This document has been prepared to serve as a guideline to those reporting adverse drug reactions. It represents the Medicines Control Council’s current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of safety data.

Guidelines and application forms are available from the office of the Registrar of Medicines and the MCC website.

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1 INTRODUCTION

This guideline does not apply to the reporting of adverse drug reactions (ADRs) and Serious Adverse Events (SAEs) related to unregistered medicines (whether used in the context of pre-registration clinical trials or in terms of Section 21 authorisations).

This guideline is intended to assist holders of a certificate of registration (holder) / applicants in the reporting of adverse drug reactions (ADRs) associated with the use of registered medicines and “Old Medicines” and in the management of safety data which arise during post-registration and post-marketing clinical trials.

For the purposes of this guideline, “MCC” refers to the Medicines Control Council, and “NADEMC” refers to the National Adverse Drug Event Monitoring Centre. The terms “holder of certificate of registration” (holder) and “applicant” are used interchangeably. The terms “medicine” and “drug” are also used interchangeably.

1.1 Legal Basis

The guideline pertains to Regulation 37 issued in terms of the Medicines and Related Substances Act, 1965(Act 101 of 1965) as amended.

2 DEFINITIONS

2.1 Adverse Event

“Adverse event/experience” is any untoward medical occurrence in a patient or clinical trial subject administered a medicine that may present during treatment with that medicine but which does not necessarily have a causal relationship with this treatment.

An adverse event can be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicine, whether considered related to the medicine, or not.

2.2 Adverse Drug Reaction (ADR) or Adverse Reaction

“Adverse drug reaction” or “adverse reaction” means a response to a medicine in humans which is noxious and unintended, including lack of efficacy, and which occurs at doses normally used in man and which can also result from overdose, misuse or abuse of a medicine.

The definition of an adverse drug reaction or adverse reaction applies to registered medicines, medicines for which the applicant holds an application for registration (“Old Medicines”), as well as unregistered medicines being used under section 21 of Act 101 (1965).

Response in this context means that a causal relationship between a medicine and an adverse event is at least a reasonable possibility.

An adverse reaction includes adverse clinical consequences associated with the use of a medicine outside the terms of the approved package insert/ applicable product information or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).
A reaction, contrary to an event (as in 2.1), is characterised by the occurrence of a suspected causal relationship between the drug and the reaction, as determined by the reporter or a reviewing healthcare professional. The fact that the healthcare provider / professional is making a report to a holder of a certificate of registration, serves as an indication that the observed event may be caused by the medicine. All spontaneous reports are, therefore, suspected adverse drug reactions.

In the case of pre- and post-marketing studies, adverse “events” are usually systematically solicited. In cases where there is uncertainty as to whether or not an event is a reaction, it is better to treat the event as a reaction. For the purpose of post-marketing clinical trials, an adverse drug reaction includes any adverse event where the contribution of the study medication, concomitant medication or other medicinal intervention of the clinical trial, cannot be ruled out.

2.3 Serious Adverse Drug Event or Adverse Drug Reaction

A serious adverse event/experience or reaction is any untoward medical occurrence that at any dose:
- results in death;
- is life-threatening;
- requires patient hospitalisation or prolongation of existing hospitalisation;
- results in a congenital anomaly/birth defect;
- results in persistent or significant disability/incapacity; or
- is a medically significant / important event or reaction.

The term “life-threatening” in the definition of “serious” refers to a reaction/event in which the patient was at risk of death at the time of the reaction/event; it does not refer to an event which, hypothetically, might have caused death if it were more severe.

Medical and scientific judgement should be exercised when deciding whether other situations are serious or not. Such instances could include medical events that may not be immediately life-threatening or result in death or hospitalisation, but which may jeopardise the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples include blood dyscrasias or convulsions not resulting in hospitalisation, or development of drug dependency or drug abuse.

The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious”, which is based on patient/event outcome or action criteria.

2.4 Unexpected (unlisted) Adverse Drug Reaction

For the purposes of this guideline, an “unexpected” adverse reaction is one in which the nature, specificity, severity and outcome is not consistent with the approved package insert for a registered medicine

An unexpected reaction includes class-related reactions which are mentioned in the applicable medicine information but which are not specifically described as occurring with a medicine. When the outcome of the adverse reaction is not consistent with the applicable medicine information the adverse reaction should be considered as unexpected.

