PHARMACOVIGILANCE/POST MARKETING SURVEILLANCE NEWSLETTER

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Sulfadoxine/Pyrimethamine and Stevens-Johnson Syndrome

Content

EDITOR'S NOTE...

On behalf of the NPC, I wish to express appreciation to our numerous stakeholders that have been working tirelessly with the National Pharmacovigilance Centre (NPC) to ensure the safe use of medicines in Nigeria. The NPC is committed to making quarterly newsletters available 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 spontaneous reporting of adverse drug reactions.

This issue of the newsletter focuses on Sulfadoxine/Pyrimethamine (SP) and Stevens-Johnson syndrome (SJS). A Review of the NPC database, revealed 276 cases of SP related ADRs including 120 cases of Stevens - Johnson syndrome or Toxic epidermal Necrolysis (SJS/TEN) reported to the NPC since 2004 with a reporting rate of 1.27%. 22 (7.97%) of the cases were life threatening, 7 (2.54%) resulted in death, 8 (2.90%) resolved with disability and 124 cases (44.92%) resolved/recovered completely.

The centre has sustained its efforts in curbing the circulation of fake and substandard antimalarial medicines in Nigeria. NAFDAC collaborated with the United States Pharmacopeia (USP) to Conduct Round 3 Survey on Quality of Antimalarial Medicines in circulation in Nigeria. The result shows failure rate of 1.6% as against 4.3% in Round 2.

We encourage Health care Professionals and other stakeholders to continue to report all adverse drug reactions.

Your valued comments and acknowledgement of receipt of this issue through our email addresses (nafdac_npc@yahoo.com; 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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Text any DRUG RELATED PROBLEM to the SHORT CODE 20543 (For free on MTN, Glo, Etisalat and Airtel) for action by the Pharmacovigilance Centre.

Sulfadoxine / Pyrimethamine induced Stevens - Johnson syndrome

Introduction

Sulfadoxine and Pyrimethamine (SP) is an antimalarial drug marketed in Nigeria under several brand names including Fansidar, Amalar, Antimal, Astab, Celoxine, Dupridox, Malareich, Laridox,[1] etc. SP is a fixed combination of Sulfadoxine 500mg and Pyrimethamine 25mg. Sulfadoxine (a sulphonamide) and Pyrimethamine (an antiprotozoan) are both folic acid antagonists. The two constituents sequentially block two enzymes involved in the biosynthesis of folinic acid within the malaria parasites. Sulfadoxine inhibits the activity of dihydropteroate synthetase whereas Pyrimethamine inhibits dihydrofolate reductase. This ultimately results in cell growth arrest and death of the malaria parasite.[2]

Recommendations for use of SP

Previously, SP was indicated for treatment of acute, uncomplicated *Plasmodium falciparum* malaria for those patients in whom chloroquine resistance was suspected. SP was also recommended as Prophylaxis for travellers to areas where chloroquine-resistant *P. falciparum* malaria was endemic[3].

The use of SP in Malaria treatment has evolved. Currently, SP is recommended for intermittent preventive treatment of malaria in pregnant women during the second and third trimesters of pregnancy[1]. Malaria treatment with Sulfadoxine/Pyrimethamine is no longer recommended. Furthermore, SP is no longer recommended for prevention of malaria in travellers to endemic areas in the United States of America. Sulfadoxine/Pyrimethamine (marketed as Fansidar) has been discontinued in the US and is no longer commercially available.

This change in recommendation for use of SP is attributed to wide spread resistance of *Plasmodium Falciparum* to SP observed in several parts of the world. In addition, severe and sometimes fatal adverse reactions have been reported with the once-weekly regimen of the fixed combination of Sulfadoxine and Pyrimethamine used for prevention of malaria.[4]

Use of SP in Nigeria.

