6 hours for one day or 40mg/Kg per oral stat dose.

Tapeworms: 5-25mg/Kg per oral once.

Liver fluke: 25mg/Kg per oral every 4-6 hours for one day.

Dosages above are for patients over 4years old and are to be taken with food or a few minutes before a meal. Quickly swallow the tablets or tablet fragments with a full glass of water

#### *Side effects*

Most are due to the release of the contents of the parasites into the systemic circulation as they are killed and the consequent host immune reaction. The heavier the parasite burden, the more frequent or stronger the side effects normally are.

**CNS:** dizziness, headache, malaise, somnolence, fatigue, vertigo.

**GIT:** abdominal pain/cramps, nausea, vomiting, diarrhoea, bloody stool

**Liver:** asymptomatic and transient increases in liver enzymes (AST & ALT).

**Sensitivity reactions:** urticarial, rash, pruritus, eosinophilia in WBC counts.

**Others:** lower back pain, myalgia, arthralgia, fever, sweating, various cardiac arrhythmias, hypotension.

### *Drug interactions*

Rifampicin, carbamazepine, phenytoin, chloroquine decrease plasma concentration of praziquantel. Antacids and H<sub>2</sub> antagonists increase praziquantel bioavailability.

### *Warnings*

- Do not chew, crush or suck the tablets as the bitter taste may cause gagging or vomiting.
- Avoid eating grapefruit or drinking grapefruit juice while using this medication.

### **Albendazole**

Is an orally administered broad-spectrum anthelmintic. It is poorly absorbed from the GIT, but oral bioavailability is enhanced when albendazole is co-administered with a fatty meal. It works by inhibiting tubulin polymerisation which results in the loss of cytoplasmic microtubules. It should be taken with food.

### *Indications:*

- Neurocysticercosis, due to lesions caused by larval forms of the pork tapeworm, *Taenia solium*.
- Hydatid disease, of the liver, lung and peritoneum; caused by the larval form of the dog tapeworm, *Echinococcus granulosus*.

### *Dosage and administration:*

- Vary depending upon which of the parasitic infections is being treated.
- In young children, the tablets should be crushed or chewed and swallowed with a glass of water OR a liquid suspension is administered.

### *Side Effects*

Abnormal liver function tests, abdominal pain, nausea and vomiting, headache, dizziness/vertigo, raised intracranial pressure, meningeal signs, reversible alopecia, fever, leukopenia and hypersensitivity reactions (including rash and urticaria).

### *Drug Interactions*

The following drugs tend to increase or prolong the effects of albendazole:

- Dexamethasone
- Praziquantel
- Cimetidine

### *Warnings*

Albendazole has been shown to be teratogenic in pregnant rabbits and rats, thus, should not be administered in pregnant women except in circumstances where no alternative management is appropriate. In over-dosage cases, symptomatic therapy and general supportive measures are recommended.



## TSR Monitoring of Praziquantel and Albendazole

### Background

The Pharmacovigilance division (PVCT) of the MCAZ conducted a Targeted Spontaneous Reporting (TSR) exercise of Praziquantel and Albendazole, at the invitation of the MoHCC Directorate Pharmacy Services (DPS). This followed the deworming exercise carried out by the MoHCC in 2012. It was a national program on Schistosomiasis (Bilharzia) and intestinal worms. A total of forty-seven ADR reports were received, mainly rash convulsions, gastric intestinal (GI) disturbances, headache and dizziness. The adverse reaction profile for Albendazole and Praziquantel were similar as illustrated in figure 5 below. The denominator was not available from the reporting rates hence it was not possible to calculate the incidence of ADR reports, and there was also the limitation of under-reporting. Figure 6 shows the eleven districts that reported.

### A. Praziquantel

Mechanism of action – disruption of Ca<sup>2+</sup> homeostasis leading to paralysis of Schistosomiasis species. It disrupts the organism’s tegument unmasking more antigens leading to increased susceptibility to host defences

#### *Common adverse effects*

It has transitory, minimal AEs, rarely of clinical significance - if there are many worms, the AEs may be severe. It is safe in pregnancy.

