

**TANZANIA FOOD AND DRUGS AUTHORITY**



***COHORT EVENT MONITORING OF  
DIHYDROARTEMISININ +  
PIPERAQUINE: IMPLEMENTATION  
MANUAL***

**January 2011**

## Contents

Abbreviations .....	3
Acknowledgements .....	4
Foreword.....	4
1. Introduction.....	6
2. Objectives.....	7
2.1 Broad Objective.....	7
2.2 Specific Objectives .....	7
3. CEM Design .....	7
4. Cohort Size.....	7
5. Administrative structure.....	7
5.1 Pharmacovigilance Technical Committee (PVTC) .....	7
5.2 CEM Coordinating/implementing Team (CEM CT/IT) .....	8
5.3 Implementers at site level.....	8
6. CEM Sites .....	9
7. Training of CEM implementers at site levels .....	11
8. Data management .....	12
Database.....	12
8.3 Data entry .....	12
8.4 Quality control of data.....	12
8.5 Data analysis .....	13
9. Follow-up of patients.....	13
10. Tracking of registered patients .....	13
11. Reviewing the events .....	14
12. Communication.....	14
13. Information Education and Communication (IEC).....	14
13.1 Brochures.....	14
13.2 Summary of Product Characteristics (SmPC)/ or Patient Information Leaflet (PIL).....	14
14. Monitoring and Evaluation (M&E).....	15
15. Advocacy and sensitization .....	15
16. Report writing.....	15
17. Publication of results.....	16
18. Standard Operating Procedures .....	16
Appendix 1 .....	17
Pre-treatment Form (A) .....	17
CEM ID No.....	17
Appendix 2 .....	19
Post-treatment Form (B) .....	19
Appendix 3 .....	21
CEM Patient Identification Card.....	21
Appendix 4 .....	22
CEM Brochure (English Version).....	22
Appendix 5 .....	26
CEM Brochure (Swahili Version).....	26
Appendix 6 .....	32
PATIENT INFORMATION LEAFLET FOR DUO-COTECXIN (DHA+PPQ) .....	32
Appendix 7 .....	34
Site Monitoring Form.....	34
APPENDIX 8: SOP for distribution of forms, data collection on Cohort Event Monitoring (CEM) of DHA + PPQ .....	36
Appendix 9: SOP for data entry, cleaning and validation of cohort event monitoring of DHA + PPQ.....	38
Appendix 10: SOP for causality assessment/signal detection of cohort event monitoring data .....	40

## Abbreviations

<b>ADRs</b>	-	Adverse Drug Reactions
<b>AEs</b>	-	Adverse Events
<b>DHA+PPQ</b>	-	Dihydroartemisinin + Piperaquine
<b>BNF</b>	-	British National Formulary
<b>CEM</b>	-	Cohort Event Monitoring
<b>CEM CT/IT</b>	-	Cohort Event Monitoring Coordinating Team/Implementing Team
<b>PVTC</b>	-	Pharmacovigilance Technical Committee
<b>CTPVO</b>	-	Clinical Trials and Pharmacovigilance Officer
<b>DG</b>	-	Director General
<b>DMC</b>	-	Director – Medicines and Cosmetics
<b>HQ</b>	-	Headquarters
<b>ID card</b>	-	Identification card
<b>IEC</b>	-	Information Education and Communication
<b>MCTPV</b>	-	Manager – Clinical Trials and Pharmacovigilance
<b>MQM</b>	-	Manager – Quality Management
<b>M&amp;E</b>	-	Monitoring and Evaluation
<b>MoHSW</b>	-	Ministry of Health and Social Welfare
<b>NCR</b>	-	Non-Carbon Required
<b>NMCP</b>	-	National Malaria Control Programme
<b>PDR</b>	-	Physician Desk Reference
<b>PIL</b>	-	Patient Information Leaflet
<b>PV</b>	-	Pharmacovigilance
<b>FA</b>	-	Form A
<b>FB</b>	-	Form B
<b>SOP</b>	-	Standard Operating Procedure
<b>SmPC</b>	-	Summary of Product Characteristics
<b>TFDA</b>	-	Tanzania Food and Drugs Authority
<b>TNF</b>	-	Tanzania National Formulary
<b>UMC</b>	-	Uppsala Monitoring Centre
<b>WHO</b>	-	World Health Organization

## **Acknowledgements**

This Manual has been developed by Tanzania Food and Drugs Authority (TFDA) to enable effective and efficient implementation of Cohort Event Monitoring (CEM) of Dihydroartemisinin + Piperaquine (DHA+PPQ) at various levels. The draft manuscript was initially prepared by TFDA staff namely Mr. M.A. Fimbo, Mr. H. Irunde, Ms. A. Mssusa, Dr. A. Nkayamba, Mrs. G. Shimwela, Mr. D. Matiko, Ms. C. Luanda and Mr. S. Kisoma, Mr. N. Faustine from Ministry of Defence and National Services was also involved in the drafting team. Sincere thanks are therefore extended to them for drafting, critical reviewing and organization of the document.

Special gratitude is also due to TFDA Management for positive inputs and constructive criticism when revising and approving the final manuscript.

**Mitangu.A. Fimbo**  
**Acting Director – Medicines and Cosmetics**  
**Tanzania Food and Drugs Authority**

## **Foreword**

An adverse event is any untoward medical occurrence in a patient who has administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. Such events need to be monitored and reported either by pharmaceutical industries, patients, medical doctors, pharmacists, nurses or any other healthcare professionals. It is through reporting that regulatory authorities will be able to identify adverse drug reactions, detect signals, conduct analysis and devise mechanisms for prevention. This in practice results into improvement of public health and safety in relation to the use of medicines.

Taking this context into perspective, the Tanzania Food and Drugs Authority (TFDA) has decided to monitor all adverse events that occur as a result of using an anti-malarial agent namely Dihydroartemisinin + Piperaquine(DHA+PPQ) by employing an active surveillance approach technically known as Cohort Event Monitoring (CEM).

The programme intends to involve patients, medical doctors, pharmaceutical personnel and nurses working in health facilities (Hospitals and pharmacies located in Dar-es-Salaam, Mbeya, Tanga, Morogoro, Mwanza and Arusha. TFDA zonal offices and pharmacovigilance centres serving in these regions will also be involved. The regions/sites have been selected due to existing pharmacovigilance infrastructure, availability of

private health facilities, malaria epidemiology and possibility of attaining cohort size.

It is envisaged that the programme will contribute in the assessment of benefit, harm, effectiveness and risk of DHA+PPQ and thereafter encourage its safe, rational and more effective use. Education and clinical training in pharmacovigilance and its effective communication to health professionals and the public will also be promoted during implementation.

Experience gained from this programme will provide a framework for designing and implementing similar approaches to cover other types of medicines as well as incorporating other regions in future.

Comments, new ideas and inputs are invited to improve the Manual and make it more user-friendly for effective implementation of the programme.

**Hiiti B. Sillo**  
**Acting Director General**  
**Tanzania Food and Drugs Authority**

## 1. Introduction

Tanzania Food and Drugs Authority (TFDA) is the regulatory body under the Ministry of Health and Social Welfare (MoHSW) which was established under the Tanzania Food, Drugs and Cosmetics Act, No.1, 2003. Section 5(c) of the Act, provides for monitoring and reporting of existing and new adverse events including adverse drug reactions (ADRs) associated with the use of medicinal products in Tanzania.

The Authority has been using the spontaneous (voluntary) system of monitoring adverse events since 1993. The system involves the use of yellow forms which are printed and distributed in health facilities across the country to capture information on adverse events occurring to patients when using medicines.

