



MINISTRY OF HEALTH
BRUNEI DARUSSALAM

BRUNEI DARUSSALAM PHARMACOVIGILANCE GUIDELINES:

PART 1 - GUIDELINE FOR HEALTHCARE
PROFESSIONALS

PART 2 - GUIDELINE FOR:

- LICENSED MANUFACTURERS
- LICENSED WHOLESALERS
- LICENSED IMPORTERS
- PRODUCT LICENCE HOLDERS

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PREFACE

This document is intended to provide guidance on the requirements and procedures for submission of adverse drug reaction (ADR) reports as well as submitting information regarding product safety to the Brunei Darussalam Medicines Control Authority (BDMCA). This guideline does not cover the entire scope of pharmacovigilance. It uses the World Health Organization definition of the term 'pharmacovigilance' as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems" (1).

Although we have tried to ensure that the information contained here is accurate, we do not, however, warrant its accuracy or completeness. The Brunei Darussalam Medicines Control Authority (BDMCA) accepts no liability for any errors or omissions in this document, or for any action / decision taken or not taken as a result of using this document.

ABBREVIATIONS

| | |
|---------|--|
| ADR | - Adverse Drug Reaction |
| BDMCA | - Brunei Darussalam Medicines Control Authority |
| CIOMS | - Council for International Organizations of Medical Sciences |
| DHCPL | - Dear Healthcare Professional Letter |
| DLP | - Data Lock Point |
| IBD | - International Birth Date |
| ICH | - International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| MoH | - Ministry of Health, Brunei Darussalam |
| NADRMCM | - National Adverse Drug Reaction Monitoring Centre, Department of Pharmaceutical Services, Ministry of Health, Brunei Darussalam |
| NCE | - New Chemical Entity |
| PBRER | - Periodic Benefit-Risk Evaluation Report |

INTRODUCTION

Objective

These guidelines provide healthcare professionals, licensed manufacturers, licensed wholesalers, licensed importers or product licence holders with guidance in reporting adverse drug reactions (ADRs) of medicinal products to the Brunei Darussalam Medicines Control Authority (BDMCA) *via* the National Adverse Drug Reaction Monitoring Centre (NADRM), Ministry of Health, Brunei Darussalam.

Background

The safety profile of a medicinal product before it has been given marketing authorization (i.e. registered in a country) by any **National Regulatory Authority** is limited to its use in clinical trials (2). The conditions under which patients are studied prior to marketing authorization approval do not necessarily reflect the way the product will be used in general practice once it is marketed, as circumstances during clinical trials are usually strictly defined and use of such products are controlled (2). No matter how extensive the pre-clinical work in animals and the clinical trials in patients, certain adverse effects may not be detected until a very large number of patients have received the said product (2).

Pharmacovigilance is the process of:

- monitoring medicinal products as used in everyday practice *to identify previously unrecognized adverse reactions or changes in the patterns of their adverse effects* (2);
- assessing *the risks and benefits* of medicinal products in order to determine what actions, if any, is necessary to improve their safe use (2); and
- providing information to users to *optimize the safe and effective use* of medicinal products (2).

Information from the activities of pharmacovigilance which includes spontaneous ADR reporting schemes, literature review, clinical and epidemiological studies are used to aid in decision-making (2). Information from all these sources can lead to changes such as restrictions in use, refinement of dosage instructions and strengthening of specific warnings that allow products to be used safely (2). Occasionally, when a risk is considered unacceptable, a product may have to be withdrawn from the market (2).

The primary objectives of ADR monitoring are as follows (2):

- To detect ADRs as early as possible especially if serious, unexpected or rare (2).
- To determine the incidence (rate of occurrence) of ADRs (2).

- To specify the incidence of well recognized ADRs (2).
- To identify the risk factors that may pre-dispose, induce or influence the development, severity and incidence of ADRs e.g. demographic, ethnic and genetic factors, drug interactions, underlying conditions, etc (2).
- To maintain a database for compiling, analysing and sharing information relative to the safety of the medicinal products used in Brunei Darussalam (2).

Scope

The *Brunei Darussalam Pharmacovigilance Guidelines* serve as tools for healthcare professionals, licensed manufacturers, licensed wholesalers, licensed importers or product licence holders in guiding them to fulfil their obligation of safety monitoring and adverse drug reaction reporting. The guidelines are divided into two parts:

- Part 1 - Guideline for healthcare professionals
- Part 2 - Guideline for licensed manufacturers, licensed wholesalers, licensed importers or product licence holders.

PART 1

GUIDELINE FOR HEALTHCARE PROFESSIONALS

1.0 GUIDELINE FOR HEALTHCARE PROFESSIONALS

The healthcare professionals in this guideline are defined as doctors, dentists, pharmacists, nurses, pharmacy technicians and other allied health professionals e.g. optometrists, podiatrists, physiotherapists, radiographers, dieticians, etc ⁽³⁾ that uses medicinal products in their practice. This guideline is to assist the healthcare professionals in reporting an adverse drug reaction (ADR) by clarifying the requirements ⁽²⁾. The purpose of soliciting ADRs is solely for monitoring the safety profile of products and for formulating regulatory actions to minimise risks to consumers ⁽²⁾.