An expected ADR with a fatal outcome should be considered unexpected unless the South African labelling specifically states that the ADR might be associated with a fatal outcome.
2.5 Adverse Drug Reaction Report (Individual Case Safety Report)

An adverse drug reaction report is a detailed record of all relevant data associated with the use of a medicine in a subject or patient.

2.6 Spontaneous Report or Notification

A spontaneous report is a communication to a company, regulatory authority or other organisation that describes a suspected adverse drug reaction in a patient given one or more medicines, and which does not derive from a study.

2.7 Solicited Reports

Solicited reports are defined as those derived from organised data collection systems, which include clinical trials, registries, post-approval named patient programmes, other patient support and disease management programmes, surveys of patients or healthcare providers, or information gathering on efficacy or patient adherence.

For the purpose of safety reporting, solicited reports should be classified as Individual Case Safety Reports.

2.8 Reportable Adverse Reaction – Minimum Information

A reportable ADR requires the following minimum information:

- an identifiable source (reporter) of the information. This should include the name or initials and address of the reporter and the reporter’s qualification (e.g. doctor, dentist, pharmacist, nurse or layperson);
- an identifiable patient. A patient may be identified by surname and forename(s) or initials of surname and forenames, or by a reference number, or by age or gender;
- suspected medicine(s); and
- suspected reaction(s).

Information, additional to the minimum, should be actively sought and submitted as soon as it becomes available.

2.9 Periodic Safety Update Reports / Periodic Benefit-Risk Evaluation Reports

A periodic safety update report (PSUR) or a Periodic Benefit-Risk Evaluation Report (PBRER) is an update of the world-wide safety experience of a medicine at defined times post-registration, as determined from the international birth date.

Each safety update report should cover the period of time since the last update report. The PSUR or PBRER should be compiled in accordance with the requirements of the current ICH E2C Expert Group on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs.
2.10 Line Listings

A line listing provides key information but not necessarily all the details customarily collected on individual cases. Reactions are classified by body system for the most serious-presenting sign or symptom. The headings usually included are:

- country of occurrence (if relevant);
- source (e.g. spontaneous, clinical trial, literature, regulatory authority);
- age;
- gender;
- dose(s) of suspected medicine(s);
- formulation and/or route of administration, batch number when applicable;
- duration of treatment (prior to event) time to onset;
- description of reaction (as reported);
- patient outcome (e.g. fatal, resolved, etc.); and
- comment (if relevant)

In some instances, depending on the type or source, ADR reports should be presented as line listings. A line listing serves to help the MCC to identify cases that it might wish to examine more completely by requesting full case reports.

2.11 Risk-Benefit Balance Evaluation

An evaluation of the positive therapeutic effects of the medicine in relation to the risks (any risk relating to the quality, safety or efficacy of the medicine as regards patients’ health or public health).

2.12 Healthcare Professional / Provider

For the purposes of reporting suspected adverse reactions, “healthcare professionals/providers” are medical practitioners, pathologists, dentists, pharmacists, nurses, and other healthcare professionals including allied healthcare professionals.

When reports originate from pharmacists or nurses, further information about the case should, where possible, be sought from a medical practitioner responsible for the patient. Furthermore, if there is more than one reporter, the healthcare professional directly involved with the patient’s care and who provides the most complete and clinically relevant information, will be considered the primary reporter.

2.13 Abuse of Medicine

“Abuse of Medicine” refers to the persistent or sporadic, intentional excessive use of medicines which is accompanied by harmful physical or psychological effects.