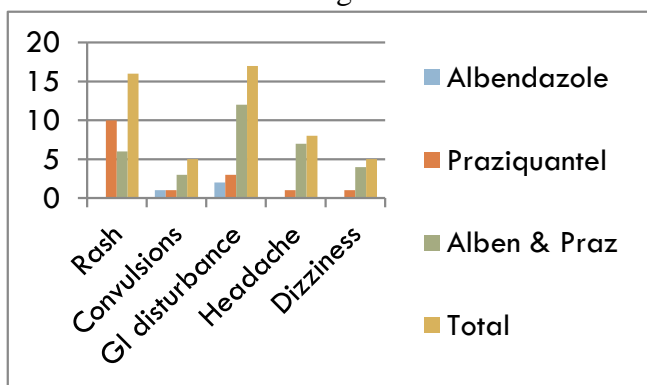
### B. Albendazole –

Modified benzimidazole with selective inhibitory action in helminths. Absorption is increased by a fatty meal.

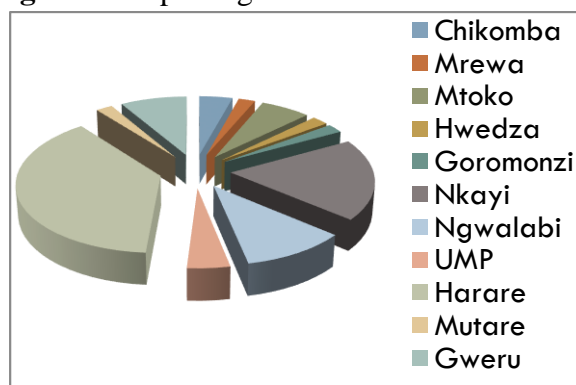
#### *Common adverse effects*

- GI disturbances
- allergic reactions
- dizziness
- headache
- fevers and rashes

**Figure 5:** Number of reports from Praziquantel, Albendazole and both drugs and the associated reactions



**Figure 6:** Reporting sites



## Implications

Targeted Spontaneous Reporting (TSR) helps in tracking adverse events (drug related harmful or unintended occurrences), including those for Albendazole and Praziquantel. This help in management and patient education improved TSR programme albendazole and praziquantel required to identify ADR's and denominator data and the risk benefit profiles. There is need for more collaboration of the MoHCC Mass Drug Administration (MDA) sites with the MCAZ in improving the reporting rate.

## Recommendations

Encourage at least a fatty meal before taking Albendazole – to increase bioavailability. Encourage data collection for joint publications and drug information bulletins.

## Recent Changes in Category of Distribution of Medicines in Zimbabwe

The MCAZ Pharmacovigilance and Clinical Trials Division is also responsible for review of safety of new and old medicines including category for distribution of medicines. During the last 5 year period, the MCAZ recategorised the following medicines as listed in table 1 below, and the reasons therefore. Letters to applicants and Circulars were already written to their effect and the medicines new categories for distribution will be gazetted as such in the near future.

**Table 1** shows the changes in category for distribution, and reasons, of the below mentioned medicines.

Trade Name	Generic Name	Registration number	New Category for distribution	Reason
Relcer Gel	Aluminium and Magnesium Hydroxide, Liquorice, Simethicone	2001/16.1/3931	From Pharmacy medicines (P) to Household Remedies (HR)	All similar products are registered in the HR category.
All brands	Ibuprofen 200mg	All registered products	Pharmacist Initiated Medicines (PIM) to Household Remedies (HR) for pack sizes of 20 dosage units or less	There was a request by a manufacturer and after in-depth review of available evidence, the re-categorisation was approved.
All brands	Ibuprofen 400mg	All registered products	Prescription Preparations (PP) to Pharmacist Initiated Medicines	There was a request by a manufacturer and after in-depth review of available evidence, the re-categorisation was approved.
Coartem Lumartem Lumither	Artemether and Lumefantrine 20mg/120mg	2000/7.5/3664 2009/7.5/4574 2014/7.5/4919	Prescription Preparations (PP) to	Recategorisation was after a request from the Ministry of Health and

			Pharmacist Initiated Medicines (PIM)	Child Care, and as the recategorisation is in line with the new World Health Organisation (WHO) recommendation and the current National policy on Malaria, it was approved.
Patanol	Olapatadine Hydrochloride 0.1%	2002/19.9/4020	Prescription Preparations (PP) to Pharmacist Initiated Medicines (PIM)	There was a request from the manufacturer and after in-depth review of available evidence, the recategorisation was approved.