1.1 Basic Principles When Reporting ADR

- i. Reporting of spontaneous ADR events (defined as a system whereby ADR reports are voluntarily submitted from healthcare professionals soon after it occurs) are usually within three days (72 hours) of the event ⁽²⁾.
- ii. It is preferable and encouraged to report an ADR whilst the patient is still easily accessible (e.g. if patient is still warded) to the reporter so that s/he can easily be questioned about the event and the details entered promptly in the '**Suspected ADR Reporting Form**' (Annex I) as completely if possible ⁽²⁾.
- iii. Enquire specifically whether the patient had also taken any other medicinal or healthcare products which may have contributed towards the event, e.g. other concomitant drugs, traditional medicines, health supplements ⁽²⁾.
- iv. A follow-up report should be submitted if any additional data becomes available later, e.g. if the same patient develops the effect again or if something happens which increases your suspicions or seems to exclude the effect ⁽²⁾.
- v. In cases where the patient who sustained the ADR is a foetus or breastfed infant, information on both the mother and the child/ foetus should be provided ⁽²⁾.
- vi. ADR reports of patients must be treated with utmost confidentiality ⁽²⁾.
- vii. All reports must have the following four minimum data elements ^(2, 4):
 - a) A suspected medicinal product ^(2, 4);
 - b) An adverse reaction ^(2, 4);
 - c) An identifiable patient ^(2, 4), and
 - d) An identifiable reporter ^(2, 4).

If any of these data elements (vii. a-d) remain unknown, a report on the incident **should not** be submitted because reports without such information make interpretation of their significance difficult, at best, and impossible in most instances ^(2, 4).

1.2 Confidentiality

All reports submitted to the National Adverse Drug Reaction Monitoring Centre (NADRMCM), Ministry of Health, Brunei Darussalam are treated confidentially (2).

1.3 ADR Reporting Mechanism

i. Every healthcare institution may decide the most appropriate facilitator within its organization; and it is recommended that the Pharmacy be given the role (2). The facilitator's responsibilities are as follows (2):

- To receive the filled ADR forms and ensure the completeness of the ADR form before submitting them to the NADRMCM (2).

Note: Healthcare institutions that **do not have a Pharmacy** can submit the filled ADR form directly to the NADRMCM (2).

- ii. The reporter should bear in mind that s/he could be reporting suspicions, where s/he thinks that a drug has caused a particular adverse event. S/he should not wait until s/he feels certain that a causal link can be considered proven or otherwise (2).
- iii. Healthcare professionals should also report any ADRs encountered in patients where the products were used for off-label indications or in doses differing from the recommended doses, as this information will provide a better understanding of the product concerned (2).
- iv. ADR reports are to be submitted using the '**Suspected ADR Reporting Form**' (**Annex I**) which is obtainable from any Ministry of Health (MoH) Pharmacies or downloaded from MoH website [<http://www.moh.gov.bn/SitePages/Downloads.aspx>] or requested by e-mailing to: **nadrmc.dps@moh.gov.bn**

Filled ADR reports are to be submitted to:

National Adverse Drug Reaction Monitoring Centre (NADRMCM)

c/o Pharmacovigilance Section

1st Floor, Department of Pharmaceutical Services Building

Simpang 433, Rimba Highway

Kg Madaras, Bandar Seri Begawan

BB1514

Brunei Darussalam

Telephone Number: +673 2392398/ 2393301 Ext 201, 206, 207

Fax Number: +673 2393036

E-mail: nadrmc.dps@moh.gov.bn

PART 2

GUIDELINE FOR:

- LICENSED MANUFACTURERS
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2.1 Legal Obligations

Under the Standard Provisions for Product Licence stipulated in *Regulation 4 of the First Schedule of the Medicines (Licensing, Standard Provisions and Fees) Regulations, 2010* ⁽⁵⁾:

"The holder of the licence shall inform the Authority within 7 days upon receipt of any report of which he is aware of adverse effects in one or more human beings or animals associated in that report resulting from the use of any medicinal product to which the license relates, which shall be open to inspection by a person authorized by the Authority, who may take copies thereof and, if the Authority so directs, the holder of the license shall furnish the Authority with a copy of any such report of which he has a record or of which he is or subsequently becomes aware".

In line with Brunei Darussalam's related Medicines Regulations, hence Product License Holder is legally obligated to report ADRs to the Brunei Darussalam Medicines Control Authority (BDMCA). Under the *Medicines Order, 2007, Section 77* ⁽⁶⁾:

Compounding of offences

"The Authority may compound any offence against this Order or under any rules made thereunder by collecting from the person reasonably suspected of having committed the offence a sum not exceeding \$2,000".

Under the *Medicines Order, 2007, Section 78* ⁽⁶⁾:

Penalty for offences not otherwise provided for.

"Any person who commits any offence against this Order for which no penalty is provided is liable on conviction to a fine not exceeding \$1,000".

ADR monitoring activities of NADRMCA are facilitated by Pharmacovigilance Section, Department of Pharmaceutical Services, Ministry of Health, Brunei Darussalam.