2.14 Consumer

A consumer is defined as a person who is not a healthcare professional / provider, such as a patient, lawyer, friend, relative or carer of a patient.
3 PHARMACOVIGILANCE OBLIGATIONS OF THE HOLDER OF A CERTIFICATE OF REGISTRATION / APPLICANT

3.1 The Role and Responsibilities of the Holder of a Certificate of Registration / Applicant

(i) The holder or applicant should ensure that it has in place an appropriate system for pharmacovigilance that will provide for the proper management of safety data for its medicines and to ensure that appropriate action can be taken when necessary. It is strongly recommended that the applicant has available, in South Africa, a full-time qualified person responsible for pharmacovigilance and post-marketing surveillance i.e. pharmacovigilance officer. This person should have experience and training in all aspects of pharmacovigilance and, if not a healthcare professional / provider, should have access to a medically qualified person.

(ii) The Responsible Pharmacist of a holder or applicant must nominate a specific individual, i.e. pharmacovigilance officer responsible for pharmacovigilance activities. The MCC and NADEMC must be informed in writing who the person is who will assume responsibility for all matters pertaining to pharmacovigilance, including the person’s contact details (postal and e-mail addresses and telephone and fax numbers).

(iii) The holder or applicant should ensure that there is full documentation covering all procedures and activities of the pharmacovigilance officer and that mechanisms are in place to ensure that the pharmacovigilance officer may receive or seek all relevant information.

3.2 The Role and Responsibilities of the Holder of a Certificate of Registration’s / Applicant’s Pharmacovigilance Officer

Responsibilities of the holder’s or applicant’s pharmacovigilance officer should include:

(i) the establishment and maintenance of a system which ensures that information about all suspected adverse reactions, which are reported to the holder or applicant, including to medical representatives and clinical research associates, is collected and collated so that it is accessible at a single point;

(ii) serving as a contact person for the MCC and NADEMC for all matters relating to pharmacovigilance;

(iii) the preparation of the following, either directly or by delegation/supervision, for submission to the MCC:
   - adverse drug reaction reports;
   - summary evaluation statement of non-serious ADRs occurring in South Africa;
   - summary report of ADRs occurring in South Africa;
   - Periodic Safety Update Reports (PSURs) or Periodic Benefit-Risk Evaluation Reports (PBRER), when necessary;
   - company-sponsored post-registration study reports, when required; and
   - ongoing pharmacovigilance evaluation during the post-registration period; and

(iv) ensuring that any request from the MCC for additional information deemed necessary for the evaluation of the risk-benefit ratio of a medicine, is provided to the MCC promptly and in accordance with all requirements.

3.3 Contractual Arrangements

A holder or applicant may contract any or all of the pharmacovigilance tasks and functions, including the role of pharmacovigilance officer, to another person or organisation, but the ultimate responsibility for the fulfilment of all pharmacovigilance obligations and the quality and integrity of this always resides with the holder or applicant.
4 ADVERSE DRUG REACTION REPORTS

4.1 Time frames for ADRs occurring in South Africa
   (i) All serious, suspected adverse drug reactions, whether expected or unexpected, occurring in South Africa with any medicine, must be reported by the holder or applicant within 15 calendar days of receipt of such information.
   (ii) All non-serious, unexpected, suspected adverse drug reactions, occurring in South Africa with any medicine, must be reported by the holder or applicant, within 15 calendar days of receipt of such information. In addition non-serious, unexpected ADRs should be included in the SES (see 5.6 on the summary evaluation statement). The applicant is not required to report non-serious expected adverse drug reactions as individual case safety reports.

4.2 Time frames for reactions occurring outside South Africa
   (i) Foreign individual case reports should not be forwarded to the MCC on a routine basis, but should be reported in the context of a specific safety issue or in response to a specific request by the MCC.
   (ii) The holder or applicant should advise the MCC of any action relating to safety that has been taken by a medicines regulatory agency in another country, including the basis for such action, within five (5) calendar days of first knowledge of such action.

4.3 Periodic Safety Update Reports / Periodic Benefit-Risk Evaluation Reports
   (i) PSURs/PBRERs should only be submitted in the following situations:
      • Whenever requested by the MCC.
      • When the submission of PSURs/PBRERs is a condition of registration for a new medicine or range of medicines. The holder/applicant must submit these PSURs/PBRERs within 30 calendar days of initial receipt from the parent company.
      • As part of a submission to amend the conditions of registration when the PSUR/PBRER contains information supporting the amendment.
   (ii) The holder or applicant should inform the MCC of any steps, which are taken, or to be taken, with regard to safety concerns raised in the PSUR/PBRER at the time of the submission.

