

## Supplement 1

Operational plan for Pharmacovigilance Activities for Visceral  
Leishmaniasis - Bangladesh

Effective Date: 15/SEP/2014

# OPERATIONAL PLAN FOR PHARMACOVIGILANCE ACTIVITIES FOR VISCERAL LEISHMANIASIS IN BANGLADESH

Document Version	1.00			
Effective Date	15 SEPTEMBER 2014			
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## 1 ACRONYMS AND ABBREVIATIONS

ADRAC	Adverse Drug Reactions Advisory Committee
AE	Adverse Events
CDC	Centre of Disease Control
DGDA	Directorate General of Drug Administration
GoB	Government of Bangladesh
HCP	Health Care Professionals
ICH	International Conference on Harmonisation
LAMB	Liposomal amphotericin B
PDS	Pharmacoepidemiology and Drug Safety
PKDL	Post Kala-azar Dermal Leishmaniasis
PV	Pharmacovigilance
SAE	Serious Adverse Events
UHC	Upazilla Health Complex
VL	Visceral Leishmaniasis (VL);
WHO	World Health Organization
WHO-UMC	World Health Organization – Uppsala Monitoring Centre

## 2 BACKGROUND

The National Guideline on Kala-azar and PKDL case management in Bangladesh 2013 has been updated and enforced.<sup>1</sup>This operational plan recommends various regimens with the use of following drugs for treatment of Kala-azar:

- 1) Liposomal amphotericin B (LAMB)
- 2) Amphotericin B
- 3) Miltefosine
- 4) Paromomycin

All these drugs are used in Bangladesh for prescription to VL and or PKDL patients under the National VL Elimination program.

This operational plan also recommends that pharmacovigilance<sup>1</sup> data on the safety of above drugs and their regimen should be systematically collected from the various health facilities in the country. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems<sup>2</sup>.

Adverse effects due to drugs used for treatment of Kala-azar can significantly affect the quality of life and adherence to therapy.<sup>3</sup> An effective model of pharmacovigilance with particular focus to Kala-azar will ensure that the patients of this disease are able to accrue the maximum therapeutic benefit by early detection and prevention of adverse effects of these drugs. This will be possible by following a systematic system for surveillance, collection, detection, assessment and monitoring of adverse effects.

This document details the pharmacovigilance activities to be carried out by the health care professionals involved in the management of patients of Kala-azar as well as Post Kala-azar Dermal Leishmaniasis (PKDL). The pharmacovigilance program will act in harmony with the Kala-azar elimination national program to collect data regarding adverse drug reactions and

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<sup>1</sup> Pharmacovigilance isThe science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.

also assess and evaluate these reactions for causality and benefit-risk profile and, in future may provide the basis for risk mitigation plans. This activity will not only strengthen the capacity of the Kala Azar Elimination Program but also the National Pharmacovigilance Program of the Government of Bangladesh.

### **3 PURPOSE**

This Pharmacovigilance activity is designed to improve patient outcomes associated with the use of medicines for VL. The primary objective of this document is to define the procedures for pharmacovigilance of anti-leishmanial drugs used in Bangladesh for establishing the practical working methods for reporting adverse events (AE) by health care professionals (HCP).

### **4 SCOPE**

This operational plan applies to all Healthcare Professionals (HCP) engaged with diagnosis or treatment of Visceral Leishmaniasis (VL) and Post Kala azar Dermal Leishmaniasis (PKDL). It should also apply to those dispensing drugs used for treatment of these disease conditions; provide nursing care to such patients or other personnel directly involved in the collection and analysis of adverse drug reaction data for these drugs. This document should be used as an operational plan by the personnel listed above. All activities will be conducted in accordance with this plan and the national guidelines for treatment of VL/PKDL. The most recent approved version of this guidance document will take precedence over any other version.

### **5 Procedures**

All reports of adverse events following administration of a drug or drugs for treatment of Kala-azar will be collected and reported. Details of this procedure are as follows:

#### **5.1 Roles and Responsibilities**

##### **5.1.1 Healthcare Professional (HCP)**

All Healthcare Professionals (HCP) engaged with the following activities have a role to play in the AE reporting:

- Diagnosis or treatment of Visceral Leishmaniasis (VL) and Post Kala azar Dermal Leishmaniasis (PKDL), or
- Dispensing of drugs used for treatment of these disease conditions, or
- Providing nursing care to such patients, or
- Personnel directly involved in the collection and analysis of AE data for these drugs

#### 5.1.2 Focal Person at Kala-azar Treatment Centers:

- A Focal Person will be identified by Head of the treatment center at each centre. Their contact details will be made available to the Centre of Disease Control (CDC), GoB
- The identified focal persons will undergo a targeted training on the operational plan
- Focal person will be responsible for filling the AE form. The treating physician will sign the form in the end, before sending it to CDC.
- In case the focal person is the treating physician he/she will sign the AE form(s).