The spontaneous system alone has proven to be inadequate in monitoring medicines safety therefore the Authority has decided to introduce another system to complement the existing one. This new system essentially involves active surveillance of adverse events using Cohort Event Monitoring (CEM) approach. CEM is a prospective observation of adverse events that occur during the use of medicines of public health importance in the early post-marketing phase. It ensures that patients are monitored from the time they begin treatment.

This manual outlines implementation strategy for active surveillance of adverse events associated with the use of Dihydroartemisinin + Piperaquine (DHA+PPQ) in selected private health facilities in Tanzania by TFDA in collaboration with other stakeholders. DHA+PPQ has been chosen because is registered by TFDA and widely used by the private health facilities for the treatment of acute, uncomplicated *Plasmodium falciparum* malaria and its safety in large scale use has not been fully assessed.

The manual highlights surveillance objectives, sites selected for implementation, training methods that will be adopted and methods of data collection. Other details include advocacy and sensitization techniques, communication channels and publication mechanisms that will be used.

The manual necessitates active involvement of medical/clinical officers, pharmacists, pharmaceutical technicians, Pharmaceutical assistants, nurses and designated pharmacovigilance focal persons in the selected sentinel sites. Their participation in the surveillance is highly encouraged as it will enable immediate detection, understanding, assessment and prevention of adverse events due to the use of DHA+PPQ in the country. These stakeholders together with others who have been delineated in the manual are therefore requested to read this manual to ensure its effective and successful implementation. The surveillance will begin in January, 2011 and enrollment will be completed once a cohort of 10,000 has been attained.

## **2. Objectives**

### **2.1 Broad Objective**

To improve public health by monitoring adverse events associated with DHA+PPQ when used for treatment of malaria in Tanzania using Cohort Event Monitoring (CEM) technique.

### **2.2 Specific Objectives**

To estimate the incidence rates of adverse events associated with DHA+PPQ among users

To characterize the known adverse reactions of DHA+PPQ

To identify and detect signals of unexpected, unrecognized reactions associated with DHA+PPQ

To detect drug interactions between DHA+PPQ and other medicines - conventional medicines or complementary and alternative medicines

To detect interactions of DHA+PPQ with concomitant diseases

To determine safety of DHA+PPQ in these concomitant diseases

To identify risk factors for adverse events associated with DHA+PPQ

To assess the safety of DHA+PPQ in pregnancy, lactation, children and elderly

To detect rate of inefficacy of DHA+PPQ and the possible causes for inefficacy.

To provide cohorts for further study of safety issues if required in the future

## **3. CEM Design**

CEM is a prospective, cohort observation and investigation of adverse events due to the use of DHA+PPQ.

## **4. Cohort Size**

CEM will cover a cohort of 10,000 patients treated with DHA+PPQ of which 9000 will be enrolled from private pharmacies and 1000 from private hospitals.

## **5. Administrative structure**

### **5.1 Pharmacovigilance Technical Committee (PVTC)**

The PVTC is composed of the following members:

- a. Mr. George Mlavwasi
- b. Dr. John Pemba
- c. Dr. Aziza Mwisongo
- d. Dr. Omari Minzi
- e. Dr. Venance Maro
- f. Director of Medicines and Cosmetics (DMC)

The roles and responsibilities of the PVTC will be:

- i. To oversee the implementation of CEM
- ii. To provide inputs and advice on CEM
- iii. To enhance collaboration amongst stakeholders in CEM
- iv. To solicit additional funding for CEM
- v. To review progress of CEM implementation

The Committee will meet three times. One meeting before the program commences, one during progression and one at the end of the program.

## **5.2 CEM Coordinating/implementing Team (CEM CT/IT)**

The CEM coordinating/implementing team will be composed of the following members:

- a. Director – Medicines and Cosmetics (1)
- b. Manager – Clinical Trials and Pharmacovigilance (PV)(1)
- c. Clinical Trials and Pharmacovigilance Officers (2)
- d. Manager – Technical Support and Research(1)
- e. Manager – Lake Zone (1)
- f. Manager-Northern Zone (1)
- g. Manager-Eastern Zone(1)
- h. Manager-Southern Highlands(1)
- i. Drug registration officers (2)
- j. Community pharmacists (2)
- k. Drug Inspectors (2)
- l. Laboratory analysts(2)
- m. Representative from NMCP (1)

The roles and responsibilities of the CEM CT/IT will be:

- a. To ensure that implementers at site level follow CEM protocol
- b. To provide inputs and advice on CEM design and conduct
- c. To ensure quality control and quality assurance of all CEM activities
- d. To ensure that data collection tools are available at CEM sites
- e. To train implementers at site level on CEM activities
- f. To ensure that communication between implementers is facilitated
- g. To conduct sensitization and advocacy on CEM
- h. To visit CEM sites as defined in the relevant SOPs
- i. To analyze data and prepare reports
- j. To monitor and provide overall supervision of CEM
- k. To organize CEM Technical committee meetings

## **5.3 Implementers at site level**

### **5.3.1 Medical and/or clinical officers at hospitals**

Medical and/or clinical officers will be responsible for:

- a. Diagnosis and treatment of malaria patients with DHA+PPQ
- b. Filling up of forms
- c. Follow up patients
- d. Conduct initial assessment of events

- e. Medical care of patients who have experienced adverse events
- f. Submit completed forms to pharmacist or pharmacovigilance focal person or designated personnel, zone offices, PV centers or TFDA headquarters, where applicable
- g. Encouraging patients to report adverse events
- h. Sensitizing healthcare providers to report adverse events through clinical review meetings or any other gatherings

### **5.3.2 Pharmaceutical personnel or any other designated personnel or Pharmacovigilance Focal Person at hospitals or community pharmacies**

Pharmaceutical personnel or pharmacovigilance focal person or any other designated personnel for handling medicines will be responsible for:

- a. Dispensing medicines including DHA+PPQ
- b. Filling up of forms
- c. Follow up patient appointments including defaulters
- d. Conduct initial review of the form to see if the data is adequate
- e. Submit completed forms to zone offices, PV centers or TFDA headquarters, where applicable
- i. Encouraging patients to report adverse events
- j. Sensitizing healthcare providers to report adverse events through clinical review meetings or any other gatherings

## **6. CEM Sites**

Based on the inclusion and exclusion criteria provided in the protocol, CEM of DHA+PPQ will be implemented at the following sites:

### **6.1. Dar-es-Salaam**

- 1) Agakhan Hospital
- 2) TMJ Hospital
- 3) Regency Medical Centre
- 4) Ibrahim Hajj Hospital
- 5) Hindu Mandal Hospital
- 6) Furaha Pharmacy
- 7) Mtongani Pharmacy
- 8) Mbagala Pharmacy
- 9) Shama Pharmacy
- 10) Shine Care Pharmacy
- 11) Supreme Pharmacy
- 12) Well care Services
- 13) Kakapela Pharmacy
- 14) Ferry Pharmacy
- 15) Kijichi Pharmacy
- 16) Amazon Pharmacy (Mwenge)
- 17) Butiama Pharmacy (Mwenge)
- 18) Nakiete Pharmacy
- 19) Damaco Day & Night Pharmacy
- 20) E.R Pharmacy
- 21) Faru Pharmacy