2.2 Responsibilities of the Licensed Manufacturers, Licensed Wholesalers, Licensed Importers and Product Licence Holders

2.2.1 All relevant licence holders should ensure responsibility for its products in the market and have proper systems in place to take appropriate action, when necessary (2). Written procedures for the receipt, evaluation and reporting of ADRs should be established (2).

2.2.2 All relevant licence holders should appoint a personnel responsible for matters relating to pharmacovigilance/ product safety and this person will be the point of contact for Ministry of Health for safety matters and updates (2).

2.2.3 It is the responsibility of the relevant licence holder to inform the NADRM proactively:

- the name of responsible person (2).
- designation (2).
- telephone number (2).
- facsimile number (2).
- email address and mailing address (2).
- update the information whenever there are any changes (2).
- the contact details of this personnel should be kept up to date at all times (2).

2.2.4 NADRM expect that the responsibilities of the designated personnel shall include:

- To report all relevant safety information relating to the medicinal product to Ministry of Health (MoH), in accordance with the local requirements stipulated in this guideline (2).
- To be aware of and to ensure compliance with any local post-marketing requirements, obligations or commitments relating to the safety of the medicinal product, e.g. safety restrictions imposed on use of medicinal products (2).
- To respond promptly to any request from MoH for the provision of information necessary for the benefit-risk evaluation of a medicinal product, e.g. list of purchasers (2).
- To provide prompt inputs, when required by MoH, on significant safety concerns so that timely and appropriate regulatory action(s) can be taken, e.g. safety communications to healthcare professionals or patients, press releases (2).

2.3 Adverse Drug Reaction (ADR) Reporting

2.3.1 Local Adverse Drug Reaction Reports (Occurring in Brunei Darussalam)

For medicinal products registered in Brunei Darussalam, all reports of suspected spontaneous ADR associated with their use in Brunei Darussalam must be submitted to the NADRMCM within the timelines stipulated (Table 1). The standard '**Council for International Organizations of Medical Sciences (CIOMS) form (7), (Annex II)**' should be used by relevant licence holders for ADR reports. This form can be downloaded from the CIOMS website [<https://cioms.ch/wp-content/uploads/2017/05/cioms-form1.pdf>] (7).

2.3.1.1 Reporting Time Frames

- **All serious fatal or life-threatening spontaneous ADR reports** occurring in Brunei Darussalam that arise from the use of the medicinal product should be reported to the NADRMCM **as soon as possible or within 24 hours after first awareness by the relevant licence holders but no later than 7 calendar days** (Table 1). The clock for reporting starts as soon as any personnel of the relevant licence holder, including sales representatives, is aware of the ADR (Table 1). The ADR report can be sent by email/ facsimile (telephone the NADRMCM to ensure receipt of ADR report). A complete report should be submitted within 8 additional calendar days from when the first report was submitted (Table 1). This report should include an assessment of the additional findings.
- **All other serious and non-serious spontaneous ADR reports** occurring in Brunei Darussalam that arise from the use of the medicinal product should be reported to the NADRMCM **no later than 7 calendar days** after first awareness by the relevant licence holders (Table 1). The clock for reporting starts as soon as any personnel of the relevant licence holder, including sales representatives, is aware of the ADR (Table 1). A complete report should be submitted within 8 additional calendar days from when the first report was submitted (Table 1). This report should include an assessment of the additional findings.

2.3.1.2 Reporting Requirements

The relevant licence holders are responsible for reporting spontaneous suspected ADRs to MoH and should keep a record of, or have access to, all reports of suspected ADRs that are received from all sources including healthcare professionals, published / unpublished studies and reports (2). The ADR reports should be as complete as possible and contain essential information to facilitate assessment (2). The minimum information required for the submission of an initial ADR report are:

- A suspected medicinal product (2, 4);

- An adverse reaction (2, 4);
- An identifiable patient (2, 4), and
- An identifiable reporter (2, 4).

The relevant licence holders should include the name, profession and place of practice of the person making the report to facilitate the detection of duplicate reports (8). The relevant licence holders should comment on whether there is a causal association between the suspected product(s) and ADR(s) and should provide the explanation on which the causality assessment is made (8).

2.3.1.3 Follow-Up Reports

To assist in the evaluation of the ADR reports, additional information not available at the time of the initial report should be provided in the form of follow-up reports **within 8 additional calendar days from when the first report was submitted** (Table 1). The reports should be clearly labelled as **Follow-Up Reports** (with appropriate cross-referencing to the initial ADR report).

2.3.2 Foreign Adverse Drug Reaction Reports (Occurring Outside Brunei Darussalam)

- ADR reports originating from outside Brunei Darussalam **need not be submitted to the NADRCM on a routine basis** (Table 1) but only in the context of an emerging safety issue or upon specific request by the NADRCM.
- The relevant licence holders are expected to inform the NADRCM **no later than 7 calendar days of any posting and/ or action taken by foreign Regulatory Health Authorities relative to the safety or benefit/ risk of a medicinal product marketed in Brunei Darussalam.**
- Information on **withdrawal of the registration status in any country must be notified to the Product Regulation Section no later than 7 calendar days after first awareness by the relevant licence holders.**

2.3.3 Emerging Safety Issues

- Events may occur, which do not fall within the definition of individual ADR reports (2). However, these events may significantly impact the benefit / risk assessment of a product or be sufficient to consider changes in the conditions of registration of the said product (2). Examples include:
 - i. Major safety findings from a newly completed non-clinical study/ review including international regulatory decisions (2).
 - ii. Major safety concerns identified in a clinical trial (2).