#### 5.1.3 Nursing Staff

- Nursing staff should promptly report to the doctor any suspected adverse drug reaction coming to their notice.

#### 5.1.4 Responsible Person at the CDC

- Provide list of the Upazilla Health Complex and name of the participants to be trained and who will be responsible for reporting from their respective UHCs
- Facilitate and support training of Medical Doctors, Nurses and reporting personnel from Upazilla Health Complex (UHC)
- Collect through e-mail/Fax/Courier/Web based system the Adverse Event Report prepared by Upazilla Health Complex (UHC)
- Verify for completeness of the form and get updates from UHC in need
- Approve the form for data entry and send it to DGDA and icddr,b
- Conduct the data entry and share it with icddr,b periodically.

- Select the members for Causality Assessment Committee and chair the committee.
- Support and facilitate the meeting of the Causality Assessment Committee and present the analyzed data to the committee

#### **5.1.5 icddr,b**

- Maintain liaison with PDS, CDC and DGDA and contribute to preparation of form and manual
- Obtain all required approval from competent authorities of icddr,b for this activity
- Support training of Medical Doctors, Nurses and reporting personnel from Upazilla Health Complex (UHC)
- Prepare database program for data entry following the indicators in the reporting form
- Provide human resource to support CDC for performing data entry and to support the VL surveillance team
- Arrange the meeting of the Causality Assessment Committee and present the analyzed data to the committee
- Share the report of the committee with CDC and DGDA

#### **5.1.6 DGDA**

- Support training of Medical Doctors, Nurses and reporting personnel from Upazilla Health Complex (UHC)
- Receive soft copy of the AE form from CDC
- Enter data in Vigiflow
- Present data to National Adverse Drug Reaction Committee
- Send recommendations from ADRAC to CDC-Kala Azar Elimination Program and DGDA for regulatory action

## 5.2 Information to be collected

All patients should be monitored regularly for signs and symptoms indicative of an AE. Any suspected AE in a patient undergoing treatment of Kala-azar or PKDL should be collected and recorded promptly. For timelines on reporting of the AEs to the CDC and Directorate General of Drug Administration (DGDA), the following should be kept in mind while reporting:

- Cases of death and life threatening events/incidents must be given highest priority and reported on an expedited basis
- Both known and unknown AEs should be reported.

## 5.3 Reporting Format and Procedures

The Adverse Drug Reaction Reporting form (AE Reporting Form, Appendix 1) must be filled for an individual patient. Separate such forms should be filled for different patients. Responsibilities for filling this form are as follows:

- Focal person will be responsible for filling the AE form.
- The doctor/treating physician will sign the form in the end, before sending it to CDC
- The narrative for every new AE should be written on an additional sheet of paper and appended to the AE reporting form
- Each AE form must have the following mandatory information:
  - An identifiable patient
  - A suspect medicinal product
  - An identifiable reporting source
  - At least one adverse drug reaction
- As much information about the patient's history and the AE should be captured for more effective analysis. Address for Sending the AE Report
- Filled and signed form should be sent as hard copy via web based, or by fax, or by soft copy as attachment via email data transfer to the CDC. The address to send is given below:



Send to: Ms. Fahima Yeasmin  
Address: CDC, DGHS, GoB,  
Mohakhali, Dhaka-1212  
Email ID: lira\_urp@yahoo.com  
Phone: +880-2- 8816412

Fax: +880-2-8813875

## **5.4 Timelines/Frequency of Reporting**

### **5.4.1 Fatal Cases**

- Fatal cases suspected as a result of AEs due to anti Kala-azar drug(s) should be reported within seven calendar days of knowledge of such event

### **5.4.2 Non-fatal AEs**

- All other AEs irrespective of seriousness or expectedness should be reported on a monthly basis. Following will apply for monthly reporting:
  - AE reporting forms should be sent by 15th of every month, and will contain data from first to last day of the previous month
  - If an AE report is received on 28th of a month, then the initial report will be sent to CDC within that month's reporting cycle. CDC physician will revert to the district /zonal centers on inadequate data in the form and if it is not enough to assess causality.