- 22) Faberk Pharmacy
- 23) F.G Pharmacy
- 24) J.D Pharmacy mlimani city
- 25) Mchito Pharmacy tegeta
- 26) Lifecare pharmacy
- 27) Madukani Pharmacy
- 28) Engen all night pharmacy mbezi beach
- 29) New Magomeni pharmacy
- 30) Morocco Pharmacy
- 31) Palestina pharmacy
- 32) Shekilango Pharmacy
- 33) Sirajudini Pharmacy
- 34) Wendy Pharmaceuticals Company Pharmacy
- 35) Tip top pharmacy
- 36) Kawe Pharmacy
- 37) Temboni Pharmacy
- 38) Kimara Pharmacy
- 39) MGR Hope Pharmacy
- 40) Platinum Pharmacy
- 41) Premier care pharmacy
- 42) Oysterbay pharmacy
- 43) Arafa Pharmacy (Segerea branch)
- 44) Amazon Pharmacy Co.ltd (mkunguni branch)
- 45) Bakamba Pharmacy
- 46) Bachu Pharmacy
- 47) C.N Pharmacy
- 48) Coast Pharmacy
- 49) Family Care Clinic & Pharmacy
- 50) Flamingo Pharmacy
- 51) Greenlanes Pharmacy
- 52) Henrik's Pharmacy
- 53) JD Pharmacy (Azikiwe Samora)
- 54) Janis Medical store
- 55) Kabora 2000 Pharmacy
- 56) Kiomboi Kisiriri
- 57) Mwanacoco Pharmacy
- 58) The Pharmacy
- 59) Shamshu Pharma ltd
- 60) Lifeline Pharmacy
- 61) U care Pharmacy

## **6.2 Mbeya**

- 1) Uyole Hospital
- 2) Maranatha Pharmacy
- 3) Babito Pharmacy
- 4) Bhojani Chemist
- 5) Kissa Pharmacy
- 6) Mina Pharmacy

## **6.3 Arusha**

- 1) Arusha Lutheran Medical Centre

- 2) Acacia Pharmacy
- 3) Arusha Pharmacy
- 4) Burka Pharmacy
- 5) Hakimia Pharmacy
- 6) Mak medics ltd (arusha branch)
- 7) Mbauda Pharmacy
- 8) MMT Pharmaceuticals Pharmacy
- 9) Moonas Arusha branch Pharmacy
- 10) Quality Pharmacy
- 11) Suji Investments Pharmacy

#### **6.4 Mwanza**

- 1) Mwanza women clinic
- 2) Atlas pharmacy
- 3) CF Medipharma Pharmacy
- 4) Ebenezer Pharmacy
- 5) FDS Pharmacy
- 6) Galaxy Pharmacy
- 7) Global Pharmacy
- 8) Kayonza Pharmacy
- 9) New Bugando Pharmacy
- 10) Makalwes Pharmacy
- 11) Msua Chemist

#### **6.5 Tanga**

- 1) Tumaini Health Centre
- 2) FK Pharmacy
- 3) Mwafrika Pharmacy
- 4) MD Pharmacy
- 5) International Pharmacy
- 6) MD Pharmacy branch
- 7) Alzahar Pharmacy

#### **6.6 Morogoro**

- 1) Shalom Hospital
- 2) Pole Pharmacy
- 3) Uluguru day and Night
- 4) Marhaba pharmacy
- 5) Holyland Pharmacy
- 6) Msafiri Pharmaceuticals

### **7. Training of CEM implementers at site levels**

All those who will be involved in CEM will be trained. Training will be organized by the CEM CT/IT and will focus on orienting implementers on the CEM manual. The following modules will also be included:

- a. An overview of TFDA structure, functions and activities
- b. Basic principles of pharmacovigilance
- c. Passive and active pharmacovigilance methods

- d. Cohort event monitoring (CEM)
- e. Data processing and management including data security
- f. Ethical aspects

The training methodology will include power-point presentations, group discussions, case studies and practical work. Pre and post training evaluation will also be conducted at the end of each training session.

## **8. Data management**

### **8.1 The department of Clinical Trials and Pharmacovigilance will be responsible for management of all data. The responsibilities will include:**

- a. Sorting of data
- b. Data entry
- c. Data entry checks
- d. Statistical treatment of data
- e. Training of data processors
- f. Ensure data security and confidentiality
- g. Quality assurance of data including validation and cleaning

### **Database**

The *CEMFlow* database developed by WHO - Uppsala Monitoring Centre (UMC) will be used for CEM. This will be installed in computers at TFDA headquarters.

### **8.2 Data collection and Enrollment of patients**

Pre-treatment form A (FA) (**Appendix 1**) and post-treatment form B (FB) (**Appendix 2**), will be used to collect data. These will be printed in duplicate copies and in pads using non-carbon required (NCR) papers.

Medical/clinical officers, pharmacists and other designated personnel will be trained on filling in the forms.

Every patient dispensed with DHA+PPQ should be included in the cohort where CEM is undertaken and should have FA completed (and FB at follow-up).

### **8.3 Data entry**

Data entry will be done at TFDA headquarters by data processors. These will be recruited to enter data on temporary basis. Data will be transferred from the completed forms to the database (i.e. *CEMFlow*).

### **8.4 Quality control of data**

Quality control of data will be done at facility level, TFDA zone offices, and TFDA headquarters. Pharmacovigilance focal persons or pharmacist in charge and zonal managers will check for completeness of forms at facilities and TFDA zone offices.

Systematic data checks at TFDA will be done by the CTPV Department on regular basis. Data processors will check for errors and accuracy during data entry.

### **8.5 Data analysis**

Data analysis will be done using CEMFlow. Training on how to undertake and evaluate the analyses available in CEMFlow will be undertaken.

## **9. Follow-up of patients**

Follow-up will be done on day 10 from the first day of treatment at site, when form B will be completed. The FA form number will be noted on the FB form for the patients coming for the follow up visit. In case the patient does not come for follow up visit he/she will be contacted either through phone (land phone/cell phone) or home visit and form B (FB) will be completed.

The timeline of follow-up of defaulters will be no later than 7 days after the missed follow-up appointment.

For patients participating in CEM at Hospitals and returning to the site for follow up, all efforts will be made to ensure post-treatment evaluation by the same medical/clinical officer, who diagnosed malaria and prescribed DHA+PPQ for treatment and made the pre-treatment assessment. The patients will be educated to report such events to the medical/clinical officer at the site.

For treatment failures, drug samples will be collected, analyzed and reported to confirm efficacy. Sampling will be done in sites where medicines had been supplied.

All deaths will be actively followed up and recorded where deaths have occurred.

At follow up 'lack of efficacy' and 'reasons for lack of efficacy' will be recorded. "Recrudescence" occurs as an event within 28 days after the start of treatment with DHA+PPQ.

## **10. Tracking of registered patients**

It is likely that a patient entered in cohort may not return for follow up or may be treated on more than one occasion, and he/she may not always go to the same site for diagnosis and treatment. Since patient details will be maintained at study sites only, a potential problem for duplication may arise, when a registered patient seeks health care elsewhere. The purpose of CEM is to monitor patients and while protection of patient privacy is important, it is important to ensure that denominator data of the CEM cohort is not confounded with duplication of patients. This is more important, if registered patient/s return with a second or third bout of malaria.

The patient name will be linked with the patient CEM ID number (**Appendix 3**) at the site for retrieval of the appropriate forms, when the registered patient presents for follow-up. Each site will establish and maintain a tracking system.

## **11. Reviewing the events**

This means deciding the correct event terms to be entered in the database and doing a relationship assessment for each event. The review process will be done at TFDA Headquarters.

## **12. Communication**

Communication will involve TFDA, medical/clinical officers, pharmacists, nurses and pharmacovigilance focal persons. Others would embrace zone offices, PV centers, NMCP and WHO HQ & UMC. This will be done through regular phone calls, internet, fax, mails or any other possible means.

The Manager – Clinical Trials and Pharmacovigilance will be the focal person for communications. However, all communications will be addressed to the Director General – TFDA.