## Access Programme for Safe, Quality and Efficacious Veterinary Medicines in Zimbabwe

The key function of the Medicines Control Authority of Zimbabwe, (MCAZ) is to register both human and veterinary medicines intended for sale in Zimbabwe. All medicines sold in Zimbabwe must be registered as stipulated in the Medicines and Allied Substances Control Act [15:03], (MASCA) and its regulations S.I. 150 of 1991. There are special exemptions for importation of unregistered medicines for individuals in terms of Section 75 of MASCA. This facility is intended to ensure availability of essential, life-saving, veterinary medicines for those animals which require them.

As a result of its regular liaison meetings with the Department of Veterinary Services, Animal Health Industry Committee, Council of Veterinary Surgeons of Zimbabwe and other stakeholders, the Authority has lowered the application fees for registration of foreign veterinary products from US\$2250.00 to US\$1500.00. This was done to encourage foreign applicants and principals to register veterinary medicines in Zimbabwe thereby improving availability of medicines.

The Authority has also made amendments to the provisions for the importation of unregistered medicines by allowing the importation of unregistered medicines manufactured from countries with Stringent Regulatory Authorities (SRAs). This has resulted in publication of the Medicines and Allied Substances Control Regulations 2012 (No 26) S.I. 186 of 2012, which has broader provisions for the importation of unregistered Veterinary Medicines under Section 75 application.

Four categories for authorisation to import registered medicines (Category I only) and unregistered medicines (Categories II, III and IV) have been created by this provision. The requirements for each category are explained overleaf.

### **Category 1: Registered Veterinary Medicines**

These medicines are registered in Zimbabwe and registration certificates are issued. An annual retention fee of US\$300 for imported products and US\$200 for locally manufactured products is paid per product each year. These products are imported via the normal MCAZ Import/Export Regulations (S.I. 57 of 2008).

### **Category 2: Unregistered Veterinary Medicines**

These medicines are not yet registered in Zimbabwe, but applications for registration have been made and products are undergoing evaluation by MCAZ. The medicines should have been registered by SRAs. The applicant or local importing company pays US\$300 for authority to import the product for a year, plus verification fees each time a consignment is cleared.

Once MCAZ has registered the medicine, it moves to Category 1. If registration is unsuccessful due to safety, quality and efficacy concerns, importation of such a product is not permitted and further application for importation will be refused.

### **Category 3: Unregistered Veterinary Medicines**

These medicines are not registered in Zimbabwe and there are no registered alternatives. The medicines are imported in low volumes - that is, total annual sales below US\$30 000 free on board (FOB). If imported volumes exceed the US\$30 000 FOB per annum per product, the product is moved to Category 2, which means an application for registration is now required. If imports remain less than US\$30 000 FOB, the product is moved to Category 4.

For new products which were not previously registered by the Authority, the local company is required to submit, prior to authorization, additional documentation which assists the Authority to better estimate quality or risk of the product. The information includes a current Good Manufacturing Practise (cGMP) certificate of manufacturer, registration certificate from country of origin or from other countries to which the product is exported (excluding SADC countries) and package inserts and labels for the product information.

The authorised importer pays US\$500 per product per year plus verification fees of 0.05% of FOB each time a consignment is cleared.

### **Category 4: Unregistered Veterinary Medicines**

These medicines are not registered in Zimbabwe, they are usually imported in very low volumes and their sales are far below US\$30 000 FOB per annum. Examples of such veterinary products that fall into this category include, ketamine, detomidine, Antisedan, ketoprofen, prostoglandins, yohimbine, etc. Applications to import these medicines are initiated by the end-users i.e. veterinary surgeons/surgeries and farmers, but not wholesalers. The individual prescriptions and farmers' requests are subject to a fee of \$5.00 and veterinary surgeries and hospitals are required to pay US\$25 per application. The new provisions have seen a 25% increase in availability of essential life-saving veterinary medicines in 2013 as compared to 2012. Requests for the importation of unregistered veterinary medicines in Categories 2 and 3 should come from veterinary wholesalers, pharmacies and some veterinary medicine general dealers only.

MCAZ advises importers to first consider products that were previously registered and were deregistered due to non-payment of retention fees as safety, efficacy, etc., will have already been established at previous registration.