## **5.5 Analysis of the Reported Adverse Drug Reactions information**

The AE data collected at CDC will be shared with the Directorate general of Drug Administration, , Government of Bangladesh.

The following steps will be executed at the CDC by the responsible person after receipt of the AE information:

- An acknowledgement of the receipt will be sent back to the sender

- A unique identification number will be allotted to each patient. Receipt of any follow up information will be added under this unique number. The same patient will not be given a new number
- Data will be quality checked, medically evaluated and causality will be assessed according to the WHO-UMC causality assessment algorithm (Appendix 2)
- The data will be analyzed for signals/alerts

Based on the data analysis & processing, appropriate recommendations & risk mitigation plans will be generated & communicated to various stakeholders

#### **5.5.1 Expert committee**

An Expert Committee at the CDC will be formed to recommend actions based on the data analysis.

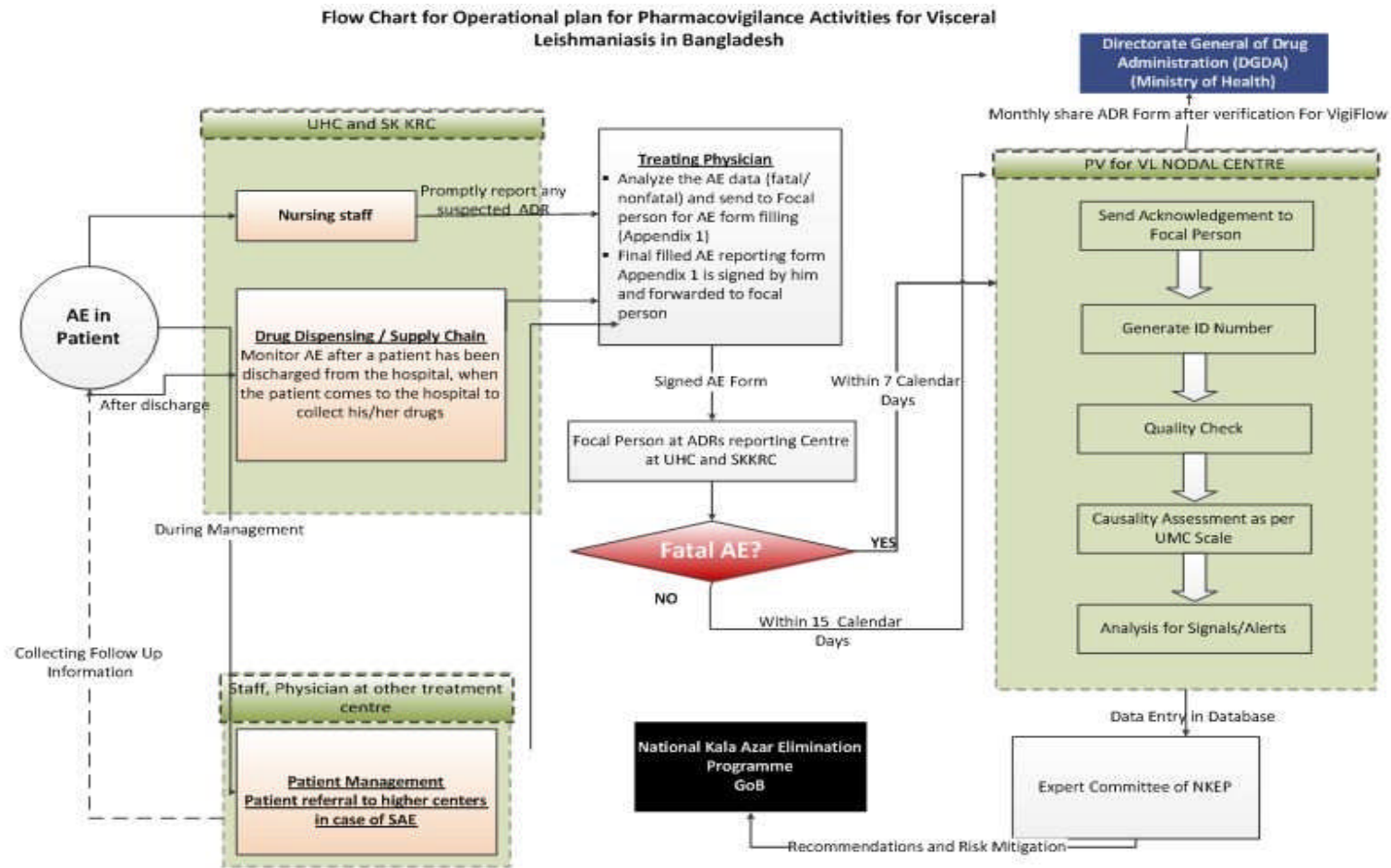
The Expert Committee will consist of the following members:

- CDC director: Chair
- Academia: Pharmacology/pharmacy – 2 persons as member
- One DGDA representative as member
- Two Senior physician (Kala-azar expert) as member
- One International PV Expert as member as on need basis

Role of the Expert Committee will be as follows:

- Review the data/information: half yearly, or as required
- Make recommendation to Kala-azar elimination program

6 Flowchart



## **Appendix 1: Adverse Drug Reaction Reporting Form**

### **Suspected Adverse Event reporting Form**

**Identities of reporter, patient, institution, and product trade name(s) will remain confidential**



# Suspected Adverse Drug Reaction or Adverse Event Reporting Form

Identities of reporter, patient, institution, and product trade name(s) will remain confidential



ADR report number \_\_\_\_\_

(For office use only)

Date received \_\_\_\_\_

A. PATIENT AND HOSPITAL INFORMATION	
Name of health facility: _____	
Patient name :	Registration no: _____
Patient address: District: _____	Upazila: _____
Union/ Moholla/Street no.: _____	Village/Holding no./Para: _____
Contact number: _____	
Age (Years) _____ Weight (kg) _____ Height(cm) _____	Gender <input type="radio"/> Male <input type="radio"/> Female
Pregnant : <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Unknown <input type="radio"/> Not applicable	
Don't enter Full name in excel sheet, Please enter initial	

B. HISTORY OF VL THERAPY					
Treatment received	<input type="radio"/> Combo Therapy		<input type="radio"/> Mono Therapy		
Drug received	<input type="checkbox"/> Liposomal Amphotericin B	<input type="checkbox"/> Miltefosine	<input type="checkbox"/> Paromomycin	<input type="checkbox"/> Non-Liposomal Amphotericin B	<input type="checkbox"/> Sodium Stibo Gluconate
Trade name	_____	_____	_____	_____	_____
Drug dose	_____	_____	_____	_____	_____
Drug start date*	_____	_____	_____	_____	_____
Drug start time**	_____	_____	_____	_____	_____
Drug stop date *	_____	_____	_____	_____	_____
Drug stop time**	_____	_____	_____	_____	_____

\*Date format: DD/MM/YYYY; \*\*Time format: HH:MM AM/PM

C. SUSPECTED ADVERSE EVENT INFORMATION		
<b>Type of event</b> <input type="checkbox"/> Adverse drug reaction <input type="checkbox"/> Product quality problem <input type="checkbox"/> Medication error <input type="checkbox"/> Other: _____	<b>Suspected product</b> Trade name _____ Generic name _____ Indication _____ Dose [strength, unit] _____ Dosage form _____ Frequency _____ Batch/Lot number _____ Manufacturer _____	
<b>Describe event including relevant tests and laboratory results:</b> _____ _____		
Date & Time the event started _____ (DD/MM/YYYY; HH:MM AM/PM)	Date & Time the event was reported _____ (DD/MM/YYYY; HH:MM AM/PM )	Date & Time the event stopped _____ (DD/MM/YYYY; HH:MM AM/PM)
<b>Was the adverse event treated?</b> <b>If yes, please specify</b>	<input type="radio"/> Yes <input type="radio"/> No	

<b>Action taken after the Adverse Drug Reaction or Adverse Event</b> <input type="radio"/> Dose stopped <input type="radio"/> Dose reduced <input type="radio"/> No action taken	<b>Did reaction subside after stopping/reducing the dose of the suspected Product?</b> <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not applicable  <b>Did reaction appear after reintroducing the suspected product?</b> <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Not applicable
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<b>Seriousness of the adverse event:</b> <input type="radio"/> Not serious <input type="radio"/> Hospitalization or prolongation of hospitalization <input type="radio"/> Disability or permanent damage <input type="radio"/> Congenital anomaly/birth defect <input type="radio"/> Life threatening <input type="radio"/> Other serious <input type="radio"/> Death	<b>Outcomes of the adverse event:</b> <input type="radio"/> Recovered <input type="radio"/> Recovered/resolved with sequela <input type="radio"/> Not recovered <input type="radio"/> Unknown <input type="radio"/> Fatal (date of death: _____)
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Other relevant history (including pre-existing medical conditions, allergies, pregnancy, smoking, alcohol use, liver or kidney problems, hypersensitivity, history of ADRs, etc.):