- iii. Safety issues published in the scientific and medical literature ⁽²⁾.
 - iv. Safety issues arising from the signal detection activity which can impact on the benefit-risk balance of the medicinal product and/or have implications for public health ⁽²⁾.
- The relevant licence holders must **write to NADRM** no later than **7 calendar days after first awareness of emerging safety issue** (Table 1) and indicate the points of concern with the actions proposed in relation to the concerned product ⁽²⁾.
 - The NADRM can request additional pharmacovigilance information as the situation warrants, data such as case reports, usage data, the regulatory status of the product in other countries, independent pharmacoepidemiology studies, pre-clinical studies or significant product quality data; as part of environmental scanning of emerging drug safety issues ⁽²⁾. This must be submitted within a time period specified by the NADRM.

2.3.4 Periodic Benefit-Risk Evaluation Report (PBRER)

2.3.4.1 Introduction

The Periodic Benefit-Risk Evaluation Report (PBRER) described in this guideline is intended to be a common standard for periodic benefit-risk evaluation on marketed products. The main objective of a PBRER is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile ⁽⁹⁾.

The required format and content of PBRER are to be based on the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Guideline E2C (R2) ⁽⁹⁾. Take note that the PBRER replaces the Periodic Safety Update Report (PSUR) format previously described in the Brunei Darussalam Guidelines on Reporting of Adverse Drug Reactions for Product Licence Holders, January 2013.

2.3.4.2 Requirement of PBRER for Innovator Product (New Chemical Entity)

- i. The PBRER should contain an evaluation of new information relevant to the medicinal product that became available to the relevant licence holders during the reporting interval, in the context of cumulative information ⁽⁹⁾. The relevant licence holders are required to:
 - Summarize the relevant new safety information that could have an impact on the benefit-risk profile of the medicinal product ⁽⁹⁾.
 - Summarize any important new efficacy/effectiveness information that has become available during the reporting interval ⁽⁹⁾;

- Examine whether the information obtained by the relevant licence holder during the reporting interval is in accordance with previous knowledge of the medicinal product's benefit and risk profile;
 - Conduct an integrated benefit-risk evaluation for approved indications whenever important new safety information has emerged ⁽⁹⁾;
 - Propose action(s) in the PBRER to optimize the benefit-risk profile when appropriate ⁽⁹⁾.
 - Report **urgent safety information** in a letter and submit *via* email to the Secretary of BDMCA and NADRMCM ⁽⁹⁾.
- ii. The relevant licence holders should submit **any consequential variations** (e.g. package insert changes) simultaneously with the PBRER at the time of its submission, in order to prevent any unnecessary duplication of effort to the Secretary of BDMCA. **A copy of the most updated relevant package insert/ Summary of Product Characteristics should be submitted together with the PBRER to the Secretary of BDMCA.**
- iii. PBRER of each medicinal product should state the International Birth Date (IBD) which is the date of the first marketing approval for any product containing the active substance granted to any company in any country in the world ⁽⁹⁾. When a report contains information on different dosage forms, formulations, or uses (indications, routes and/or populations), **the date of the first marketing approval for any of the various authorisations should be regarded as the IBD** ⁽⁹⁾. This is in order to determine the Data Lock Point (DLP) which is the date designated as the cut-off date for data to be included in a PBRER ⁽⁹⁾.
- iv. The relevant licence holders who have registered a medicinal product in Brunei Darussalam containing a New Chemical Entity (NCE) which is **less than five years** of the IBD must routinely submit PBRER on that product **6 monthly for the first 2 years from the date of its registration in Brunei Darussalam and annually for the subsequent 3 years** (Table 1). The relevant licence holders are required in the following:
- The first PBRER should be **submitted no later than 6 months after its registration in Brunei Darussalam.**
 - Each PBRER should cover the period of time since the last updated report by the relevant licence holders and must be submitted to NADRMCM **within 90 calendar days from the DLP.**
- v. The relevant licence holders who have registered a medicinal product in Brunei Darussalam containing a New Chemical Entity (NCE) which is **more than five years of the IBD need not submit the latest PBRER on that product unless upon request** (Table 1) which may be due to safety issue(s) . The relevant licence holders are required to:

- Submit latest PBRER to NADRMCM **within 90 calendar days from date of request.**

vi. Submission of PBRER should be sent to:

a. National Adverse Drug Reaction Monitoring Centre (NADRMCM)

c/o Pharmacovigilance Section

1st Floor, Department of Pharmaceutical Services Building

Simpang 433, Rimba Highway

Kg Madaras, Bandar Seri Begawan

BB1514

Brunei Darussalam

Telephone Number: +673 2392398/ 2393301 Ext 201, 206, 207

Fax Number: +673 2393036

E-mail: nadrmcm.dps@moh.gov.bn

b. Secretary of BDMCA

Department of Pharmaceutical Services,

2nd Floor, Department of Pharmaceutical Services Building

Simpang 433, Rimba Highway

Kg Madaras, Bandar Seri Begawan

BB1514

Brunei Darussalam

Telephone Number: +673 2392398/ 2393301 Ext 225

Fax Number: +673 2393297

E-mail: drugregistration@moh.gov.bn

2.3.4.3 Submission of PBRER for Generics

As a general rule, PBRERs for generics are not required to be submitted (2). But, it is expected that the relevant licence holders will continue to evaluate the safety of their products on a regular basis and report any new safety information that impacts the benefit-risk balance or the product information (2). **PBRER for generics is to be submitted only if required by NADRMCM (Table 1). Submission of Generics PBRER is within 90 calendar days from date of request.**

Table 1. Summary of Reporting Time Frame for Relevant Licence Holders

| TYPE OF REPORT | DESCRIPTION OF ADVERSE EVENT | TIME FRAME FOR REPORTING |
|--|---|--|
| Local Spontaneous Suspected ADR Reports | Serious (life-threatening or fatal) | As soon as possible or within 24 hours after first awareness by the relevant Licence Holder but no later than 7 calendar days. A complete report should be submitted within 8 additional calendar days from when the first report was submitted. This report should include an assessment of the additional findings. |
| | Serious (non-life threatening or non-fatal) and non-serious | No later than 7 calendar days after first awareness by the relevant License Holder. A complete report should be submitted within 8 additional calendar days from when the first report was submitted. This report should include an assessment of the additional findings. |
| Foreign Spontaneous Suspected ADR Reports | Serious and non-serious | Not required on a routine basis. |
| Emerging Safety Issues | New information impacting on risk - benefit profile of product including international regulatory decisions | No later than 7 calendar days after first awareness by relevant License Holder. |
| Periodic Benefit-Risk Evaluation Report (PBRER) | All NCE with International Birth date within 5 years of registration in Brunei Darussalam | 6 monthly for the first two years. Annually for the subsequent 3 years. |
| | After 5 years of registration in Brunei Darussalam (All products including NCE and generics) | When requested only. |

2.4 Safety Communication

2.4.1 Introduction

Communicating safety information to patients and healthcare professionals is a public health responsibility (2). It is essential for achieving the objectives of pharmacovigilance in terms of

promoting the rational, safe and effective use of medicines, preventing harm from ADRs and contributing to the protection of patients' and public health safety (2).

Safety communication in this context refers to message addressed to healthcare professionals *via* Dear Healthcare Professional Letter (DHCPL) by the relevant licence holders or NADRCM (in special cases), to inform them of the need to take certain actions in relation to a medicinal product (2).

The preparation of DHCPL involves cooperation between the relevant licence holders and NADRCM (2). Agreement between these two parties should be reached before a DHCPL is issued by the relevant licence holders (2). The agreement will cover both the content of the information and the communication plan, including the intended recipients, the timetable for disseminating the DHCPL and the dissemination mechanism (2).

A DHPCL should be disseminated in the following situations when there is a need to take immediate action in relation to a medicinal product (2):

- new major warnings or precautions for use in the product information (2);
- new data identifying a previously unknown risk or a change in the frequency or severity of a known risk (2);
- substantiated knowledge that the medicinal product is not as effective as previously considered (2);
- new recommendations for preventing or treating ADRs or to avoid misuse or medication error with the medicinal product (2);
- ongoing assessment of an important potential risk, for which data available at a particular point in time are insufficient to take regulatory action (in this case, the DHPCL should encourage close monitoring of the safety concern in clinical practice and encourage reporting, and possibly provide information on how to minimise the potential risk) (2).

To distribute a DHPCL in Brunei Darussalam, the relevant licence holder should submit a draft communication plan to the NADRCM for approval that includes (2):

- i. Objective (2);
- ii. Scheduled timeline proposed (2);
- iii. Recipients (2);
- iv. Dissemination method (2);
- vi. Other related communications and post-communication strategy (2).

The appended template for DHCPL (Annex III) should be followed and attached to the communication plan. Further recommendations on DHCPL:

- Safety information should be clear and concise; it should not exceed three (3) pages (2);
- The reason for dissemination should be explained (e.g. Availability of new data) (2);
- Recommendations to healthcare professionals should be given on how to minimise risk, if known and information for the general public (2);
- The safety concern should be placed in the context of the overall benefit of treatment (2).

GLOSSARY

Adverse Drug Reaction

A response to a medicinal product which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of a disease or for the modification of physiological function (10).

This includes adverse reactions which arise from:

- The use of a medicinal product within the terms of the marketing authorization (2);
- The use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors (2);
- Occupational exposure (2);

Adverse Event

Any untoward medical occurrence that may present during treatment with a medicinal product but which does not necessarily have a causal relationship with the treatment (4).

In pre-marketing studies and clinical trials, adverse events are usually systematically solicited and monitored as it is not yet known whether the event is related to the medicinal product under study or not (4).

A reaction, contrary to an event, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected i.e. judged possible by the reporting or review in health care professional (4).