Use of Sulfadoxine-Pyrimethamine in Nigeria is as recommended by the World Health Organization (WHO). The WHO recommends the use of SP in the intermittent prevention of malaria in pregnant women in the malaria endemic Sub Saharan region. Intermittent preventive treatment in pregnancy with Sulfadoxine/Pyrimethamine (IPTp-SP) has been effective to reduce the burden of

[1] Emdex Vol. 1:June 2016-May2017 Edition
[2] http://www.drugbank.ca/drugs/DB01299)
[3] https://www.drugs.com/pro/fansidar.html viewed 2/8/2018
[4] https://pubchem.ncbi.nlm.nih.gov/compound/pyrimethamine#section viewed 8/9/2017

malaria during pregnancy in Africa. Sulfadoxine/Pyrimethamine use in IPTp programmes in Africa, with 2-4 treatment doses over 6 months, has been well tolerated in multiple IPTp trials. IPTp-SP is based on administering at least two treatment doses of Sulfadoxine/ Pyrimethamine to pregnant women at predefined intervals after quickening (around 18-20 weeks) during the second and third trimesters of pregnancy.[5]

WHO also recommends the use of Amodiaquine in combination with SP for Seasonal Malaria Chemoprevention (SMC) in areas of highly seasonal malaria transmission in the Sahel Sub-region. SMC is the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent illness. The objective is to maintain therapeutic drug concentrations in the blood throughout the period of greatest risk[6]. This is currently being implemented in Sokoto and Zamfara States.

SP is not recommended for the treatment of Malaria in Nigeria. The treatment of choice for uncomplicated malaria is Artemisinin Based Combination Therapy (ACT). The recommended ACTs in Nigeria are Artemether-Lumefantrine and Artesunate-Amodiaquine.

Sulfadoxine/Pyrimethamine like any other drug has some side effects following its use in humans. Some of the side effects includes diarrhoea, rash, headaches and hair loss. Severe cutaneous reactions have also been reported with the use of Sulfadoxine/Pyrimethamine, some of which have been fatal. The use of sulphonamides including Sulfadoxine is associated with increase in the risk of serious dermatologic reactions. Fatalities resulting from severe cutaneous reactions have been reported with the fixed-combination of Sulfadoxine and Pyrimethamine. Such severe cutaneous reactions include erythema multiforme, Stevens-Johnson syndrome (SJS), and Toxic Epidermal Necrolysis (TEN)[7].

Stevens-Johnson Syndrome is a rare but serious disorder that affects the skin, mucous membrane, genitals and eyes. Cutaneous manifestation of SJS is often preceded with signs and symptoms such as high fever, severe headache, stomatitis, conjunctivitis, rhinitis, urethritis and balanitis. This is followed by a red or purple rash that spreads and forms blisters. The affected skin eventually dies and peels off.

SJS is often caused by an adverse reaction to certain medications. Anti- infective Sulphonamides (such as Cotrimoxazole and Sulfadoxine) are among the classes of

[5] Peters PJ[1], Thigpen MC, Parise ME, Newman RD, Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. Drug Saf. 2007;30(6):481-501. Available at https://www.ncbi.nlm.nih.gov/pubmed/17536875 viewed 8/9/2017

[6] NAFDAC Mannual of PHARMACOVIGILANCE TRAINING FOR HEALTH CARE PROVIDERS (Doctors, Pharmacists & Nurses)2016

[7] NIH US National Library of Medicines https://pubchem.ncbi.nlm.nih.gov/compound/pyrimethamine#section=Top viewed 8/9/2017

drugs associated with high risk of SJS. Other drugs associated with high risk of SJS include allopurinol, carbamazepine, lamotrigine, nevirapine, phenobarbital, phenytoin, sertraline and certain types of NSAIDs including meloxicam, piroxicam and tenoxicam.