**D. OTHER CONCOMITANT PRODUCT INFORMATION**

	Product 1	Product 2	Product 3	Product 4
Trade name				
Generic name				
Indication				
Dosage form				
Route				
Dose				
Frequency				
Date started*				
Time started**				
Date stopped*				
Time stopped**				

\*Date format: DD/MM/YYYY; \*\* Time format: HH:MM AM/PM

**E. REPORTER INFORMATION**

Name \_\_\_\_\_ Designation \_\_\_\_\_

Email address \_\_\_\_\_

Mobile phone \_\_\_\_\_ Land phone \_\_\_\_\_

Signature \_\_\_\_\_ Date of submission \_\_\_\_\_

# List of Adverse Events

<b>General</b>
<input type="checkbox"/> Fever
<input type="checkbox"/> Chills
<input type="checkbox"/> Rigor
<input type="checkbox"/> Peripheral edema
<input type="checkbox"/> Asthenia
<input type="checkbox"/> Malaise
<input type="checkbox"/> Fatigue
<input type="checkbox"/> Lethargy
<input type="checkbox"/> Sweating
<input type="checkbox"/> Facial flushing
<input type="checkbox"/> Rash
<input type="checkbox"/> Vertigo
<b>Respiratory</b>
<input type="checkbox"/> Dyspnea
<input type="checkbox"/> Cough
<input type="checkbox"/> Lung disorder
<input type="checkbox"/> Pleural effusion
<input type="checkbox"/> Rhinitis
<input type="checkbox"/> Hypoxia
<input type="checkbox"/> Hyperventilation
<input type="checkbox"/> Asthma
<input type="checkbox"/> Atelectasis
<input type="checkbox"/> Hemoptysis
<input type="checkbox"/> Hiccup
<input type="checkbox"/> Flu-like symptom
<input type="checkbox"/> Lung edema
<input type="checkbox"/> Pharyngitis
<input type="checkbox"/> Pneumonia
<input type="checkbox"/> Respiratory insufficiency
<input type="checkbox"/> Sinusitis
<b>Cardio-vascular</b>
<input type="checkbox"/> Hypotension
<input type="checkbox"/> Tachycardia
<input type="checkbox"/> Hypertension
<input type="checkbox"/> Chest pain
<input type="checkbox"/> Phlebitis
<input type="checkbox"/> Arrhythmia
<input type="checkbox"/> Atrial fibrillation
<input type="checkbox"/> Bradycardia
<input type="checkbox"/> Cardiac arrest
<input type="checkbox"/> Cardiomegaly
<input type="checkbox"/> Hemorrhage
<input type="checkbox"/> Postural hypotension
<input type="checkbox"/> ECG abnormalities
<input type="checkbox"/> Venous pain
<input type="checkbox"/> Venous thrombosis

<b>Gastro-intestinal</b>
<input type="checkbox"/> Dyspepsia
<input type="checkbox"/> Hematemesis
<input type="checkbox"/> Anorexia
<input type="checkbox"/> Diarrhea
<input type="checkbox"/> Vomiting
<input type="checkbox"/> Abdominal pain
<input type="checkbox"/> Nausea
<input type="checkbox"/> Abdominal distention
<input type="checkbox"/> Constipation
<input type="checkbox"/> Dysphagia
<input type="checkbox"/> Flatulence
<input type="checkbox"/> Melena
<input type="checkbox"/> Peptic ulcer
<input type="checkbox"/> Dry mouth
<input type="checkbox"/> Epigastric pain
<b>Hepato-biliary</b>
<input type="checkbox"/> Jaundice
<input type="checkbox"/> Hyperbilirubinemia
<input type="checkbox"/> Hepatomegaly
<input type="checkbox"/> Veno-occlusive disorder
<input type="checkbox"/> Rise in hepatic enzymes
<input type="checkbox"/> Pancreatitis
<b>Renal</b>
<input type="checkbox"/> Nephrotoxicity
<input type="checkbox"/> Renal failure
<input type="checkbox"/> Serum creatinine elevation
<b>Genito-urinary</b>
<input type="checkbox"/> Hematuria
<input type="checkbox"/> Dysurea
<input type="checkbox"/> Urinary incontinence
<input type="checkbox"/> Vaginal hemorrhage
<input type="checkbox"/> Testicular pain
<input type="checkbox"/> Testicular swelling
<input type="checkbox"/> Scrotal pain
<input type="checkbox"/> Decreased ejaculate volume
<input type="checkbox"/> Absent ejaculation
<b>Nervous</b>
<input type="checkbox"/> Insomnia
<input type="checkbox"/> Confusion
<input type="checkbox"/> Peripheral neuropathy
<input type="checkbox"/> Motion sickness
<input type="checkbox"/> Headache
<input type="checkbox"/> Dizziness
<input type="checkbox"/> Somnolence
<input type="checkbox"/> Paresthesia
<input type="checkbox"/> Ototoxicity

