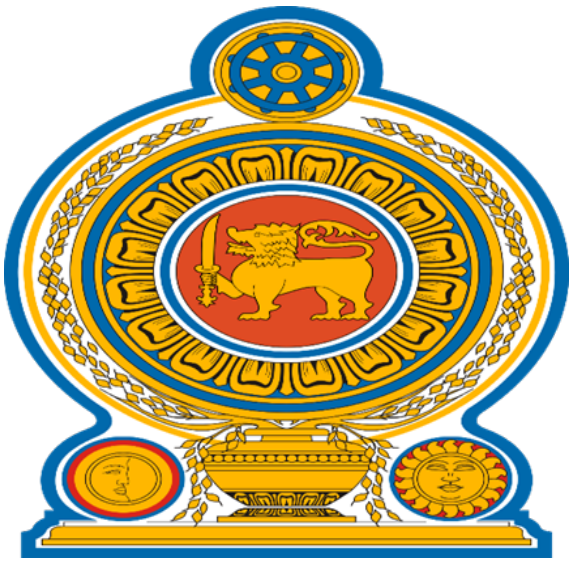


GUIDELINES FOR MONITORING AND REPORTING ADVERSE DRUG REACTIONS

For Healthcare professionals & Patients

NATIONAL MEDICINES REGULATORY AUTHORITY

NORIS CANAL ROAD, COLOMBO 10, SRI LANKA

Preface

Patients expect the medicines they receive to be safe and effective. Healthcare professionals expect the medicines they prescribe, dispense or administer are potentially safe. Safety of medicinal products is the primary concern of any Medicines Regulatory Body in the world. Although the duties, responsibilities and scopes of these different parties may be different invariably the objective of safety remains comparable. Being vigilance on medicinal product is an integral element towards assurance of the safety of medicinal products.

Success of any pharmacovigilance system depends on the receipt of the reports and the subsequent procedures. This document provides guidance to all healthcare institutes and individuals as well as the patients who submit reports about their role and the good practices in detection & reporting of adverse drugs reactions.

Contents

ABBREVIATIONS

ADRs - Adverse Drug Reactions

CEO - Chief Executive Officer

ICSR - Individual Case Safety Report

MEC - Medicines Evaluation Committee

MSD – Medical Supplies Division

NMQAL - National Medicines Quality Assurance Laboratory

NMRA - National Medicines Regulatory Authority

PV division – Pharmacovigilance Division

SAFRESC- Safety and Risk Evaluation Sub Committee

UMC - Uppsala Monitoring Centre

WHO - World Health Organization

WHO-ART - WHO Adverse Reaction Terminology

GLOSSARY OF TERMINOLOGY

Adverse Event:

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

Adverse Reaction:

A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Causality Assessment

The evaluation of the likelihood that a medicine was the causative agent of an observed adverse event in a specific individual. Causality assessment is usually made according to established algorithms.

Individual Case Safety Report (ICSR)

A document providing the most complete information related to an individual case at a certain point of time. An individual case is the information provided by a primary source to describe suspected adverse reaction(s) related to the administration of one or more medicinal products to an individual patient at a particular point of time.

Quality Failure

Any deviation of a genuine medicine authorized by the National Medicines Regulatory Authority, from the quality specifications set for them by national standards.

Serious Adverse Event:

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose

- results in death;
- is life-threatening;

- requires inpatient hospitalization or prolongation of hospitalization;
- results in persistent or significant disability/incapacity;
- is causing congenital anomaly/birth defect;
- 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 above. Medical and scientific judgment should be exercised in these events

Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). i.e. expected and unexpected ADR can refer to labeled vs unlabeled (for official data sheets/package inserts for marketed products)

Signal:

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

Introduction

National Medicines Regulatory Authority Act No. 05 of 2015 and rules and regulations thereof provide legal provisions for pharmacovigilance in Sri Lanka. Pharmacovigilance, as defined by the WHO is "the science and activities related to the detection, assessment, understanding and prevention of adverse drug effects or any other possible drug-related problems. Furthermore, adverse drug reaction is defined as a response which is noxious and unintended.

Underlying objectives of our pharmacovigilance system is preventing harm from adverse reactions or any other drug related problems and promoting the safe and effective medicines in particular through providing timely information about the safety of medicines to patients, healthcare professionals and general public.

Ultimate objective of Pharmacovigilance is therefore safety of medicines.

Of late number of New Chemical Entities and Similar Bio Therapeutic Products that received market authorization in Sri Lanka has been significantly increased. Due to the policy of the government to encourage local manufacturing of pharmaceuticals considerable number of new manufacturers has emerged within the Island. In this scenario strengthening Pharmacovigilance system in Sri Lanka has been a timely necessity.