Parties involved should be proactive in communicating and share the experience or any problems related to CEM implementation. Among issues which would need to be communicated actively include:

- a. Shortage of forms at facilities (ideally, should not be less than 10 at all times for each type of form)
- b. Low recruitment rate
- c. Problems in follow-up of patients
- d. Problems in distribution of forms
- e. Problems in filling in and collection of forms
- f. Problems in sending of forms to TFDA
- g. Any other related issues

## **13. Information Education and Communication (IEC)**

### **13.1 Brochures**

The English and Swahili versions of CEM brochures (**Appendix 4** and **5** respectively) will be designed and printed on continuous basis to sensitize stakeholders and make them aware of CEM and the procedure they should follow to report adverse events.

### **13.2 Summary of Product Characteristics (SmPC)/ or Patient Information Leaflet (PIL)**

The Summary of Product Characteristics (SmPC)/PIL of Dihydroartemisinin + Piperaquine attached as **Appendix 6** will be used together with other reference materials when conducting clinical review of collated events.

## **14. Monitoring and Evaluation (M&E)**

Monitoring of CEM implementation at site level will be done using form attached as **Appendix 7** to this manual. The form will be signed by monitors and submitted to the CTPV Department together with a report. The CTPV Department will then discuss the report and take appropriate action where applicable and thereafter notify the PVTC.

Initial evaluation will be done by TFDA after one month of CEM implementation and final evaluation will be done after the study has been completed.

## **15. Advocacy and sensitization**

Advocacy and sensitization will be organized by the CEM CT/IT. This will involve distribution of CEM brochures, media, informative discussions, presentations in clinical review meetings in hospitals as well as stakeholders meetings.

Two stakeholders meetings will be conducted in each region at the beginning of the implementation and after completion of the programme.

## **16. Report writing**

The final study report will be prepared by TFDA. The report will contain the following details:

Title of study

Titles, names, qualifications and roles of all people involved in conducting the study

Acknowledgements

Executive summary

Introduction

Rationale of the study

Objectives of the study

Methodology

- Study design
- Identity of the site(s) at which the study was conducted
- Materials and methods used in the study
- Key study dates?
- Patient selection and identification
- Details of study participants
- Where applicable, details of any concomitant treatment administered during the study, either prior to, during or after treatment with the study drug and details of any interactions observed
- Details of the study drug including strength, dosage form, route and frequency of administration
- Duration of treatment and observation periods
- Statistical methods used

Results

- Full description of the results of the study, including tables of

all data recorded

Discussion

- Interpretation of results including details of AEs occurring during the study and causality assessment

Conclusions

Recommendations

References

Appendices

## **17. Publication of results**

Publication of results will be organized by the CEM CT/IT. The team will prepare a manuscript depending on the requirements of a designated journal identified for publication. The proposed journals include “*Drug Safety*”, “*British Journal of Clinical Pharmacology*”, “*The Lancet*”, “*British Medical Journal*”, “*New England Journal of Medicine*”, “*WHO Drug Bulletin*”, “*East African Medical Journal*”, “*TFDA Drug Bulletin*” etc.

## **18. Standard Operating Procedures**

The following SOPs will be used for effective implementation of CEM.

- a. SOP for form distribution and data collection
- b. SOP for data entry, cleaning and validation
- c. SOP for causality assessment/signal detection

Details of these SOPs to include purpose, scope, responsible personnel, distribution list and stepwise procedures are attached as **Appendices 8, 9 and 10** to this manual.

**COHORT EVENT MONITORING (CEM) OF DIHYDROARTEMISININ (DHA) + PIPERAQUINE (PPQ)**

**Pre-treatment Form (A)**

CEM ID No.

**Health facility/Pharmacy:** .....

**1. Patient details:**

First name..... Last name .....

Patient File number (if available).....

Date of birth: .... / .... / .... Age: .....years; for children <1 year:.....months

Gender: Male  Female  Weight (kg): .....Height (cm): .....

Address: .....

Patient Cell Phone number (for follow-up purposes).....

Name and phone number of nearest contact person for patient follow-up: .....

Pregnant?: No  Uncertain  Yes  If yes specify: 1st  2nd  3rd  trimester

Is the patient breast feeding an infant? Yes , No

**2. Symptoms and signs at presentation:**

.....

.....

**3. Malaria Laboratory tests results (Blank row is for any additional test)**

Test	Date	Result (Pos or Neg)	Test	Date	Result
Microscopy	.... / .... / ....		Hb/Ht	.... / .... / ....	
Rapid diagnostic test	.... / .... / ....				

**4. All medical events which began in the last 10 days (other than malaria)**

Events

**5. Other current or important past medical conditions**

Conditions (tick if present or past)	Present	Past

**6. Medicines prescribed/dispensed at this visit**

Name (Record DHA+ PPQ first, using brand name )	Batch No.	Indication	Dose/Route & frequency	Date started	Expected completion
		Malaria		.... / .... / ....	.... / .... / ....
				.... / .... / ....	.... / .... / ....
				.... / .... / ....	.... / .... / ....
				.... / .... / ....	.... / .... / ....

**7. Date of planned follow-up visit to health facility:** .... / .... / ....

**8. Reporter (Medical/clinical officer, pharmaceutical personnel, nurse)**

(Please circle as appropriate):

Name.....Signature:..... Date.... / ,.... / ..... Mobile phone number .....

**CEM focal person:** Name..... Mobile ..... Signature..... Date.... / ... / .....

**9. Reporter (Medical/clinical officer, pharmaceutical personnel, nurse) (Please circle as appropriate):**

Name.....Signature:..... .Date... / ... / .....

Mobile phone number .....

**CEM focal person:** Name.....Signature:.....Date.... / ... / .....

Mobile phone number .....

**PLEASE SEND THIS FORM TO:** Tanzania Food and Drugs Authority, P.O. Box 77150, Dar-es-Salaam, Tanzania, Tel +255 22 2450715 & +255 22 2450512, Fax: +255 22 2450793

**This report should be sent immediately if the outcome of the adverse event is: death, life-threatening, caused or prolonged hospitalization.** Completion of this form is not an admission of causation by, or contribution to, the adverse event by the medicine(s) or by the reporting professionals. This information will be analyzed and will contribute to the safe use of antimalarials.



**COHORT EVENT MONITORING (CEM) OF DIHYDROARTEMISININ (DHA)+PIPERAQUINE (PPQ)**
**Post-treatment Form (B)**

 CEM ID No. 
**Health facility/Pharmacy:**.....

**1. Patient details:**

First name..... Last name.....

Patient File number (if available).....

**2. Type of follow-up**

- Lost to follow-up   
 Telephone interview  Date .... / .... / ....  
 Attendance at health centre/Pharmacy  Date .... / .... / ....  
 Visit at home  Date .... / .... / ....  
 Other (specify) ..... Date .... / .... / ....

Follow-up visit at home by:

Name.....Signature:.....

**3. All medicines taken at any time during DHA+PPQ treatment (days 0-3)**

Name (Record DHA+PPQ first, using brand name)	Batch No.	Indication	Dose/Route & frequency	Date started	Date stopped**
		Malaria		... / ... / ...	... / ... / ...
				... / ... / ...	... / ... / ...
				... / ... / ...	... / ... / ...
				... / ... / ...	... / ... / ...

\*\*Please enter 'C' in this column if the medicine is continuing

 Traditional medicines taken during DHA+PPQ treatment? No  Yes 

If yes please specify .....

**4. Outcomes noted at post-treatment visit**

 Treatment adherence  Complete  Incomplete

**Reason for incomplete adherence** .....

 Clinical condition: Improved  Deterioration  No change 

 Referral to health centre/hospital Yes  No 

Reason for referral: .....

**5. Describe new events or worsening problems after starting DHA+PPQ treatment**

Description of event	Severity		Date event started	Date event stopped**	Outcome <sup>a</sup> (A,B,C etc)
	Mild	Severe			
1.			... / ... / ...	... / ... / ...	
2.			... / ... / ...	... / ... / ...	
3.			... / ... / ...	... / ... / ...	