Allied Healthcare Professional

A person who has a professional qualification in any of the allied health professions listed in the Schedule 10: Allied Health Professions of Brunei Darussalam Order, 2017 (3).

Data Lock Point

For a PBREER, the date designated as the cut-off date for data to be included in a PBREER, based on the international birth date or the date of registration approval (2, 9).

Drug

Any pharmaceutical (medicinal) product that is a new chemical entity, established medicinal products, biotechnology-derived medicinal products and vaccines.

Healthcare Professionals

For the purposes of reporting suspected adverse drug reactions, healthcare professionals are defined as medically qualified persons, such as doctors, dentists, pharmacists, nurses, pharmacy technicians and other allied health professionals e.g. optometrists, podiatrists, physiotherapists, radiographers, dieticians, etc (3) that uses medicinal products in their practice.

International Birth Date

The date on which a medicinal product is first registered by the Regulatory Authority of any country (2, 9).

Medicinal Product

The meaning of 'medicinal product' and related expressions as stated in the Medicines Order, 2007 (Part 1: Section 4) (6):-

- (1) Subject to the following provisions of this section, in this Order "medicinal product" means any substance or article (not being an instrument, apparatus or appliance) which is manufactured, sold, supplied, imported or exported for use wholly or mainly in either or both of the following ways (6):-
 - (a) use by being administered to one or more human beings or animals for a medicinal purpose (6);
 - (b) use as an ingredient in the preparation of a substance or article which is to be administered to one or more human beings or animals for a medicinal purpose (6).

- (2) In this Order, "a medicinal purpose" means any one or more of the following purposes (6):-
 - (a) treating or preventing disease (6);
 - (b) diagnosing disease or ascertaining the existence, degree or extent of a physiological condition (6);
 - (c) contraception (6);
 - (d) inducing anaesthesia (6);
 - (e) otherwise preventing or interfering with the normal operation of a physiological function, whether permanently or temporarily, and whether by way of terminating, reducing or postponing, or increasing or accelerating, the operation of that function or in any other way (6).

- (3) Notwithstanding anything in subsection (1), in this Order "medicinal product" does not include any substance or article which is manufactured for use wholly or mainly by being administered to one or more human beings or animals, where it is to be administered to them (6):-
 - (a) in the course of the business of the manufacturer or on behalf of the manufacturer in the course of the business of laboratory or research established carried on by another person (6);
 - (b) solely by way of a test for ascertaining what effects it has when so administered (6); and
 - (c) in circumstances where the manufacturer has no knowledge of any evidence that those effects are likely to be beneficial to those human beings, or beneficial to, or otherwise

advantageous in relation to, those animals, as the case may be, and which (having been so manufactured) is not sold, supplied or exported for use wholly or mainly in any way not fulfilling all the conditions specified in paragraphs (a), (b) and (c) (6).

(4) In this Order, a “medicinal product” does not include (6):-

- substances used in dental surgery for filling dental cavities (6);
- bandages and other surgical dressings, except medicated dressings where the medication has a palliative or curative function which is not limited to sterilising the dressings (6); and
- substances and articles of such other description or classes as may be specified by order made by the Minister (6).

(5) Where in accordance with subsections (1) to (4) a substance or article is a medicinal product immediately after it has been manufactured, imported or exported as mentioned in subsection (1), or immediately after the first occasion on which it has been sold or supplied as mentioned in that subsection, then it shall not cease to be a medicinal product for the purposes of this Order by reason only that, at any subsequent time, it is sold, supplied, imported or exported for the use wholly or mainly in a way other than those specified in subsection (1) (6).

(6) For the purposes of this Order, medicinal products are of the same description if (6):-

- (a) they are manufactured to the same specification; manufacturing methods and processes; equipment and manufacturing plant (6); and
- (b) they are, are to be, sold, supplied, imported or exported in the same pharmaceutical form (6).

(7) For the purposes of this Order a document, advertisement or representation shall be taken to be likely to mislead as the uses or effects of medicinal products of a particular description if it is likely to mislead as to any of the following matters (6):-

- (a) any purposes for which medicinal products of that description can with reasonable safety be used (6);
- (b) any purposes for which such products cannot be so used (6); and
- (c) any effects which such products when used, or when used in any particular way referred to in the document, advertisement or representation, produce or are intended to produce (6).

Innovator Product (New Chemical Entity - Brunei Darussalam Context)

Applies to new medicinal product containing:

- a new chemical/biological entity;
- a new combination of existing chemical/biological entity(s);
- existing chemical/biological entity(s) in a new dosage form;
- existing chemical or biological entity(s) for use by a different route of administration.

Pharmacovigilance

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects of medicine-related problem (1).

Periodic Benefit-Risk Evaluation Report (PBRER)

Format and content for providing an evaluation of the benefit-risk balance of a medicinal product for submission by the product licence holder at defined time points after the approval of registration (9).

Serious Adverse Event

Any untoward medical occurrence that at any dose of medicinal product (2, 4):

- results in death (2, 4),
- is life-threatening (2, 4),
- requires inpatient hospitalization or prolongation of existing hospitalisation (2, 4),
- is a congenital anomaly/birth defect (2, 4),
- is involving persistent or significant disability or incapacity (2, 4),
- is medically significant (medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above e.g. intensive treatment in an emergency room; or development of medicinal product dependency or medicinal product abuse) (2, 4).