## Adverse Drug Reaction Monitoring

### What to report

The Pharmacovigilance and Clinical Trials Committee of the Medicines Control Authority would like to thank all ADR and AEFI reporters and encourage you to report all **suspected** adverse reactions to drugs and adverse events following immunisation. The reporting of a seemingly insignificant or common adverse reaction or side-effect may help pinpoint a more widespread prescribing problem.

*The Committee would therefore like you to:*

#### **1. Report all suspected adverse effects, side effects or adverse events to all medicines or vaccines.**

*This includes:*

- Cases of suspected therapeutic failure
- Adverse consequences when changing between branded and generic products
- Adverse effects to herbal products and traditional remedies
- Adverse reactions to unregistered or Section 75 specially imported drugs
- Adverse reactions to vaccines
- Adverse Events Following Immunisation (AEFIs)

**References:**

1. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *Lancet* 2000; 356(9239): 1423-30.
2. Ickovics JR, Cameron A, Zackin R, et al. Consequences and determinants of adherence to antiretroviral medication: results from Adult AIDS Clinical Trials Group protocol 370. *Antiviral therapy* 2002; 7(3): 185-93.
3. Eluwa GI, Badru T, Agu KA, Akpoigbe KJ, Chabikuli O, Hamelmann C. Adverse drug reactions to antiretroviral therapy (ARVs): incidence, type and risk factors in Nigeria. *BMC clinical pharmacology* 2012; 12: 7.
4. Centers for Disease C, Prevention. Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures--worldwide, 1997-2000. *MMWR Morbidity and mortality weekly report* 2001; 49(51-52): 1153-6.
5. Saint-Marc T, Partisani M, Poizot-Martin I, et al. A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. *Aids* 1999; 13(13): 1659-67.
6. Dormann H, Muth-Selbach U, Krebs S, et al. Incidence and costs of adverse drug reactions during hospitalisation: computerised monitoring versus stimulated spontaneous reporting. *Drug safety: an international journal of medical toxicology and drug experience* 2000; 22(2): 161-8.
7. Ciorciaro C, Hartmann K, Kuhn M. [Differences in the relative incidence of adverse drug reactions in relation to age? An evaluation of the spontaneous reporting system of SANZ (Swiss Drug Monitoring Center)]. *Schweizerische medizinische Wochenschrift* 1998; 128(7): 254-8.
8. Kaur S, Kapoor V, Mahajan R, Lal M, Gupta S. Monitoring of incidence, severity, and causality of adverse drug reactions in hospitalized patients with cardiovascular disease. *Indian journal of pharmacology* 2011; 43(1): 22-6.
9. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA: the journal of the American Medical Association* 1998; 279(15): 1200-5.
10. Pal SN, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes: complementing spontaneous reporting systems. *Drug safety: an international journal of medical toxicology and drug experience* 2013; 36(2): 75-81.
11. Zimbabwe National Pharmacovigilance Policy and Guideline Handbook. November 2013.



MEDICINES CONTROL AUTHORITY OF ZIMBABWE

Form: PVF01

Spontaneous Adverse Drug Reaction Report (ADR) Form						
Identities of Reporter, Patient and Institute will remain confidential						
MCAZ Reference Number (MCAZ use only)						
Patient Details (to allow linkage with other reports)						
Clinic/hospital Name:		Clinic/Hospital Number				
Patient Initials:		VCT/OI/TB Number				
Date of Birth:		Weight (Kg)		Sex:		
Age:		Height (meters)				
Adverse Reaction						
Date of Onset:						
Duration:	Less than one hour	Hours	Days	Weeks	Months	
Description of ADR						
Serious: Yes <input type="checkbox"/>  No <input type="checkbox"/>	Reason for Seriousness	<input type="checkbox"/> Death		<input type="checkbox"/> Life-threatening		
		<input type="checkbox"/> Hospitalization/prolonged		<input type="checkbox"/> Disabling		
		<input type="checkbox"/> Congenital-anomaly		<input type="checkbox"/> Other medically important condition		
Relevant Medical History						
Relevant Past Drug Therapy						
Outcome of ADR	Recovered	Not yet recovered	Fatal	Unknown		
Current Medication						
Generic Name	Brand Name	Batch Number	Dose	Indication	Date Started	Date Stopped
Concomitant (Other) drugs taken & Dates/period taken:	Name of drug:				Date started	Date stopped
Suspected drug (s), if known:						
Laboratory tests results:						
Reported by						
Forename (s) & Surname:						
Designation:						
Address:						
Signature:				Date:		
Send to: The Director-General, Medicines Control Authority of Zimbabwe 106 Baines Avenue, P O Box 10559, Harare Tel: +263-4-708255 or 792165, E-mail: mcaz@mcaz.co.zw, website: www.mcaz.co.zw						