\*\*Please enter 'C' in this column if the event is continuing

Outcome: A resolved B resolving C resolved with sequelae D not resolved E death F unknown

**If a woman was breast feeding**, were there any abnormalities in the infant? Yes  ; No 

Describe any abnormality:.....

**6. Abnormal laboratory tests results after starting DHA+PPQ treatment**

Test	Date	Result	Test	Date	Result
	... / ... / ...			... / ... / ...	

**7. Reporter (Medical/clinical officer, pharmaceutical personnel, nurse) (Please circle as appropriate):**

Name.....Signature:.....Date... / ... / .....

Mobile phone number .....

**CEM focal person:** Name.....Signature:.....Date... / ... / .....

Mobile phone number .....


**PLEASE SEND THIS FORM TO:** Tanzania Food and Drugs Authority, P.O. Box 77150, Dar-es-Salaam, Tanzania, Tel +255 22 2450715 & +255 22 2450512, Fax: +255 22 2450793

***This report should be sent immediately if the outcome of the adverse event is: death, life-threatening, caused or prolonged hospitalization.*** Completion of this form is not an admission of causation by, or contribution to, the adverse event by the medicine(s) or by the reporting professionals. This information will be analyzed and will contribute to the safe use of antimalarials.

Appendix 3

**CEM Patient Identification Card**

Front of the card;

<p style="text-align: center;"><b>Patient Identification Card</b> <i>Cohort Event Monitoring of Dihydroartemisinin (DHA) + Piperaquine (PPQ)</i></p> <p style="text-align: center;"> <small>Tanzania Food &amp; Drugs Authority</small></p>
<p><b>Name and address of Hospital/Pharmacy:</b>.....</p> <p><b>CEM ID No.</b>.....</p> <p><b>Name of patient:</b>.....</p> <p><b>Name/address and phone number of health professional.</b>.....</p>
<p style="text-align: center;"><b>Please bring this card during every visit to this hospital</b> <b>Tafadhali njoo na kadi hii kila unapokuja hospitali</b></p>

Back of the card;

<p style="text-align: center;"><b>Patient Identification Card</b> <i>Cohort Event Monitoring of Dihydroartemisinin (DHA) + Piperaquine (PPQ)</i></p>
<p><b>Date of next appointment:</b> ..... <i>(Tarehe ya kurudi)</i></p>
<p><i>This patient is participating in a programme for monitoring the safety of antimalarial medicine DHA +PPQ. In case she/he is attending a facility different from the previous facility please contact the Health facility indicated in this card or TFDA for any medical events which have occurred.</i></p> <p><i>Mgonjwa huyu anashiriki katika mpango wa ufuatiliaji wa usalama wa dawa ya kutibu malaria ya DHA +PPQ. Endapo atatibiwa katika kituo tofauti na kilichotajwa tafadhali toa taarifa ya matukio ya kiafya ambayo yametokea kwenda katika kituo cha afya kilichotajwa kwenye kadi hii au Mamlaka ya Chakula na Dawa (TFDA).</i></p> <p><i>In case of emergency contact Director of Medicines and Cosmetics at TFDA Tel: +255-22-2450512/2450751/ 2452108 Fax: +255-22-2450793, Email: info@tfda.or.tz</i></p>

**TANZANIA FOOD AND DRUGS AUTHORITY**



**Cohort Event Monitoring of  
Dihydroartemisinin +  
Piperaquine(DHA+PPQ)**

## **Introduction**

Tanzania Food and Drugs Authority (TFDA) is a regulatory body under the Ministry of Health and Social Welfare which is responsible for protecting and promoting public health by ensuring quality and safety of food, drugs, cosmetics and medical devices.

One of the core functions of TFDA is to monitor adverse drug events (ADEs). The science and activities relating to the detection, assessment, understanding and prevention of ADEs or any other drug related problem is known as pharmacovigilance. Pharmacovigilance aims at getting the best outcome of treatment with medicines/drugs. It identifies the risks and risk factors associated with drugs in the shortest possible time after marketing.

When communicated effectively, information on adverse events gathered allows for evidence based prescribing with potential for preventing many adverse reactions and ultimately helps each patient to receive optimum therapy at a lower cost to the health system.

## **What is Cohort Event Monitoring (CEM)?**

Cohort Event Monitoring (CEM) is a prospective, observational study of adverse events that occur during the use of medicines in the early post-marketing phase. It ensures that patients are monitored from the time they begin treatment. It also involves patients in watching, feeling and monitoring their treatments.

## **Objectives of CEM**

- Provide incidence rates for adverse drug events as a measure of risk
- Characterize known adverse reactions
- Detect signals of unrecognized reactions
- Detect interactions with other medicines, complementary and alternative medicines, foods and concomitant diseases
- Identify risk factors and thus provide evidence for effective risk management
- Assess safety in pregnancy and lactation
- Provide a measure of comparative risks between medicines
- Detect drug inefficacy, which might be due to: faulty administration, poor storage conditions, poor quality product, counterfeiting and drug interactions
- Provide cohorts for further study of safety issues if required in the future

## **Cohort Event Monitoring (CEM) of Dihydroartemisinin + Piperaquine(DHA+PPQ)**

TFDA is in the process of conducting CEM of an anti-malarial drug namely Dihydroartemisinin + Piperaquine(DHA+PPQ). CEM will involve documentation of safety of DHA+PPQ which is registered by TFDA and widely used in private health facilities for treatment of uncomplicated acute falciparum malaria in Tanzania. DHA+PPQ is known to be effective, but further assessment of its safety under large-scale operational needs to be fully assessed.

### **Why reporting adverse events due to DHA+PPQ?**

It is important that adverse events due to DHA+PPQ are reported in order to:-

- To detect problems related to the use of DHA+PPQ and communicate the findings in a timely manner
- Contribute to the assessment of benefit, harm, effectiveness and risk of DHA+PPQ, leading to the prevention of harm and maximization of benefit
- Improve public health, patient care and safety in relation to the use of DHA+PPQ
- Encourage the safe, rational and more effective (including cost-effective) use of DHA+PPQ
- To promote understanding, education and clinical practice in pharmacovigilance and its effective communication to the public

### **What to report?**

Any untoward medical occurrence in a patient who has administered DHA+PPQ and which does not necessarily have a causal relationship with DHA+PPQ. It can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with DHA+PPQ, whether or not related to the medicine.

The information should be communicated by filling in special Forms prepared by TFDA. The following should be included in the report:-

- Patient details,
- Patient medical history of significance,
- Details of medicines
- Reaction details
- Reporter details
- Date of report

## **Who should report?**

Medical/Clinical officers  
Pharmacists  
Pharmaceutical technicians/assistants  
Pharmacovigilance focal persons  
Nurses  
Patients

## **How to report?**

Patients should report events to medical/clinical officers, pharmacists and nurses to the hospitals, health centers and dispensaries where they were treated.

Medical/clinical officers and nurses should observe and ask for events from patients and report them to pharmacists and pharmacovigilance focal persons by filling in forms immediately.

Pharmacists and pharmacovigilance focal persons should send forms to TFDA zone offices, pharmacovigilance centers at referral hospitals and/or TFDA headquarters, where applicable

## **When to report?**

The events should be reported soon after the adverse event has occurred.