4.4 South African Case Reports from Published Scientific Literature:
   (i) Holders or applicants should report published accounts of suspected adverse drug reactions related to the active substance(s) of their medicines. A copy of the relevant scientific publication should be provided.
   (ii) An adverse drug reaction report should be completed for each identifiable patient (with an identifiable adverse drug reaction). For instance, if an article describes six identifiable patients with a given adverse experience, six adverse drug reaction reports should be submitted to the MCC.
   (iii) If more than one medicine is mentioned in the literature report, only the holder or applicant whose medicine is suspected of being the cause is required to submit a report. The suspect medicine is usually the one stated as such in the body or title of the article by the author(s).
   (iv) If the source of the medicine and/or the proprietary name is not specified and ownership of the product cannot be excluded on the basis of the active substance(s), formulation or route of administration, the holder or applicant should assume that it is one of their medicines the publication refers to, although the report should indicate that the specific medicine source and/or the proprietary name was not identified.
If the literature report is of a generalised nature with no identifiable patient, it should not be submitted as an individual case report. However, if the report identifies a safety concern this should be communicated to the NADEMC and include an opinion on the issue prepared on behalf of the holder or applicant.

4.5 Reports from Post-Registration Studies

(i) All suspected adverse drug reactions from post-registration studies taking place in South Africa must be reported according to 4.1 above. This applies to reports from any type of clinical or epidemiological investigation, regardless of design or purpose, involving a medicine.

(ii) Investigators involved in post-registration studies should be aware of the definition of what constitutes a serious adverse drug reaction, as well as the distinction between ‘reactions’ and ‘events’.

(iii) In the case of post-registration studies, adverse “events” are usually systematically solicited. In cases where there is uncertainty as to whether or not an event is a reaction, the case should be reported as an adverse reaction. Events that are clearly unrelated to the medicine should not be reported.

(iv) If the manufacturer receives a report of a serious adverse drug reaction from the investigator who is blinded to individual patient treatment, the guidelines outlined in section (v) below should be adhered to.

(v) Managing blinded therapy cases: When a serious, unexpected, suspected adverse reaction occurs which results in death or, which is life-threatening, and is, therefore, judged reportable on an expedited (rapid) basis, it is recommended that the blind be broken only for that specific patient by the sponsor, even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study’s conclusion. By retaining the blind, placebo and comparator (usually a marketed medicine) cases are filed in the database unnecessarily.

(vi) When a fatal or other serious outcome is the primary efficacy endpoint in a clinical trial, the integrity of the clinical trial may be compromised if the blind is broken. Under these and similar circumstances, agreement should be reached in advance with the MCC concerning serious events that would be treated as disease-related and not subject to expedited reporting. An independent data safety monitoring board should be established prior to commencement of the trial, and its composition and terms of reference, should be submitted with the clinical trial application documents to the MCC for evaluation.

4.6 On-Going Pharmacovigilance Evaluation

It should be noted that the requirements for on-going Pharmacovigilance Evaluation as described in this section takes precedence over other cumulative ADR reporting requirements mentioned in this guideline, such as the Summary Evaluation Statement or the Summary Report (i.e. the submission of the Summary Evaluation Statement and Summary Report do not replace the requirements for reporting stipulated in this section).

(i) Holders or applicants must inform the MCC, within three (3) calendar days of first knowledge, whenever new evidence becomes available (nationally and internationally) that could significantly impact on the benefit/risk assessment of a medicine or which would be sufficient to consider changes to the conditions of registration of the medicine.
(ii) Holders or applicants must report any change in the nature, severity or frequency of expected adverse drug reactions or any new risk factors identified within 15 calendar days. The basis on which these assessments are made should be included.

(iii) Additional pharmacovigilance data, such as actual case reports, drug usage figures, the regulatory status of the medicine in other countries, independent pharmaco-epidemiology studies, pre-clinical studies or significant product quality data may be requested by the MCC as the situation warrants. This will be requested for submission within a time period specified by the MCC.