Unexpected Adverse Reaction

An adverse reaction, the nature, specificity, severity and outcome of which is not consistent with the summary of product characteristics (2, 4).

Signal

Notice of an early concern or hypothesis about a possible drug safety problem (11).

Spontaneous ADR Reporting

System whereby case reports of adverse events are voluntarily submitted from health professionals and mandatory from pharmaceutical manufacturers to the National Regulatory Authority (NRA).

ANNEX I: SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

CONFIDENTIAL



For office use only:

BRN _____
Initial report _____
Follow-up report _____

National Adverse Drug Reaction Monitoring Centre
Ministry of Health, Brunei Darussalam

SUSPECTED ADVERSE DRUG REACTION REPORT FORM

Please report all suspected adverse drug reactions including those for vaccines, self-medication, traditional medicines and health supplements. Do not hesitate to report if some details are not known. **MANDATORY FIELDS** are marked with *. Identities of reporter and patient will be kept confidential.

(1) PATIENT DETAILS *

Patient name: _____ Date of birth: _____ Weight, if known (kg): _____

Gender: Male Female Medical record no. / BruHims no. / Identity card no. : _____

Nationality: _____ Ethnic group: Malay Chinese Other (please specify): _____

(2) ADVERSE DRUG REACTION (ADR) DETAILS *

Description of ADR(s): _____

Time to onset of ADR(s): _____ mins/ hours/ days/ months/ years Date ADR(s) started: _____ Date ADR (s) stopped: _____
(please circle)

Do you consider the ADR(s) to be serious? Yes No

If yes, please indicate why the ADR is considered to be serious (please tick all that apply):

Patient died due to reaction Life threatening Involved or prolonged in-patient hospitalisation

Congenital abnormality Involved persistent or significant disability or incapacity

Medically significant; please give details: _____

• Description of treatment of reaction: _____

• Outcome of reaction: Recovered Recovering Recovered with sequelae (any permanent complications or injuries)

Not recovered Fatal (Date of Death): _____ Unknown

(3) SUSPECTED DRUG(S)/ VACCINE(S) * (Additional pages may be attached)

| Product name, active ingredient & strength | Dosage form | Dosage regimen (dosage, frequency & route) | Product details: Batch No. (if known) | Date started | Date stopped | Prescribed for |
|--|-------------|--|---------------------------------------|--------------|--------------|----------------|
| 1. | | | | | | |
| 2. | | | | | | |
| 3. | | | | | | |

(4) OTHER DRUG(S) (INCLUDING SELF-MEDICATION, TRADITIONAL MEDICINES & HEALTH SUPPLEMENTS CONSUMED AT THE SAME TIME AND/ OR IN THE LAST 3 MONTHS BEFORE THE ADR) (Additional pages may be attached)

| Product name, active ingredient & strength | Dosage form | Dosage regimen (dosage, frequency & route) | Product details: Batch No. (if known) | Date started | Date stopped | Prescribed for |
|--|-------------|--|---------------------------------------|--------------|--------------|----------------|
| 1. | | | | | | |
| 2. | | | | | | |

CONFIDENTIAL

| | | | | | | |
|----|--|--|--|--|--|--|
| 3- | | | | | | |
| 4- | | | | | | |
| 5- | | | | | | |

(5) OTHER RELEVANT INFORMATION (Additional pages may be attached)

| | |
|--|--|
| Relevant Medical History (Include Allergies, Pregnancy Status, Smoking, Renal/ Hepatic Dysfunction etc) <i>(For congenital abnormalities, please state all other drugs taken during pregnancy and the last menstrual period)</i> | Relevant Investigations (Rechallenge If Performed/ Laboratory Data) |
| | |

(6) REPORTER DETAILS *

Name: _____ Signature: _____
Profession: _____ Institution Address : _____
Date: _____ Tel No: _____ Email: _____

Thank you for taking the time to complete this form.

FOLD HERE FIRST

GUIDANCE ON ADR REPORTING

WHAT TO REPORT?

An adverse drug reaction is a response to a drug that is noxious (harmful) and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

The Ministry of Health encourages the reporting of **all** suspected adverse reactions to drugs and medicinal substances (including self-medication, traditional medicines or health supplements). In particular, please report:

- All suspected reactions to established products and new medicines regardless of their nature and severity.
- All serious adverse reactions which include reactions suspected of causing death, danger to life, admission to hospital, prolongation of hospitalisation, birth defects, persistent or significant disability or incapacity and if medically significant.
- All suspected drug interactions

HOW TO REPORT?

The Suspected Adverse Drug Reaction Report form can be obtained from the National Adverse Drug Reaction Monitoring Centre and the nearest government pharmacy facility (hospital/ health centre). This form should be filled as completely as possible and returned to the address below or to the nearest government pharmacy facility (hospital/ health centre).

SUBMISSION OF FOLLOW-UP REPORTS

Any follow-up information for an ADR that has already been reported can be sent to us in another form or via any other modes of reporting. Please state that it is a follow-up report, indicating the date and reference number of the initial report.