## **Where to report?**

Patients should report events to

Medical/Clinical officers  
Pharmacists  
Pharmaceutical technicians/assistants  
Nurses

Medical/clinical officers, pharmaceutical personnel and nurses should send completed forms to:

TFDA headquarters  
TFDA zone offices  
Zone pharmacovigilance centres  
Pharmacovigilance focal persons

**Prepared by**

Tanzania Food and Drugs Authority (TFDA)  
P. O. Box 77150, EPI Mabibo  
Off Mandela Road  
Dar es Salaam  
Tel: +255-22-2450512/2450751/ 2452108  
Fax: +255-22-2450793,  
Email: [info@tfda.or.tz](mailto:info@tfda.or.tz),  
Website: [www.tfda.or.tz](http://www.tfda.or.tz)

<b>Lake Zone</b>	<b>Northern Zone</b>	<b>Southern Highlands Zone</b>
<b>P. O. Box 543</b>	<b>P. O. Box 16609</b>	<b>P. O. Box 6171</b>
<b>Mwanza</b>	<b>Arusha</b>	<b>Mbeya</b>

**Appendix 5**

**CEM Brochure (Swahili Version)**

**MAMLAKA YA CHAKULA NA DAWA**



**UFUATILIAJI WA KARIBU WA USALAMA  
WA DAWA MSETO YA KUTIBU MALARIA  
AINA YA  
Dihydroartemisinin +  
Piperaquine(DHA+PPQ)**

## **Utangulizi**

Mamlaka ya Chakula na Dawa (TFDA) ni taasisi iliyo chini ya Wizara ya Afya na Ustawi wa Jamii yenye jukumu la kulinda afya za wananchi dhidi ya madhara yanayoweza kujitokeza kutokana na matumizi ya vyakula, dawa, vipodozi na vifaa tiba.

Moja kati ya kazi za msingi za Mamlaka ni kuratibu na kufuatilia madhara yatokanayo na matumizi ya dawa. Sayansi ya ufuatiliaji wa usalama wa dawa (ambayo kitaalamu inajulikana kama ‘pharmacovigilance’) inajumuisha utambuzi, tathmini, uelewa na udhibiti wa madhara yatokanayo na matumizi ya dawa. Sayansi hii inalenga katika kuhakikisha kuwa matibabu yaliyosahihi yanatolewa kwa wagonjwa na inawezesha kufahamu madhara pamoja na sababu zinazosababisha madhara ndani ya siku chache baada ya dawa kuwa kwenye soko.

Upatikanaji wa taarifa za madhara ya dawa kwa haraka kunawezesha utoaji mzuri wa dawa ikiwa ni pamoja na udhibiti wa madhara na kusaidia wagonjwa kupata dawa zilizo salama na hivyo kupunguza gharama kwenye mfumo wa utoaji huduma za afya.

### **Ufuatiliaji wa Usalama wa Dawa kwa karibu (CEM) maana yake nini?**

Ufuatiliaji wa madhara ya dawa kwa karibu (yaani Cohort Event Monitoring - CEM) unajumuisha uangalizi wa madhara ya dawa wakati dawa inatumiwa na mgonjwa mara baada ya kuidhinishwa kwa matumizi ya binadamu. Mfumo huu unahakikisha mgonjwa anafuatiliwa kwa karibu mara tu aanzapo kutumia dawa. Unahusisha wagonjwa pia katika kutambua na kufahamu matibabu wanayopata na hivyo kung’amua madhara yanayoweza kutokea wakati wa matumizi ya dawa.

### **Malengo ya CEM**

- Kuainisha idadi na kasi ya kujitokeza kwa madhara ya dawa kwa watumiaji kama kipimo cha usalama wa dawa
- Kufahamu kwa undani madhara ya dawa yanayotambulika
- Kugundua madhara mapya ya dawa yasiyofahamika
- Kubaini madhara yanayoweza kutokea endapo aina mbalimbali za dawa na vyakula zitatumika kwa wakati mmoja
- Kutambua sababu zinazoweza kusababisha madhara ya dawa na hivyo kuwezesha udhibiti wa madhara kwa ufanisi
- Kutathmini usalama wa dawa kwa wanawake wajawazito na wanaonyonyesha
- Kulinganisha viwango vya usalama wa dawa mbalimbali

Kugundua dawa isiyo na ufanisi wa kitabibu ambao unaweza kusababishwa na matumizi yasiyo sahihi, mazingira yasiyo bora ya uhifadhi, viwango hafifu vya ubora na dawa bandia Kuandaa mazingira mazuri ya ufuatiliaji wa usalama wa dawa katika siku zijazo

### **Ufuatiliaji wa usalama wa dawa ya kutibu malaria ya Dihydroartemisinin + Piperaquine (DHA+PPQ)**

TFDA inafanya ufuatiliaji wa karibu wa usalama (CEM) wa dawa mseto ya kutibu malaria aina ya Dihydroartemisinin + Piperaquine(DHA+PPQ). CEM itajumuisha ukusanyaji wa taarifa za usalama wa DHA+PPQ inayotumika kama dawa ya safu ya kwanza kwa matibabu ya malaria isiyo kali nchini Tanzania. Ingawa DHA+PPQ ni dawa yenye ufanisi, bado inahitaji kuhakikiwa zaidi ili kufahamu kwa undani usalama wa matumizi yake kwa watu walio wengi.

### **Kwa nini taarifa za madhara ya DHA+PPQ zinahitajika?**

Ni muhimu kukusanya taarifa za madhara ya DHA+PPQ kwa sababu zifuatazo:

Kugundua matatizo yanayohusiana na matumizi ya DHA+PPQ na kutoa taarifa kwa wakati

Kuchangia katika kutathmini faida, madhara, ufanisi na usalama wa DHA+PPQ na hivyo kupelekea kudhibiti madhara na kuongeza faida

Kuboresha afya ya jamii, huduma kwa wagonjwa, na usalama wa dawa ya DHA+PPQ inapotumika

Kuhamasisha matumizi sahihi ya DHA+PPQ

Kuelimisha na kuhamasisha umma juu ya umuhimu wa utoaji wa taarifa za madhara yatokanayo na matumizi ya dawa ya DHA+PPQ

### **Taarifa zipi zitolewe?**

Taarifa za madhara yoyote ya kiafya yatakayojitokeza kwa mgonjwa wakati wa matumizi ya DHA+PPQ hata kama hayana uhusiano wa moja kwa moja na DHA+PPQ. Yanaweza kuwa madhara yasiyotarajiwa (ikiwa ni pamoja na vipimo vya maabara visivyo vya kawaida), dalili au ugonjwa unaohusiana au kutohusiana na DHA+PPQ.

Taarifa hizi zitolewe kwa kujaza fomu/madodoso maalum yaliyoandaliwa na TFDA. Pamoja na mambo mengine, mtoa taarifa atatakiwa kuainisha yafuatayo kwenye madodoso husika:

Taarifa za utambuzi wa mgonjwa  
Taarifa muhimu za nyuma za mgonjwa  
Taarifa za dawa  
Taarifa za madhara ya dawa  
Mtoaji taarifa  
Tarehe ya kutoa taarifa

### **Nani atoe taarifa?**

Waganga na waganga wasaidizi  
Wafamasia  
Waratibu wa madhara ya dawa  
Wauguzi  
Wagonjwa

### **Jinsi ya kutoa taarifa**

Wagonjwa watoe taarifa za madhara ya DHA+PPQ kwa waganga/waganga wasaidizi, wafamasia na wauguzi katika hospitali, vituo vya afya na zahanati walipopata matibabu  
Waganga/waganga wasaidizi na wauguzi wachunguze na kuwauliza wagonjwa juu ya madhara na watoe taarifa kwa wafamasia au waratibu wa madhara ya dawa kwa kujaza madodoso husika mara moja.  
Wafamasia au waratibu wa madhara ya dawa watume madodoso yaliyojazwa na kukamilika kwenye ofisi za Mamlaka za kanda, vituo vinavyoratibu madhara ya dawa vilivyoko kwenye Hospitali za Rufaa na/au makao makuu ya Mamlaka.