4.7 Consumer Reports

If a holder or applicant receives an adverse drug reaction report from a consumer, the holder or applicant should advise the consumer to report this reaction through his/her healthcare provider / professional. If this approach fails, the holder or applicant should attempt to obtain as much information as possible from the consumer, including medical documentation. If the minimum information for reporting has been met, and the report is deemed to be relevant by a healthcare provider / professional within the company, the case is considered reportable, in line with 4.1 (i) and (ii).

4.8 Reports relating to pregnancy and breastfeeding

The holder or applicant must report suspected adverse drug reactions related to pregnancy or breastfeeding as specified in 4.1 and 4.2 above, regardless of whether the drug is contra-indicated in pregnancy and/or lactation. Reports on pregnancy should not be forwarded before the outcome is known, unless unintended pregnancy is suspected as an adverse drug reaction. Reports on pregnancy should not be submitted if there is no adverse effect to the foetus/infant. Reports of termination of pregnancy without information on congenital malformation should not routinely be reported.

4.9 Teratogenicity and Congenital Anomalies

For reports on congenital anomalies or teratogenicity, the following information should be provided:

- age and sex of the infant
- the birth date or the date on which pregnancy was terminated
- date and/or duration of in utero exposure where possible
- any adverse reaction experienced by the mother must be considered a new initial case report on a separate report form.

4.10 Reports of lack of efficacy

“Lack of efficacy” is defined as failure to produce the expected pharmacological action. Lack of efficacy applies to registered medicines, including when used for an unapproved indication. Reports of lack of efficacy should not be routinely reported as serious adverse drug reaction reports.

Lack of efficacy with medicines used for the treatment of life-threatening diseases (e.g. antimicrobial agents), vaccines or contraceptives or other classes of medicines where lack of could result in serious consequences, require reporting. Normal progression of disease does not imply lack of efficacy. Clinical judgement should be used in considering whether a case qualifies as serious for reporting purposes.

The lot number of the suspected medicine for a report of lack of efficacy must be included in the report.
4.11 Overdose

Reports of overdose should be submitted only when the overdose was associated with an adverse reaction. Suspected adverse reactions, associated with an overdose, should be reported, as well as other reactions. This should include reports which indicate that taking of the suspect medicine led to suicidal intention and subsequent overdose of the suspect medicine, or of other medication(s). Reports of overdose that are associated with serious adverse reactions must be reported according to 4.1(i).

4.12 Medication Errors

Medication errors that are associated with serious adverse reactions must be reported according to 4.1(i). Information on medication errors, whether resulting in an adverse reaction or not, should be included in the Summary Report.

4.13 Medicine Defects

If an adverse event is suspected to be related to a medicine defect, it should be reported in the same manner as a suspected adverse reaction. The lot number of the suspected medicines must be included in the report. Holders or applicants should inform the MCC whether the implicated products have been tested for quality and what, if any, corrective actions are being or have been taken.

4.14 Interactions

If an adverse event is suspected to be related to an interaction between two or more medicines, it should be reported as an adverse reaction in the prescribed manner.

4.15 Adverse Reaction Reports from the Internet

Holders or applicants should regularly screen websites under their management or responsibility for potential ADR case reports. The frequency of the screening should allow for potential valid ADRs to be reported to the MCC within the appropriate timeframe, based on the date the information was posted. Unsolicited cases from the Internet should be handled as spontaneous reports. For determination of reportability, the same criteria should be applied as for cases provided via other means. In relation to such cases from the Internet, identifiability of the reporter refers to the existence of a natural person, i.e. it should be possible to verify that the patient and reporter exist (e.g. a valid e-mail address has been provided). Contact details should only be used for pharmacovigilance purposes.

4.16 Period after Suspension, Cancellation or Withdrawal of Holder of Certificate of Registration / Applicant

The holder or applicant should continue to collect adverse reaction reports related to the concerned medicine and continue to report if information becomes available, even after suspension, cancellation or withdrawal of registration or “Old Medicine” status.

5 PROCEDURES FOR REPORTING

5.1 To Whom to Report

All reports required by these guidelines should be sent to the MCC at the address reflected in Appendix 1.
5.2 Route of Notification

Reports should be sent by post, or by facsimile.