FOLD HERE SECOND

To: **National Adverse Drug Reaction Monitoring Centre (NADRMC)**
c/o Pharmacovigilance Section
1st Floor, Department of Pharmaceutical Services Building
Simpang 433, Rimba Highway
Kg Madaras, Bandar Seri Begawan
BB1514
Brunei Darussalam
Telephone Number: +673 2392398/ 2393301 Ext 201, 206, 207
Fax Number: +673 2393036
E-mail: nadrmc.dps@moh.gov.bn

ADR Report Form Version 1.2018

ANNEX II: CIOMS FORM

CIOMS FORM

| | |
|---|--|
| <p>SUSPECT ADVERSE REACTION REPORT</p> | |
| | |
| | |

I. REACTION INFORMATION

| | | | | | | | | |
|---|-------------|------------------|---------|--------|--------------------|--|--|---|
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | 4-6 REACTION ONSET | | | 8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION <input type="checkbox"/> PATIENT DIED <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING |
| | | Day | Month | Year | Years | | | |
| 7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) | | | | | | | | |

II. SUSPECT DRUG(S) INFORMATION

| | | |
|--|--------------------------------|---|
| 14. SUSPECT DRUG(S) (include generic name) | | 20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA |
| 15. DAILY DOSE(S) | 16. ROUTE(S) OF ADMINISTRATION | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA |
| 17. INDICATION(S) FOR USE | | |
| 18. THERAPY DATES (from/to) | 19. THERAPY DURATION | |

III. CONCOMITANT DRUG(S) AND HISTORY

| |
|---|
| 22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) |
| 23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) |

IV. MANUFACTURER INFORMATION

| | | |
|---------------------------------------|--|--|
| 24a. NAME AND ADDRESS OF MANUFACTURER | | |
| | 24b. MFR CONTROL NO. | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT SOURCE <input type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input type="checkbox"/> HEALTH PROFESSIONAL | |
| DATE OF THIS REPORT | 25a. REPORT TYPE <input type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP | |

ANNEX III: TEMPLATE FOR DEAR HEALTHCARE PROFESSIONAL LETTER

Date

Company Logo and address

Dear Healthcare Professional,

Title

Title in bold to include brand/ trade name of drug, generic name, drug strength and preparation, Brunei Darussalam registration number (if already registered with Brunei Darussalam Medicines Control Authority) and brief information of risk/ harm/ advice

1st paragraph

Must begin and include the phrase below (in italics):

The communication of this information has been agreed with the Department of Pharmaceutical Services, Ministry of Health, Brunei Darussalam.

Introduction of product and product indication.

Relation of product with risk/harm/advice.

2nd paragraph

Header: **Summary**

Summary of information in bullet points.

3rd paragraph

Header: **Recommendations for Healthcare Professionals**

Information presented in bullet points for example:

- Recommended dosing/duration of treatment
- What signs and symptoms Healthcare Professionals to be aware of from their patients
- Any extra monitoring/reassessment of patients
- Any further advice

4th paragraph

Header: **Indications & medicinal product details (where applicable) approved in Brunei Darussalam**

Information to be presented in bullet points if there are many indications for the product.

5th paragraph

Header: **Further information regarding safety concern**

Information to be presented in bullet points with information such as:

What other regulatory actions taken by either of the regulatory authorities in the benchmark countries below:

- Medicines & Healthcare products Regulatory Agency (UK)
- European Medicines Agency (EU)
- Food and Drug Administration (USA)
- Health Canada (Canada)
- Therapeutics Goods Administration (Australia)
- National Pharmaceutical Regulatory Agency (Malaysia)
- Health Services Authority (Singapore)

Benefit risk assessment (if information is available from the other regulatory authority).

6th paragraph

Header: **Action by manufacturer**

Information on any action due to risk/harm/advice, for example updating product information leaflets, providing patient medication guides, training, etc.

7th paragraph

Header: **Adverse Event Reporting**

Include manufacturer contact details on who to report for adverse events reporting.

Include Product licence holder contact details on who to report for adverse events reporting.

Must end and include the phrase below (in italics):

Healthcare professionals are encouraged to report any suspected serious adverse drug reactions related to use of <name of product> to:

National Adverse Drug Reaction Monitoring Centre (NADRMCM)

c/o Pharmacovigilance Section

1st Floor, Department of Pharmaceutical Services Building

Simpang 433, Rimba Highway

Kg Madaras, Bandar Seri Begawan

BB1514

Brunei Darussalam

Telephone Number: +673 2392398/ 2393301 Ext 201, 206, 207

Fax Number: +673 2393036

E-mail: nadrmc.dps@moh.gov.bn

Suspected ADR Reporting Form can be obtained from any Ministry of Health (MoH) Pharmacies or downloaded from MoH website [<http://www.moh.gov.bn/SitePages/Downloads.aspx>] or requested by e-mailing to: nadrmc.dps@moh.gov.bn.

Yours sincerely,

Signature of company representative

(Name)

(Job Position)

(Company name)

References

Header: **References**

Full details of the Information on the references (document / website link) cited in the letter and in numerical order.

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