NB. This form may be completed for any ADR related to medicines or medical devices



**Medicines Control Authority of Zimbabwe**

PVF 05

**PHARMACOVIGILANCE AND CLINICAL TRIALS DIVISION**

REPORT ON MEDICINAL (PHARMACEUTICAL) PRODUCT DEFECT  
OR PROBLEM

*To be completed by Pharmacists, Pharmacy Technicians, Medical Practitioners, Nurses, Veterinary Surgeons and other Distributors of Medicines.*

1. Product Name (Brand and Generic)			
2. Description of the Device/Medicine	3. Intended Use	4. Size/Type of Container	5. Registration No.
6. Batch Number		7. Expiry Date	
8. Name and Address of Manufacturer			
9. Name and Title of Reporter			
10. Your Practice Location and Address of Hospital, Clinic, Retail Surgery etc.			
11. Phone Number		12. Date Problem Occurred or Observed	
13. If requested will the actual product involved be available for examination by MCAZ.			
<b>YES</b>		<b>NO</b>	
14. Signature of Reporter		15. Date	
16. Defects/Problem Noted or Suspected (see a-j below)			

**NATURE OF DEFECT OR PROBLEM**

- |  |   |
|--|---|
| a) Presence of foreign material  | g) Wrong label, wrong packaging, wrong strength |
| b) Unusual odour   | h) Lack of therapeutic response                 |
| c) Colour changes  | i) Leakages                                     |
| d) Fungal growth   | j) Other (specify)                              |
| e) Suspected contamination   |   |
| f) Parenteral solution – leaks, particulate matter, discoloration etc. |   |

**Return To:** The Director-General  
Medicines Control Authority of Zimbabwe  
106 Baines Avenue  
P O Box 10559  
Harare  
Tel: +263-4-736981/2/3/4/5, 708255 or 792165  
Email: mcaz@mcaz.co.zw

**For Office Use Only**  
Report Number:  
Date Received:



## Editorial

Dear Reader

We wish to thank all the reporters of Adverse Drug Reactions (ADRs) and Adverse Events Following Immunisation (AEFIs) since the MCAZ National Pharmacovigilance Centre was set up in 1994. The next bulletin publication will include analysis of ADR and AEFI reports received to date. Causality assessment of the reports was done by the MCAZ Pharmacovigilance and Clinical Trials Committee and all ADR reports are uploaded into the WHO Vigiflow International Drug Safety database that is also used as the in house MCAZ database. In 2015 the MCAZ will identify and set up sentinel or regional Pharmacovigilance Centres countrywide from the TSR programme sites that report to the MCAZ National Pharmacovigilance Centre. **If you are interested in your clinic, hospital or surgery in becoming a regional or sentinel Pharmacovigilance Centre please express your interest in writing to the MCAZ Director General.** We cherish your reports and will continue the publication of the Drug Information bulletin as one of the ways of disseminating Drug Safety information to Healthcare professionals. Please note that the reporting of a seemingly insignificant or common adverse reaction or side effect may help pinpoint a more widespread adverse effect or prescribing problem. Most of the commonly reported ADRs received include Antiretroviral ADRs such as peripheral neuropathy, lipoatrophy, and lipodystrophy with stavudine containing combinations, anaemia with AZT, lactic acidosis with NRTIs, nevirapine with hypersensitivity reactions, and EPI-MoHCC AEFI vaccines related reactions such as injection site abscess, fever etc. We welcome your comments.

Thank you for Reading

### Acknowledgements

MCAZ is grateful for the support from the Ministry of Health Child Care (MoHCC), Health Trust Fund (HTF), Global Fund and United Nations Development Programme (UNDP) which made the publication of this bulletin possible.