Risk factors for Stevens-Johnson syndrome may include viral infections (e.g. HIV), a weakened immune system (as seen in AIDS), a previous history of Stevens - Johnson syndrome, a family history of Stevens - Johnson syndrome and severe allergies.[8] Also, females are slightly more at risk of developing SJS compared to males[9]

SJS and TEN are variations of the same syndrome, however, SJS has less extensive skin detachment. Consequently, TEN has a higher mortality of 30-35% compared to Stevens - Johnson syndrome and transitional forms with 5-15% mortality rate.[7]

Reports of Suspected SP induced ADRs documented in the NPC database

We reviewed Individual Case Safety Reports (ICSRs) in the NPC database from January 2004 to December 2017. A total of two hundred and seventy-six (276) ICSRs of adverse effects suspected to be associated with administration of Sulfadoxine/Pyrimethamine were revealed. This constitutes 1.27% of the 21,696 ICSRs documented in the NPC database. Table 1 shows the distribution of age and gender of patients who had SP related ADR during the reporting period. Of the 276 ICSRs sent to the NPC, 158 (57.25%) are females while 117(42.39%) are males. The gender of 1 (0.36%) patient was not reported.

In 40 cases, the specific age of the patient was either not reported or vaguely reported as adult. In 236 cases where the age was clearly reported, the age range is between 1-98 years. The most common age group that reported SP ADRs was 25<35 with 28.62% (79), followed by 15<25 with 17.39% (48) and age group 35<50, 16.30% (45). The mean ages are 29.81 and 25.19 for males and females respectively.

Table 1. Age distribution and sex of patients with suspected SP ADRs

Age/years	Male N=117 (42.39%)	Female N=158 (57.25%)	Total ICSR N=276
Mean age	29.81	25.19	
0<5	11	19	31*(11.23%)
5<15	9	6	15(5.43%)
15<25	13	35	48(17.39%)
25<35	30	49	79(28.62%)
35<50	22	23	45(16.30%)
50<65	9	6	15(5.43%)
≥65	2	1	3(1.09%)
Adult	16	11	27(9.78%)
Not reported	5	8	13(4.71%)

*The unreported gender N=1 (0.36%) falls in this age group.

[8] http://www.nhs.uk/conditions/stevens-johnson-syndrome/Pages/Introduction.aspx viewed 8/9/2017

[9] https://rarediseases.org/rare-diseases/stevens-johnson-syndrome-and-toxic-epidermal-necrolysis/ viewed 16/10/2017

Table 2, shows the indication for treatment and the prescribed drugs suspected to be responsible of the reported ADRs.

The main indication for treatment reported was malaria in 211 (76.45%) cases. In 20 (7.25%) cases, the indication is malaria prophylaxis, mostly for malaria prophylaxis in pregnancy. Fever/febrile illness is also indicated in 20 (7.25%) Other indications 13 (4.71%) include headache, headache/fever, fever/dizziness, cough/fever/headache, cough/catarrh, cough, acute plasmodiasis, HIV and skin rash.

Majority of the events described in the case reports affect the skin and subcutaneous tissues (Table3). One hundred and twenty (43.48%) of the 276 cases of SP related drug induced ADRs were Stevens-Johnson syndrome or Toxic Epidermal necrolysis (SJS/TEN); 31. 16% (86) cases of ADR were various grades and types of rashes and 14.86% (41) are various types of Gastrointestinal disorders such as anorexia, nausea, diarrhoea, abdominal pain and vomiting.

Table3 also shows the suspected drugs for the SP related ADR. 82.97% (229) of the ADRs were suspected to be caused by Sulfadoxine – Pyrimethamine (SP) only; in 9.45% (26) cases the suspect drugs were Sulfadoxine – Pyrimethamine/ Amodiaquine (SP/A). Other suspected drug causes include Sulfadoxine – Pyrimethamine/Amodiaquine-Artesunate(SP/AA), Sulfadoxine – Pyrimethamine/ Artesunate (SP/AT), Sulfadoxine – Pyrimethamine/

Table 2 showing the indication for treatment

prescribed drugs (reported suspect drugs)/ Indication	SP 227(82.25%)	SP/A 24(8.70%)	SP/AT 6(2.17%)	SP/AA 8(2.90%)	SP/Others 11(3.99%)	Total 276(100%)
Malaria	172	22	5	8	4	211 (76.45%)
Malaria Prophylaxis	19	1	0	0	0	20 (7.25%)
Fever/febrile illness	18	0	0	0	2	20(7.25%)
Others	8	0	1	0	4	13 (4.71%)
Not reported	10	1	0	0	1	12(4.35%)
Total	227	24	6	8	11	276