### **Taarifa zitolewe wakati gani?**

Taarifa zitolewe mara tu madhara ya DHA+PPQ yanapohisiwa kutokea na madodoso yajazwe kikamilifu na kutumwa kunakohusika.

### **Taarifa zitolewe wapi?**

Wagonjwa watoe taarifa kwa wafuatao:

Waganga/waganga wasaidizi  
Wafamasia  
Fundu sanifu wa dawa na fundu sanifu wasaidizi  
Wauguzi

Waganga/waganga wasaidizi, wafamasia na wauguzi wajaze madodoso na kuyatuma:

TFDA makao makuu  
TFDA ofisi za kanda  
Vituo vya madhara ya dawa vilivyoko kwenye kanda  
Waratibu wa madhara ya dawa

**Imetolewa na:**

Mamlaka ya Chakula na Dawa (TFDA)  
S. L. P 77150, EPI Mabibo  
Barabara ya Mandela  
Dar es Salaam  
Simu: +255-22-2450512/2450751/ 2452108  
Nukushi: +255-22-2450793,  
Barua pepe: [info@tfda.or.tz](mailto:info@tfda.or.tz)  
Tovuti: [www.tfda.or.tz](http://www.tfda.or.tz)

**Kanda ya Ziwa**  
**S. L. P 543**  
**Mwanza**

**Kanda ya Kaskazini**  
**S. L. P 16609**  
**Arusha**

**Kanda ya Nyanda za Juu Kusini**  
**S. L. P 6171**  
**Mbeya**

## Appendix 6

### PATIENT INFORMATION LEAFLET FOR DUO-COTECXIN (DHA+PPQ)

#### DUO-COTECXIN

Antimalarial

#### PRESENTATION

Each tablet contains 40mg of dihydroartemisinin (DHA) and 320mg of piperazine Phosphate (PQP).

One box contains a blister with 8 blue film-coated tablets.

#### PHARMACOLOGY

DUO-COTECXIN<sup>®</sup> is a synergistic combination of an artemisinin derivative and a new bisquinoline compound; it is active against the asexual forms of plasmodium, schizonts and gametocytes. Its action on schizonts insures a rapid decrease of pathogenic parasitaemia which leads to a quick disappearance of clinical signs; its action on gametocytes prevents contamination.

The absorption of DUO-COTECXIN<sup>®</sup> after oral intake is rapid and complete; it is extensively distributed in all tissues. Half life of DHA is very short (around 2 hours) whereas PPQ is long (around 9 days).

#### INDICATIONS

DUO-COTECXIN<sup>®</sup> is indicated for the treatment of all kinds of malaria, as long as patients can take oral medications. It is particularly recommended in the case of multi-resistant plasmodium falciparum malaria.

#### ADMINISTRATION AND DOSAGE

Oral administration.

Patients should follow their doctor's instruction. The recommended dosage is in the following table:

<b>Years</b>	<b>16 ≤ Age</b>	<b>11 ≤ Age &lt;16</b>	<b>6 ≤ Age &lt;11</b>
<b>Day</b>			
1 <sup>st</sup>	3 tabs.	2 tabs.	1.5 tabs.
2 <sup>nd</sup>	3 tabs.	2 tabs.	1.5 tabs.
3 <sup>rd</sup>	2 tabs.	2 tabs.	1 tab.

<b>Total</b>	<b>8 tabs.</b>	<b>6 tabs.</b>	<b>4 tabs.</b>
--------------	----------------	----------------	----------------

### **ADVERSE EFFECTS**

Few cases of adverse effects have been reported after administration of DUO-COTECXIN®. Most of them are related to PQP affecting the digestive tract (nausea, diarrhea, loss of appetite, etc.). Rare allergic reactions have also been reported (rash, pruritus, etc.).

### **CONTRAINDICATIONS**

As all new drugs, DUO-COTECXIN® is not recommended during the first trimester of pregnancy unless your doctor considers the risk of the disease to be greater.

A new course of DUO-COTECXIN® should not be taken within four weeks after the first treatment.

### **STORAGE**

Keep all medicines out of the reach of children.

Preserve in tight and lightproof containers.

Store in a cool and dry place below 30°C.

### **SHELF LIFE**

2 years.

Manufactured by Zhejiang Holley Nanhu Pharmaceutical Co., Ltd.

205, Yunhai Road, Economy Development Zone, Jiaxing City, P.R. China

Under License from **Holleypharm**

## Site Monitoring Form

## TANZANIA FOOD AND DRUGS AUTHORITY




<b>SITE MONITORING FORM</b>		
Title of Programme	Cohort Event Monitoring of Dihydroartemisinin + Piperavaquine(DHA+PPQ)	Remarks
Name and address of site		
Date of monitoring		
Name of medical/clinical officer		
Name of pharmacist/ pharmacovigilance focal person		
Monitoring visit number		
Name of Monitor(s)		
Signature of Monitor(s)		
Number of forms distributed to the site:		
Number of forms available at the site:		
Number of forms filled in:		
Number of forms sent to TFDA:		
Number of patients followed-up:		

Number of CEM brochures available at the site:		
Number of clinical review meetings conducted including CEM as agenda item:		
Number of trained staff and actively engaged in CEM:		
Number of staff not trained but engaged in CEM		
Are storage conditions adequate?		
Number of available doses of DHA+PPQ		
Are the forms correctly and adequately completed?		
Are there any losses to follow up? If yes how many?		
Are there any ruined forms?		
General observations:		

## APPENDIX 8

### SOP for distribution of forms, data collection on Cohort Event Monitoring (CEM)of DHA + PPQ

 Tanzania Food & Drugs Authority	<b>Title: SOP for distribution of forms, data collection on Cohort Event Monitoring (CEM)of DHA + PPQ</b>			<b>Revision #: 0</b>	<b>Page: 36 of 2</b> <b>Validity: 2 Years</b>
<b>SOP#:</b> TFDA/DMC/CEM/S OP/007	<b>Prepared by</b> CEM CT/IT Sign.....	<b>Checked by</b> MQM Sign.....	<b>Authorized by</b> DMC Sign.....	<b>Effective Date:</b> 17 January 2011	<b>Review Date:</b> 16 January 2013

#### 1. Purpose

To provide guidance for distribution of forms and collection of cohort event monitoring (CEM) data.

#### 2. Scope

The SOP is applicable for use at TFDA headquarters, TFDA zone offices, PV Centres and CEM sites.

#### 3. Responsibility

The MCTPV is responsible for the maintenance of this SOP.

#### 4. Accountability

Director – Medicines and Cosmetics

#### 5. Distribution List

- 5.1 Director – Medicines and Cosmetics
- 5.2 Manager – Clinical Trials and Pharmacovigilance
- 5.3 Clinical Trials and Pharmacovigilance Officers
- 5.4 Manager – Technical Support and Research
- 5.5 Manager – Lake Zone
- 5.6 Manager – Northern Zone
- 5.7 Manager – Southern highlands Zone
- 5.8 Manager – Eastern Zone
- 5.9 Health facilities personnel at CEM sites
- 5.10 PV focal persons

#### 6. Procedure

##### TFDA - CTPV DEPARTMENT

- 6.1 Print forms based on CEM site requirements.
- 6.2 Send forms physically to sites located in Dar-es-Salaam.
- 6.3 For sites outside Dar-es-Salaam, send forms by post or other appropriate means to TFDA zone offices.