5.3 Report Format and Details

(i) Reporting can be done using the adverse reaction report form available from the NADEMC, or the holders or applicants may use their in-house report forms (including the CIOMS format) provided all the necessary data elements are included on the form in a readable format.

(ii) Holders or applicants should submit **ALL** the relevant information available at the time of initial notification of an adverse drug reaction report, not only the minimum information required for a report. The attachment of discharge summaries, post-mortem reports, relevant laboratory data and other additional clinical data, is encouraged.

(iii) The original words/description (verbatim) used by the initial reporter to describe the adverse reaction should be provided. The medicine name as reported by the initial reporter must be provided, preferably the proprietary name.

(iv) Additional information, not available at the time of the initial report, should be provided in the form of follow-up reports.

(v) The holder or applicant is required to submit the name or initials, address and telephone number and qualification of the initial reporter on the adverse drug reaction report form. In order to ensure confidentiality, the initials of the reporter may be used.

5.4 Follow-Up Reports

Any follow-up information from the holder or applicant relating to an initial ADR report submitted to the NADEMC, must be cross-referenced to the unique number assigned by the or applicant. A CIOMS format “initial” report which follows a previous (first) communication from the applicant must be clearly marked that it is a follow up and linked through the applicant-assigned reference number. **This is the only reliable way to minimise the duplication of reports, submitted by holders or applicants, in the NADEMC’s database.**

5.5 Another Holder of a Certificate of Registration / Applicant’s Medicine

**Spontaneous reports:** If a holder or applicant receives a report of a suspected adverse reaction to a medicine marketed by another holder or applicant, the report should promptly be forwarded to the holder or applicant of that medicine. The holder or applicant to whom the event was originally reported should not forward such reports to the MCC to avoid duplication of reporting. A holder or applicant who receives such a report about its medicine from another holder or applicant is required to submit the report to the MCC within the same time frame applicable to other reports. Details relating to the patient and the initial reporter are required as for any other report. In order to ensure confidentiality, initials of the patient and/or reporter may be used.

5.6 Summary Evaluation Statement (for local non-serious, expected and unexpected, ADR reports)

Every holder or applicant shall submit annually to the NADEMC for each medicine a Summary Evaluation Statement (SES) relating to the evaluation of all reports for non-serious (i.e. expected and unexpected) ADRs received during the previous year. The format of the SES is available as a template (Appendix 3).
If the answer is “Yes” to any question listed under section 2 of the SES template, points (a)-(f), a complete Summary Report for that product is required. The requirements for the Summary Report are specified in Point 5.6.1.

**Time frame for submission of SES:** Each applicant or holder will specify the 12-month period which it will use for the SES. The 12-month period and the data lock-point selected by the holder or applicant should be communicated to the NADEMC. The SES should be submitted to the NADEMC within 90 days after the data lock-point.

If an applicant has received no reports during the time period, a SES must be completed and communicated to the NADEMC.

### 5.6.1 Summary Report

The submission of a Summary Report (SR) is required for any medicine for which the answer is “Yes” to any question listed under section 2 of the SES template, points (a)-(f), specified in Point 45.6. The MCC may also request a SR for any other time period if deemed necessary.

**Format of the SR:** The format used should include for each medicine the following - Template available (Appendix 4):

(i) the South African utilisation of each formulation for the review period (e.g. sales data or patient exposure).

(ii) a concise critical analysis of the reported ADRs for each medicine.

   The critical analysis should
   - identify any new ADRs and risk factors associated with the medicine
   - indicate any changes in the reporting rates of ADRs in a comparable period using estimated exposure (South African) to the medicine, and with reference to international and cumulative data
   - address any new safety issue related to drug interactions, overdose, drug abuse or misuse, use in pregnancy, use in special patient groups or effects of long-term treatment

(iii) any actions taken or to be taken, including actions taken by any other regulatory authority or marketing authorisation holder

(iv) in a conclusion a simple risk-benefit statement for ongoing use and monitoring of the medicine.