SP = Sulfadoxine/Pyrimethamine, SP/A = Sulfadoxine/Pyrimethamine + Amodiaquine, SP/AT = Sulfadoxine/Pyrimethamine +Artesunate, SP/AA = Sulfadoxine/Pyrimethamine +Artesunate/Amodiaquine,

cotrimoxazole (SP/CXT) and other combinations in 2.90% (8), 2.54% (7) 0.72% (2) and 1.45% (4) cases respectively. Njau JD et al 2013 in a finding from three district routine demographic surveillance in rural Tanzania reported 25 and 11.6 ADRs

(5.07%) patients were reported to be concomitantly taking antiretroviral therapy. Rashes are a common side effect of Nevirapine therapy commonly prescribed for HIV/AIDS patients. Nevirapine is known be a high risk drug for SJS. ADR incidence among HIV positive

Table3: Showing Types of ADR and suspected Causal Drug

Types of ADR	SP 229 (82.97)	SP/A 26(9.42)	SP/AA 8(2.90)	SP/AT 7 (2.54)	SP/CXT 2 (0.72)	Others 4 (1.45)	Total N =276(100%)
SJS/TEN	117	2	0	0	1	0	120(43.48)
Rashes	72	3	3	5	1	2	86(31.16)
GIT symptoms	20	15	4	1	0	1	41(14.86)
Weakness/Dizziness	6	3	0	1	0	1	11 (3.99)
Fever	2	3	0	0	0	0	5 (1.81)
Headaches	4	0	0	0	0	0	4 (1.45)
Others	8	0	1	0	0	0	9 (3.26)

SP = Sulfadoxine/Pyrimethamine, SP/A = Sulfadoxine/Pyrimethamine + Amodiaquine, SP/AT = Sulfadoxine/Pyrimethamine +Artesunate, SP/AA = Sulfadoxine/Pyrimethamine +Artesunate/Amodiaquine, SP/CXT = Sulfadoxine/Pyrimethamine+ Cotrimoxazole, SJN = Steven Johnson syndrome, TEN = Toxic epidermal necrolysis, ADR =Adverse drug Reaction, GIT symptoms = Gastrointestinal tract symptoms (such as nausea anorexia, diarrhoea and vomiting)

associated with SP while 5.6 with SP/AS combinations per 100,000 exposures [13]. Other studies which support our finding include a Malaysian study, where incidence of ADR due SP monotherapy was found to be 2.4% per 100,000 exposure during prophylaxis[14]. In Peru, a follow up patient on combination of SP and AT for two years reported 8% associated ADR[15].

Concomitant treatment with other drugs with a high risk for SJS can also be seen in some of the reports. Table 4 shows some of drugs with high risk for SJS that were concomitantly taken by the patients during treatment with SP. Fourteen

patients receiving SP or cotrimoxazole was reported between 4 -7% (16) Cotrimoxazole, another drug with high risk for SJS was reported as concomitant drug in 2(0.72%) cases this is in keeping with study in Blatyre SP, CXT was 0.3 to 8.4%(7)[17]. Also some anticonvulsant such as Carbamazepine and phenytoin are a high risk for SJS.

The 4 most common concomitant drugs taken were (table 5) analgesics 36 (13.04%), antibiotics 34 (12.31%) Multivitamins/Haematics 28 (10.14%), ART 15 (5.43%) and Antimalarial 12(4.35%). Patients in addition took one or more other drugs ranging from, anti-hypertensives, anticonvulsants, anti-TB, herbal preparations, etc.