- 6.4 Record the quantity and serial numbers of forms distributed.
- 6.5 Confirm if Zone Managers have received the forms through phone calls, email or any other effective means

### **TFDA Zone Managers**

- 6.6 Receive forms
- 6.7 Acknowledge receipt
- 6.8 Record the quantity and serial numbers of forms received
- 6.9 Distribute forms to the sites physically
- 6.10 Record the serial numbers of the forms distributed

### **Health facilities/Pharmacy personnel**

- 6.11 Receive forms
- 6.12 Fill in the forms
- 6.13 Return completed forms to PV focal person
- 6.14 Record the serial numbers of the forms returned


### **PV focal persons**

- 6.15 Receive forms from TFDA
- 6.16 Acknowledge receipt to TFDA
- 6.17 Record the serial numbers of forms received from TFDA
- 6.18 Distribute forms to health facilities/Pharmacy personnel
- 6.19 Record the quantity and serial number of forms distributed to the facility
- 6.20 Receive completed forms from the health facilities/Pharmacy personnel
- 6.21 Record the serial numbers of completed forms received in the CEM log book
- 6.22 Completed forms FA +FB in a pair of 25 paged booklets should be packed in a sealed packet and send them by courier to TFDA headquarters.
- 6.23 Serious cases should be reported by phone, email, fax or any other appropriate means to TFDA within one working day
- 6.24 Record the serial numbers and amount of forms sent

## **7. General considerations**

- 7.1 Health facilities /Pharmacy personnel should ensure that forms are fully completed without missing any field
- 7.2 PV focal persons should double check data accuracy and completion
- 7.3 In case of missing data, PV focal persons should consult Health facilities /Pharmacy personnel for completion of forms
- 7.4 Forms should be stored in a secured place

**Appendix 9: SOP for data entry, cleaning and validation of cohort event monitoring of DHA + PPQ**

	<b>Title: SOP for data entry, cleaning and validation of cohort event monitoring of DHA + PPQ</b>			Revision #: 0	<b>Page: 38 of 42</b> <b>Validity: 2 Years</b>
	<b>SOP#:</b> <b>TFDA/DMC/CEM/S OP/008</b>	<b>Prepared by</b> <b>CEM CT/IT</b> <b>Sign.....</b>	<b>Checked by</b> <b>MQM</b> <b>Sign.....</b>	<b>Authorized by</b> <b>DMC</b> <b>Sign.....</b>	<b>Effective Date:</b> <b>1 7January</b> <b>2011</b>

**1. Purpose**

To provide guidance for entry, cleaning and validation of cohort event monitoring (CEM) data.

**2. Scope**

The SOP is applicable for use at TFDA headquarters.

**3. Responsibility**

The MCTPV is responsible for the maintenance of this SOP.

**4. Accountability**

Director – Medicines and Cosmetics

**5. Distribution List**

- 5.11 Director – Medicines and Cosmetics
- 5.12 Manager – Clinical Trials and Pharmacovigilance
- 5.13 Clinical Trials and Pharmacovigilance Officers
- 5.14 Data Processors

**6. Procedure**

**CTPV Officers**

- 6.1 Receive and sort forms
- 6.2 Check for completeness
- 6.3 Return incomplete forms to the MCTPV
- 6.4 Transfer data from the completed forms into the CEM database
- 6.5 Check for accuracy of data entered

**MCTPV**

- 7.5 Conduct data coding
- 7.6 Clean and validate data
- 7.7 Close database
- 7.8 Analyze data by using agreed statistical package
- 7.9 Provide statistical interpretation of data

7.10 Write report and submit to Director General (TFDA)

**7. General considerations**

7.1 The MCTPV is responsible for the overall management of the database.

7.2 The MCTPV should train and supervise the CTPV Officers and other data processors.


**Appendices**

None

---

**END**

**Appendix 10: SOP for causality assessment/signal detection of cohort event monitoring data**

	<b>Title: SOP for causality assessment/signal detection of cohort event monitoring data</b>			Revision #: 0	Page: 40 of 3
					Validity: 2 Years
<b>SOP#:</b> <b>TFDA/DMC/CEM/S OP/009</b>	<b>Prepared by</b> <b>CEM CT/IT</b> <b>Sign.....</b>	<b>Checked by</b> <b>MQM</b> <b>Sign.....</b>	<b>Authorized by</b> <b>DMC</b> <b>Sign.....</b>	<b>Effective Date:</b> <b>17 January 2011</b>	<b>Review Date:</b> <b>16 January 2013</b>

**1. Purpose**

To provide guidance for assessment of adverse events and detection of signals.

**2. Scope**

The SOP is applicable for use at TFDA headquarters.

**3. Responsibility**

The MCTPV is responsible for the maintenance of this SOP.

**4. Accountability**

Director – Medicines and Cosmetics

**5. Distribution List**

- 5.1 Director – Medicines and Cosmetics
- 5.2 Manager – Clinical Trials and Pharmacovigilance
- 5.3 Clinical Trials and Pharmacovigilance Officers

**6. Procedure**

**6.1 Causality assessment (CTPV Officer)**

- 6.1.1 Assess whether the event began before using DHA + PPQ
- 6.1.2 Assess any other possible causes of the event
- 6.1.3 Assess if the duration to the onset of the event is plausible
- 6.1.4 Assess whether the event began after using other medicines
- 6.1.5 Assess whether the event occurred after the onset of some new illnesses
- 6.1.6 Assess the response to withdrawal of DHA + PPQ (dechallenge)
- 6.1.7 Assess the response to rechallenge with DHA + PPQ
- 6.1.8 Rate events as whether it is certain, probable, possible or unclear as provided in **Appendix 1.**

**6.2 Signal detection (MCTPV)**

- 6.2.1 Conduct clinical assessment of individual events
- 6.2.2 Conduct clinical review of collated events
- 6.2.3 Link records

**7. General considerations**

- 7.1 The following reference materials and sources should be used when conducting clinical review of events:

- 7.1.1 Martindale
- 7.1.2 DHA + PPQ summary of product characteristics (SmPC)
- 7.1.3 British National Formulary (BNF)
- 7.1.4 Tanzania National Formulary (TNF)
- 7.1.5 PubMed/Medline
- 7.1.6 Physician Desk Reference (PDR)
- 7.1.7 WHO database
- 7.1.8 TFDA local database
- 7.1.9 Micromedix online
- 7.1.10 Mims online

## **Appendix 1: Causality Ratings**

All reports received should be classified according to the likelihood that the reactions were caused by the drugs being taken. Four broad classifications should be employed:

1. Certain
2. Probable
3. Possible
4. Causality unclear – Reports listed as “causality unclear” should not be entered into the database

### **1. Certain**

- a. A reaction in association with a single drug which was confirmed by re-challenge
- b. A reaction in association with a single drug which is confirmed by laboratory data specifically implicating that drug
- c. A reaction onset is immediately following drug administration (within 5 minutes if injection was the method of administration and during infusion)
- d. A reaction which has precise spatial correlation with administration (e.g. at the exact site of skin patch or injection, vaccine site reaction, injection site abscess and eye application)

### **2. Probable**

- a. Temporal or spatial (e.g. skin) correlation with the administration of a single drug.
- b. A reaction in reasonable temporal association with a single drug and recovery on withdrawal of the drug if no other drug is withdrawn and no therapy given.
- c. An uncommon clinical phenomenon associated with the administration of a single drug and the reasonable exclusion of other factors.

### **3. Possible**

- a. possible alternative exists; and/or
- b. more than one drug is suspected; and/or
- c. data are incomplete; and/or
- d. recovery follows withdrawal of more than one drug; and/or
- e. time relationship is not clear; and/or
- f. the reaction has not recovered , or the outcome of the reaction is not recorded; and/or
- g. recovery follows therapy/treatment in addition to withdrawal of the drug

### **4. Unclear (General List)**

- a. Where a clinical event may well be explained as arising from factors related to underlying disease or other non-drug aetiology.
- b. Where there is no reasonable temporal association between the use of a drug and the clinical event.
- c. Where a reaction occurs at a dose not normally used.
- d. Where the report does not contain enough information for an adequate assessment.

---

**END**