<b>Hematologic</b>
<input type="checkbox"/> Anemia
<input type="checkbox"/> Leucopenia
<input type="checkbox"/> Thrombocytopenia
<input type="checkbox"/> Gum bleeding
<input type="checkbox"/> Bleeding from nose
<b>Musculo-skeletal</b>
<input type="checkbox"/> Back pain
<input type="checkbox"/> Bone pain
<input type="checkbox"/> Dystonia
<input type="checkbox"/> Myalgia
<input type="checkbox"/> Rhabdomyolysis
<input type="checkbox"/> Arthralgia
<input type="checkbox"/> Tetany
<input type="checkbox"/> Sub sternal pain
<b>Metabolic</b>
<input type="checkbox"/> Hypokalemia
<input type="checkbox"/> Hypomagnesemia
<input type="checkbox"/> Hyperglycemia
<input type="checkbox"/> Hypocalcemia
<input type="checkbox"/> Hypovolemia
<input type="checkbox"/> Hyponatremia
<input type="checkbox"/> Hypernatremia
<b>Dermatologic</b>
<input type="checkbox"/> Urticaria
<input type="checkbox"/> Pruritus
<input type="checkbox"/> Cellulitis
<input type="checkbox"/> Erythema
<input type="checkbox"/> Pyoderma
<input type="checkbox"/> Rash
<input type="checkbox"/> Urticaria
<input type="checkbox"/> Steven-johnson syndrome
<b>Immunological</b>
<input type="checkbox"/> Lymphangitis
<b>Local</b>
<input type="checkbox"/> Abscess
<input type="checkbox"/> Ear puritus
<input type="checkbox"/> Injection site swelling
<input type="checkbox"/> Injection site pain
<b>Ocular</b>
<input type="checkbox"/> Conjunctivitis
<input type="checkbox"/> Dry eye
<input type="checkbox"/> Hemorrhage

<b>Hypersensitivity</b>
<input type="checkbox"/> Allergic reaction
<b>Psychiatric</b>
<input type="checkbox"/> Anxiety
<input type="checkbox"/> Depression
<input type="checkbox"/> Hallucination
<input type="checkbox"/> Nervousness
<input type="checkbox"/> Abnormal thoughts
<b>Others</b>
<input type="checkbox"/> .....
<input type="checkbox"/> .....
<input type="checkbox"/> .....
<b>Death</b>
<b>Birth defect</b>

**Appendix 2. WHO-UMC causality assessment algorithm**

Causality term	Assessment criteria*
<b>Certain</b>	<ul style="list-style-type: none"> <li>• <b>Event or laboratory test abnormality, with plausible time relationship to drug intake</b></li> <li>• <b>Cannot be explained by disease or other drugs</b></li> <li>• <b>Response to withdrawal plausible (pharmacologically, pathologically)</b></li> <li>• <b>Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)</b></li> <li>• <b>Rechallenge satisfactory, if necessary</b></li> </ul>
<b>Probable/Likely</b>	<ul style="list-style-type: none"> <li>• <b>Event or laboratory test abnormality, with reasonable time relationship to drug intake</b></li> <li>• <b>Unlikely to be attributed to disease or other drugs</b></li> <li>• <b>Response to withdrawal clinically reasonable</b></li> <li>• <b>Re-challenge not required</b></li> </ul>
<b>Possible</b>	<ul style="list-style-type: none"> <li>• <b>Event or laboratory test abnormality, with reasonable time relationship to drug intake</b></li> <li>• <b>Could also be explained by disease or other drugs</b></li> <li>• <b>Information on drug withdrawal may be lacking or unclear</b></li> </ul>
<b>Unlikely</b>	<p><b>Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)</b></p> <ul style="list-style-type: none"> <li>• <b>Disease or other drugs provide plausible explanations</b></li> </ul>