103(56.90%) patients reported having

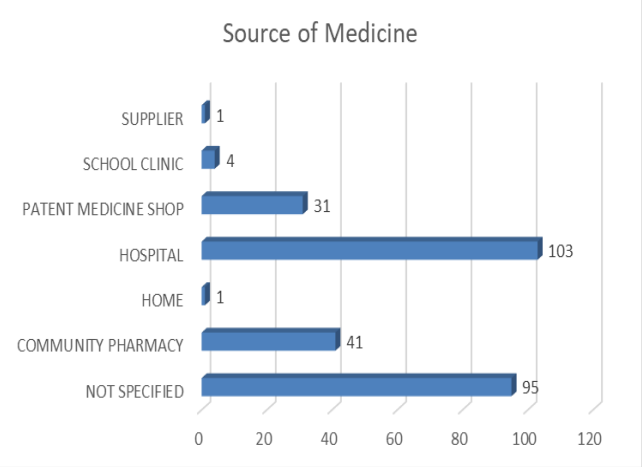
Table 5: Concomitant drug and Suspected Drug prescribed

CONCOMITANT DRUGS	SUSPECTED DRUGS						
	SP N=228 (82.60%)	SP/A N=24 (8.70%)	SP/AA N=8 (2.90%)	SP/AT N=6 (2.17%)	SP/CXT N=2 (0.72%)	Others N=8 (2.90%)	Total N=276 (100%)
Analgesics	35	0	0	0	0	1	36(13.04%)
Antibiotics	29	0	0	1	2	2	34(12.31%)
Anticonvulsants	3	0	0	0	0	0	3(1.09%)
Antihypertensive	6	0	0	0	0	0	6(2.17%)
Antimalarial	11	0	0	1	0	0	12(4.35%)
Anti-tuberculosis	1	0	0	0	0	0	1(0.36%)
ART	15	0	0	0	0	0	15(5.43)
Herbal	4	0	0	0	0	0	4(1.45%)
Multivitamins/Haematics	28	0	0	0	0	0	28(10.14%)
Others	4	0	0	0	0	0	4(1.45%)
No concomitants	92	24	8	4	0	5	133(48.19%)
Total	228	24	8	6	2	8	276

Table 6 shows the outcome of the ADR following management. One hundred and twenty four (124) patients recovered with symptoms of ADRs resolved. Death was reported as outcome in seven (7) cases. In all 7 cases of death, the ADRs are descriptive of SJS/TEN. In total, 22 of the 276 cases are life threatening, while hospitalization/ongoing, resolved with disability and cases that outcome were not stated are 33, 8 and 82 respectively. 96.67% of the 30 serious cases are ADRs pertaining to Skin and subcutaneous tissue.

The source of medicine was reported in 181 cases. Of these 181 cases, received their medications (SP) from Hospitals and only 31(17.13%) had sourced their medication from patent medicine stores (Chart 1). This is particularly thought-provoking because malaria prophylaxis (the recommended use for SP) was indicated in only 19 of

Chart 1 reported source of suspected medicines



those 181 reports.

Although Stevens - Johnson syndrome is considered rare as a whole, the frequency of cases reported in Nigeria in recent times and publicised by the media have created public concern. Some of these cases have resulted in death of the patient. In other cases, the outcome was not gruesome as there was early identification and successful treatment of the condition. Below is a case report of one of such cases.

Table 6: Showing ADR Types and Outcome of Management

Types of ADR	Resolved/ Recovered 124 (44.92%)	Resolved with Disability 8 (2.90%)	Life threatening 22(7.97%)	Resulted in Death 7 (2.54%)	Hospitalization 3 (1.09%)	Ongoing 30 (10.87%)	No outcome information 82(29.71%)	Total 276 (100%)
SJS/TEN	37	5	16	7	3	13	39	120
Rashes	40	3	5	0	0	14	24	86
Nausea/Anorexia/ Vomiting	26	0	1	0	0	3	11	41
Fever	2	0	0	0	0	0	3	5
Headaches	4	0	0	0	0	0	0	4
Weakness/Dizziness	7	0	0	0	0	0	4	11
Others	7	0	0	0	0	0	2	9