(v) a line listing which includes the source, patient gender and age, formulation (including strength), daily dose, treatment dates and duration or time to onset, adverse reaction(s), seriousness, outcome and comment (including medical history and concomitant medicines). Reports received from a consumer should be clearly identified. (See also 2.10)

Depending on the medicine or circumstances, it may be useful or practical to have more than one line-listing, such as per dosage forms or indications, if such differentiation facilitates presentation and interpretation of data.

It may also be useful to have separate tabulations for medically significant or non-significant reactions, for expected and unexpected reactions, or any other breakdown as may be useful for interpretation of the data. When the number of cases is very small, or the information is inadequate for any of the tabulations, a narrative description rather than a formal table would be considered suitable.

**Time frame for submission of SR:** Each holder or applicant will specify the 12-month period which it will use for the SR. The 12-month period and the data lock-point selected by the holder or applicant should be communicated to the NADEMC. The SR should be submitted to the NADEMC within 90 days after the data lock-point.
ADR reports to be included: All South African spontaneous reports (serious and non-serious) received by the holder or applicant during the specified 12-month period, all published reports of suspected ADRs, all lack of efficacy reports, and all reports from post-marketing studies (published and unpublished).

5.7 Confidentiality

Strict confidentiality will be maintained by the NADEMC regarding the identities of the patient and the reporter.

6 REFERENCES


7 APPENDICES

APPENDIX 1: ADDRESSES

Reportable Safety Information as reflected in the Guidelines associated with registered human medicines must be sent to:

National Adverse Drug Event Monitoring Centre
Medicines Control Council
C/o Division of Pharmacology
University of Cape Town
Observatory
7925

Tel: 021 447 1618
Fax: 021 448 6181

Registrar of Medicines
Pharmacovigilance Unit
Private Bag X828
Pretoria
0001

Tel: 012 395 9133
Fax: 012 395 8775
### APPENDIX 2: TABULATED SUMMARY OF REPORTING REQUIREMENTS

#### Post-Registration ADR Reports (registered medicines)

<table>
<thead>
<tr>
<th>Type of ADR report</th>
<th>Time frame for reporting</th>
<th>Format</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>South African Reports (spontaneous/published/study):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serious (expected and unexpected)</td>
<td>15 days</td>
<td>ADR form #</td>
</tr>
<tr>
<td>• Non-serious (unexpected)</td>
<td>15 days</td>
<td>ADR form #</td>
</tr>
<tr>
<td>• Non-serious (expected and unexpected)</td>
<td>Annually</td>
<td>SES</td>
</tr>
<tr>
<td><strong>Foreign Reports</strong> (spontaneous/published/ study):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serious</td>
<td>On request or relating to specific safety issue</td>
<td>As appropriate</td>
</tr>
<tr>
<td><strong>Notification of Change in Nature, Severity or Frequency or Risk factors</strong></td>
<td>15 days</td>
<td>Detailed report(including publications)</td>
</tr>
<tr>
<td><strong>New information impacting on benefit-risk profile of medicine including decisions by national medicines regulatory authorities other than the MCC</strong></td>
<td>3 days</td>
<td>Detailed report (including publications)</td>
</tr>
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</table>

# The holder/applicant’s in-house ADR report form or NADEMC ADR report form.
APPENDIX 3: TEMPLATE FOR SUMMARY EVALUATION STATEMENT
(for non-serious expected and unexpected ADR reports)

*The submission of this statement does not replace the criteria for ADR reporting as indicated in Section 4 of this guideline.

1 Product Details

<table>
<thead>
<tr>
<th>Name of Product</th>
<th>South African Holder of a Certificate of Registration / Applicant</th>
</tr>
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<tbody>
<tr>
<td>Registration Number</td>
<td>Review Period</td>
</tr>
<tr>
<td>Responsible Pharmacist</td>
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2 Evaluation of non-serious Adverse Drug Reaction (ADR) Reports

| a) Do the ADR reports received change the risk-benefit of this product? | ☐ YES ☐ NO |
| b) Are there any new ADRs or risk factors identified? | ☐ YES ☐ NO |
| c) Are there any changes in the reporting rate? | ☐ YES ☐ NO |
| d) Are there any other safety issues? (e.g. drug interactions, overdose, drug abuse) | ☐ YES ☐ NO |
| e) Were there any actions taken or to be taken; with regard to the use of this product; by any other medicines regulatory authority or marketing authorisation holder (including the local applicant)? | ☐ YES ☐ NO |
| f) Does the current local package insert and patient information leaflet need updating in light of these ADRs? | ☐ YES ☐ NO |