<b>Conditional/ Unclassified</b>	<ul style="list-style-type: none"><li>• <b>Event or laboratory test abnormality</b></li><li>• <b>More data for proper assessment needed, or</b></li><li>• <b>Additional data under examination</b></li></ul>
<b>Unassessable/ Unclassifiable</b>	<ul style="list-style-type: none"><li>• <b>Report suggesting an adverse reaction</b></li><li>• <b>Cannot be judged because information is insufficient or contradictory</b></li><li>• <b>Data cannot be supplemented or verified</b></li></ul>

**\*All points should be reasonably complied with**

### **Appendix 3. Definitions**

#### **1. Pharmacovigilance** [*The World Health Organization (2002)*]

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems. Pharmacovigilance is sometimes referred to as Drug Safety surveillance or Drug monitoring

Following are broadly the function of pharmacovigilance:

- Detection and study of adverse reactions
- Measurement of risk
- Measurement of effectiveness
- Benefit & harm evaluation
- Dissemination of information, education
- Early warning
- Rational and safe use of medicines

#### **2. Health Care Professional (HCP) [ICH E2D]**

An HCP is a medically-qualified person such as a physician, dentist, pharmacist, nurse, coroner, or as otherwise specified by local regulations.

#### **3. Adverse Event (or Adverse Experience) [ICH E2A]**

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

#### **4. Adverse Drug Reaction (AE) [ICH E2A]**

Pre-approval:

All noxious and unintended responses to a medicinal product related to any dose.

-causal relationship cannot be ruled out.

Marketed products:

A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

### **5. Serious Adverse Event [ICH E2A]**

An Adverse Event which:

- Results in death, OR
- Is life-threatening\*, OR
- Requires inpatient hospitalization or prolongation of existing hospitalization, OR
- Results in persistent or significant disability/incapacity, OR
- Is a congenital anomaly/birth defect, OR
- Is medically significant

\*Life threatening: If the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death. *Does not include an adverse event that, had it occurred in a more severe form, might have caused death*

In-patient Hospitalization: *Any new in-patient hospitalization or prolongation of existing hospitalization.*

*If a patient comes in the emergency due to an adverse event, the event will be assessed as serious only if the patient gets in-patient hospitalized or the investigator feels it to be serious due to some other applicable seriousness criteria*

*Hospitalization (including hospitalization for an elective procedure) for a pre-existing condition (prior to study entry) which has not worsened does not constitute a serious adverse event.*

**Persistent or significant disability or incapacity:** *If the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.*

**Congenital anomaly or birth defect:** *If there is any congenital anomaly or birth defect in offspring of subjects or their partners taking the investigational medicinal product regardless of time of diagnosis.*

**Medically significant:** *Medical and scientific judgment should be exercised in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition earlier.*

*E.g. Allergic bronchospasm requiring intensive treatment at home, convulsions that do not result in inpatient hospitalization*

#### **6. Severity - of an Adverse Event [ICH E2A]**

The term severe is used to describe the intensity of a specific event. The terms serious and severe are not synonymous.

- An event can be severe but may not be serious (e.g. severe headache). Similarly an event can be serious but may not be severe (e.g. mild myocardial infarction)

#### **7. Unexpected Adverse Drug Reaction/Adverse Event**

An adverse event, the nature, severity, specificity or outcome of which is not consistent with the applicable product information\*

\*Prescribing Information /Pack Insert/ Summary of Product Characteristics

#### **8. Relatedness – of an Adverse Event**

AE/SAE may be related or unrelated to the drug. This is done by Causality assessment, which is defined as:

“The evaluation of the likelihood that a medicine is the causative agent of an observed adverse event”

#### **9. Signals/Alerts:**

Information that arises from one or multiple sources (including observations and experiments), that suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related

events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify further action to verify. (ICH)

## References

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<sup>1</sup> The National Kala Azar Elimination Guidelines for Bangladesh are under publication and final approval by the Department of Epidemiology and Disease Control, Government of Bangladesh.

<sup>2</sup> WHO PV Definition

<sup>3</sup> Cite publications which describe the known AEs of VL Drugs