Case report

A thirteen year old boy was seen in a Secondary School in Niger State, his eyes were red, painful and with discharge. Laridox; Batch Number: B6005 and NAFDAC Registration Number 04-3353 (Sulfadoxine/ Pyrimethamine) had been prescribed for him for malaria. Few days later he had a rash on his chest and a very high fever of 39^{o}C and was prescribed Yeast, Loratadine and Gentamicin but only Loratadine was available. He was moved from his school clinic to a General Hospital in Abuja and was admitted at Emergency Paediatric Unit (EPU) where some investigations were carried out. SJS was suspected. Investigations also revealed that no internal damage had occurred except lesions and left eye contracture. There was no significant past medical history nor was the patient known to be Sulphonamide sensitive. The reaction was treated, the patient recovered and was discharged healthily. Causality assessment from the centre was Probable, ADR related to SP administration.

Conclusion

Healthcare providers are urged to consider the safety of individual patients when prescribing medications that have potential to induce serious adverse effects.

Patients should be instructed to promptly report signs and symptoms that may precede the onset of cutaneous

manifestations of Stevens-Johnson syndrome. Health care providers should counsel patients when prescribing SP to Drink lots of fluids, avoid exposure to sun and notify physician if rash, sore throat, pallor, shortness of breath or glossitis occur.

The general principle used in treatment of SJS/TEN involves prompt identification and withdrawal of the underlying cause (suspect drugs) control of symptoms and prevention of complications. The management of the patients should be undertaken in specialized intensive care units with the same main types of therapy as for burns[10].

13. Njau JD, Kabanywanyi M, Goodman CA, MacArthur JR, Kapella BK, Gimnig JE etal (2013) Adverse drug events resulting from use of drugs with sulphonamide containing anti-malarials and artemisinin based ingredients: Findings on incidence and household costs from three district with routine demorgsrphic surveillance system in rural Tanzania. Malaria Journal 12:236 https://doi;org/10.1186/1475 – 2875-12-236

14. Lyn PC, Fernandez E. Severe cutaneous adverse reactions and sulphadoxine-pyrimethamine in Sabah, Malaysia. Med J Australia. 1987;146:335–336. [PubMed]

15. Pierre-Dominique Ghislain M.D., Jean-Claude Roujeau, M.D. (2002) Treatment of severe drug reactions: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis and Hypersensitivity syndrome
Dermatology Online Journal 8(1): 5 available at http://escholarship.org/uc/item/97d8t291 viewed 8/9/2017

16. Tanzania Commission for AIDS (TACAIDS): Tanzania National Bureau of statistics (NBS) MEASURE DHS 2003 -4 Tanzania HIV/AIDS indicator survey. 2004 (MEASURE DHS)ed. Calverton,MD 20705 USA:TACAIDS.

17. Gimnig JE, MacArthur JR, M'Bang'ombe M, Kramer MH,Chizani N, Stern RS et, al (2006). Severe cutaneous reactions to sulphodoxine –pyrimethamine and trimethorprim –sulfamethoxazole in Blantyre District AM J Trop Med Hyg 74:738 - 743.

ROUND 3 SURVEY ON THE QUALITY OF ANTIMALARIA MEDICINES IN CIRCULATION IN NIGERIA BY NAFDAC IN COLLABORATION WITH USP

Summary.

The Pharmacovigilance and Postmarketing Surveillance Directorate coordinated NAFDAC collaboration with the United States Pharmacopeia (USP) to Conduct Round 3 Survey on Quality of Antimalarial Medicines in circulation in Nigeria.

The report, of the survey was disseminated to stakeholders on 12th December, 2017 at NAFDAC Office Complex Lagos. The report revealed that 883 samples out of 897 samples (98.4%) of antimalarial medicines passed quality tests while 14 samples (1.6%) failed as they did not conform to specification.

The failed samples included nine (9) Artemether+Lumefantrine tablets, one (1) Sulfadoxine Pyrimethamine tablet, two (2) Quinine Sulfate tablets, one(1) Artesunate+Amodiaquine tablet and one(1) Others.