(If yes to any questions listed a-df, kindly submit a complete summary report for this medicine)

3 Additional Comments (if any) __________________________________________________________

____________________________________________________

4 Signature

I certify that the above information is complete and correct.

____________________________________________________

RESPONSIBLE PHARMACIST Date

---

2.33_ADR_reporting_post-marketing_Jul16_v4.1_showing_changes.doc Nov 2016 Page 18 of 22 Back to ToC
APPENDIX 4: TEMPLATE FOR SUMMARY REPORT

Each holder of a certificate of registration / applicant should submit a single summary report (SR) which covers all medicines for which it received ADR reports. If a holder or applicant has received no reports during the time period, it must communicate this to the NADEMC.

The format of the SR used should include for each medicine:

1. **Review period**
   Specify the dates for the 12-month period applicable to the data presented. If periods differ for different medicines, this needs to be specified. It should be kept in mind that the data must be presented annually.

2. **South African usage of each formulation for the review period**
   This may be sales data or patient exposure.

3. **Critical (concise) analysis of the reported ADRs for each medicine**
   3.1 New ADRs identified
      Indicate whether any new ADRs have been identified and whether such are serious or non-serious.
   3.2 New risk factors identified
   3.3 Changes in reporting rate
      Any changes in reporting rate(s) of ADRs reported in a comparable period, using estimated South African exposure of the medicine, and with reference to international and cumulative data.
   3.4 Other new safety issues
      This includes any new safety issue related to drug interactions, overdose, drug abuse or misuse, use in pregnancy, use in special patient groups or effects of long-term treatment, if not included in any of the above points.
   3.5 Actions taken or to be taken
      This includes actions taken or to be taken by any other regulatory authority or marketing authorisation holder (includes the local holder of a certificate of registration / applicant).

4. **Conclusion**
   A simple risk-benefit statement for ongoing use and monitoring of the medicine is required.

5. **Line-listing**
   The line listing should include the source, patient gender and age, formulation (including strength), daily dose, treatment dates and duration or time to onset, adverse reaction(s), seriousness, outcome and comment (including medical history and concomitant medicines). Reports received from a consumer should be clearly identified.
Depending on the medicine or circumstances, it may be useful or practical to have more than one line-listing, such as dosage forms or indications, if such differentiation facilitates presentation and interpretation of data. It may also be useful to have separate tabulations for serious reactions and for non-serious reactions, for expected and unexpected reactions, or any other breakdown as may be useful for interpretation of the data. When the number of cases is very small, or the information is inadequate for any of the tabulations, a narrative description rather than a formal table would be considered suitable.

The line-listing should include all South African spontaneous reports (serious and non-serious) received by the holder or applicant during the specified 12-month period, all published reports of suspected ADRs, all lack of efficacy reports, and all reports from post-marketing studies (published and unpublished).
8 GLOSSARY AND ABBREVIATIONS

CIOMS  Council for International Organisations of Medical Science
HCR    Holder of Certificate of Registration
ICSR   Individual case safety report
MCC    Medicines Control Council
NADEMC National Adverse Drug Event Monitoring Centre
PBRER  Periodic Benefit-Risk Evaluation Report
PSUR   Periodic Safety Update Report
SES    Summary Evaluation Statement
SR     Summary Report
9 UPDATE HISTORY

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<td>Version 1_1 Oct 2010</td>
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<td>1 Inclusion of the section on Summary Report</td>
<td>Version 2 July 2011</td>
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<td>2 Inclusion of additional information under the section on &quot;Healthcare professional&quot;</td>
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<td>7 2.11 addition of “evaluation”</td>
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<td>8 2.13 replacement of “drug” with “medicinal product”</td>
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