Four (4) samples failed disintegration tests (1 AA and 3 AL); 2 samples failed assay, (2 AA); 5 sample did not contain the stated Active Pharmaceutical Ingredient (API) (2 AL, 2 QN and 1 SP); 1 Sample has low API (1 Others).

The failure rate of antimalarial medicine in Round 3 survey is 1.6% as against 4.3% in Round 2.

The 897 samples procured for the survey were from FCT, Abuja (NCZ), Adamawa State (NEZ),
45Zamfara State (NWZ), Enugu State (SEZ), Cross Rivers State (SSZ) and Osun State (SWZ).
617 samples were procured from the private sector, representing 68.8 percent of the total sample. 280 samples (31.2%) were procured from the public sector.
ACTs represented the largest share of samples collected. The ACTs included Artemether+Lumefantrine with 445 (49.6%), and Artesunate+Amodiaquine with 171 (19.1%). 119 samples of Sulfadoxine Pyrimethamine were procured, representing 13.3% percent of the total samples. 101 samples of Quinine were procured representing 11.3% while 61 samples of others representing 6.8% of the total sample were procured.

Procured samples were first tested for quality using the Minilab test kits. All samples that failed Minilab testing were subjected to confirmatory testing in the NAFDAC Zonal laboratories. Twenty five percent (25%) of all samples that passed Minilab testing were further subjected to confirmatory testing. The results of this quality monitoring revealed that 98.4% passed while 1.6% failed.

REPORTS FROM THE WHO PHARMACEUTICALS NEWSLETTER 2017 NO.1

Mefloquine

Risk of long-lasting and permanent neurological and psychiatric adverse events

Canada. Health Canada has recommended that the product information for mefloquine should be updated to explain the risk of vestibular damage more clearly. A checklist to assist health-care professionals in deciding whether to prescribe mefloquine to individual patients will be developed to prevent mefloquine from being prescribed to patients who are contraindicated (for example past or ongoing neurological or psychiatric conditions). Mefloquine is a prescription drug to prevent and treat malaria.

Health Canada reviewed the potential risk of rare long-lasting (lasting for 90 days or more) and permanent neurological and psychiatric adverse events with the use of mefloquine.

From 1993 to 30 September 2016, Health Canada has received 27 Canadian reports of adverse events that were potentially long-lasting. In addition, 37 international reports (from databases and published literature) of adverse events included five reports of permanent damage to the vestibular system.

The vast majority of the reports (61 out of 64) were deemed to have a possible link between the use of mefloquine and the long-lasting or permanent adverse events. However, insufficient information was available to conclude that mefloquine use was responsible for the adverse event(s) reported. The review also found that some patients were prescribed mefloquine even though the use was contraindicated because they had past or ongoing neurological or psychiatric conditions. The current product information for mefloquine describes the potential for long-lasting neurological and psychiatric adverse events that aligns with the review findings. However, the risk of rare permanent vestibular damage could be more clearly explained.

Reference:

Summary Safety Review, Health Canada, 1 June 2017 (www.hc-sc.gc.ca) (See WHO Pharmaceuticals Newsletters No.6, 2013: Strengthened warnings on neuropsychiatric side effects in the United Kingdom and No.5, 2013: Risk of serious psychiatric and nerve side effects in the US)

CODEINE AND TRAMADOL

Restriction of use in children and advice against use in breastfeeding women

USA. The US FDA has changed the labels of prescription medicines containing codeine and tramadol to inform of the restriction of use in children and recommend against the use of codeine and tramadol medicines in breastfeeding mothers due to risk of serious adverse reactions in breastfed infants. These adverse reactions include excess sleepiness, difficulty breastfeeding or serious breathing problems that could result in death.

Codeine and tramadol are approved to treat pain, and codeine is also approved to treat cough.

The FDA reviewed adverse event reports submitted to the FDA from January 1969 to May 2015 and identified 64 cases of serious breathing problems, including 24 deaths, with codeine-containing medicines in children younger than 18 years. Nine cases of serious breathing problems, including three deaths, with the use of tramadol in children younger than 18 years from January 1969 to March 2016 were also identified. The majority of serious adverse effects with both codeine and tramadol occurred in children younger than 12 years, and some cases occurred after a single dose of the medicine.

In a review of the medical literature the FDA found numerous cases of excess sleepiness and serious breathing problems in breastfed infants, including one death.

Reference:

Drug Safety Communication, US FDA, 20 April 2017 (www.fda.gov) *(See WHO Pharmaceuticals Newsletters No.2 and No.l, 2017, No.6 and No.l in 2016, No.6, No.5, No.4 and No3 in 2015, No.5 and No.4 in 2013, and No.5 in 2012 for related information)*

DIPEPTIDYLPEPTIDASE-4 (DPP-4) INHIBITORS

Risk of arthralgia

Canada. Health Canada has updated the product safety information for all dipeptidylpeptidase-4 (DPP-4) inhibitors to include information on the risk of arthralgia (severe joint pain).

DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin and sitagliptin) are used to treat type-2 diabetes in adults. They are used along with an appropriate diet and exercise to control blood sugar. In some cases, they are used with another anti-diabetic drug.

Health Canada reviewed the potential risk of arthralgia with the use of DPP-4 inhibitors following the identification of reports of adverse effects in the published literature and in the US FDA Adverse Event Reporting System (FAERS) database.

At the time of the review, Health Canada received 10 Canadian reports of severe joint pain and 20 international reports from the manufacturers associated with the use of a DPP-4 inhibitor (saxagliptin, sitagliptin or linagliptin).

Of all the reports, 17 noted that the patient developed joint pain within the first 30 days of taking the DPP-4 inhibitor. The majority of patients either improved or recovered from their joint pain after the treatment was stopped.

Some of the cases have also reported medical conditions that may have contributed to the joint pain including gout, pre-existing rheumatoid arthritis, Crohn's disease and obesity.

Health Canada's review of the available information concluded there is a potential link between the use of DPP-4 inhibitors and the development of severe joint pain.

Reference:

Summary Safety Review, Health Canada, 27 April 2017 (www.hc-sc.gc.ca) *(See WHO Pharmaceuticals Newsletters No.6, 2015: Risk of severe joint pain in Egypt and No.5, 2015: DPP-4 inhibitors for Type 2 diabetes may cause severe joint pain in the USA)*

LOPERAMIDE (HIGH DOSE)

Risk of serious cardiac adverse events

Malaysia. The National Pharmaceutical Regulatory Agency (NPRA) has updated the package inserts for all products containing loperamide with warnings and safety information related to the risk of serious cardiac adverse events with high doses.

Loperamide is an antidiarrhoeal medicine.

Between 2000 to December 2016, the NPRA has received 14 reports containing a total of 29 adverse events suspected to be related to loperamide use in Malaysia. More than half the adverse events (15 events, 52%) were related to skin disorders such as rash and pruritus. Other adverse events reported were anaphylaxis, shortness of breath, dizziness, dysaesthesia, face and mouth oedema, nausea, oculogyric crisriskis, stomatitis, and throat tightness. To date, the NPRA has not received any reports of

cardiac adverse events related to loperamide use.

A search of the WHO global database of Individual Case Safety Reports (ICSRs), VigiBase, identified 7431 individual case safety reports involving loperamide since year 1977. A total of 328 reports involved cardiac disorders such as ventricular tachycardia (60 reports), cardiac arrest (50), and torsades de pointes (46).

The NPRA has issued advice to health-care professionals, alerting them on potential risks of cardiac events, susceptible individuals, drug interactions, and management of suspected cardiotoxicity with loperamide use.

Reference:

Reaksi Drug Safety News, NPRA, No. 35, July 2017

(See WHO Pharmaceuticals Newsletter No.4, 2016: Serious heart problems with high doses in the US)