The need for pharmacovigilance

The information collected during the pre-marketing phase of medicines development is inevitably incomplete with regard to possible ADRs. This is mainly because:

- Tests in animals are insufficient to predict human safety;
- Patients used in clinical trials are selected and limited in number, the conditions of use differ from those in clinical practice and the duration of trials is limited;
- By the time of medicine licensing, exposure of less than 5000 human subjects to a medicine allows only the more common ADR to be detected; while at least 30,000 people need to be treated with a medicine to be sure that you do not miss at least one patient with an ADR which has an incidence of 1 in 10,000 exposed individuals;
- Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available

Thus, continuous safety monitoring of medicines which is the main objective of pharmacovigilance is important to permit detection of less common, but sometimes very serious ADRs. Therefore, health professionals and patients worldwide should report on ADRs as it can save lives of their patients and others.

Objectives of Pharmacovigilance

In addition to the beneficial therapeutic outcomes that medicines can have, they can also cause harm to patients. The pharmacovigilance can help to reduce this harm and support safer and more effective use of medicines for everyone by:

1. Early detection and investigation of previously unknown adverse reactions or any other medicines related problems
2. Recognition and investigation of the increases in frequency or any new aspects of already known adverse reaction
3. Generate new hypothesis on ADRs that are specific to the local population
4. Quantitative analysis of benefit/risk ratio
5. Dissemination of information on ADRs and safe use of medicines for rational prescribing and regulations
6. Identifying problems with batches or brands of medicines
7. Encouraging safe and rational use of medicines, including cost-effectiveness.

WHO Programme for International Drug Monitoring

The World Health Organization (WHO) Programme for International Drug Monitoring (PIDM) was established in 1968 in response to the thalidomide disaster in which thousands of infants were born with congenital deformations following fetal exposure to thalidomide, a medicine that had been used to treat morning sickness in pregnancy. Initially a pilot project in 10 countries with established national reporting systems for ADRs, the network has since expanded significantly as more countries worldwide developed national Pharmacovigilance centers.

The PIDM provides a forum for WHO member states to collaborate in the monitoring of medicines safety, and notably, the identification and analysis of new adverse reaction signals from data submitted to the WHO global individual case safety report (ICSR) database by member countries, Vigibase.

The programme consists of a three-part network:

- National Pharmacovigilance Centers (usually base in the regulatory authorities) from WHO member countries are responsible for the running national pharmacovigilance system, collecting, analyzing and sending national case reports to the WHO global database;
- Uppsala Monitoring Center (UMC) oversees the WHO programme operations, including:
  - maintaining the global Individual Case Safety Reports (ICSRs) database, Vigibase

- collecting, assessing and communicating information from member countries about the benefits, harm, effectiveness and risks of medicines;
- collaborating with member countries in the development and practice of pharmacovigilance;
- alerting NMRAs of member countries about potential medicines safety problems via the WHO signal process.

- WHO headquarters in Geneva, Switzerland is responsible for policy issues.

The Scope of Pharmacovigilance

Since the start of pharmacovigilance practice and over time, globally the pharmacovigilance focus has shifted from the medicines to the patient and the scope of pharmacovigilance has been extended regarding the following:

- ***Use of Medicines*** scope of pharmacovigilance include the monitoring of safety problems or adverse effects related to the use of medicines whether used within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors, as highlighted below:
  - **Adverse drug reaction (ADR)** is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility
  - **Medication error** is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. For example, a medicine could be wrongly prescribed by a doctor, wrongly dispensed by a pharmacist or nurse, or administered incorrectly by a patient. Since most medication errors are a result of system failures, for example lack of staff resulting in a heavy workload, that is why reporting culture in Sri Lanka ensure that individuals are not blamed and punished, but instead focus to identify the underlying causes and take proper action to prevent the same error from happening again.

  - **Drug interaction** occurs when the effects of one medicine are changed in the presence of another drug, food or drink. Resulting in making the medicine more or less effective. Although many interactions are well known, irrational combinations are still prescribed, causing unwanted side effects. Many patients, especially the elderly, may take several

medicines each day. Obviously, the risk of developing an undesired drug interaction increases with the number of medicines used.

- **Off-label use** means situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorization. For example, when a different indication, route of administration or dosage is used, or when a medicine is used in a different age group. Previously, children were usually excluded from clinical trials resulting in a lack of data and the need for special dosage adjustments. New legislation has increased the number of medicines licensed for pediatric use, but there is still room for improvement.

- **Abuse, misuse** and related events is when a medicinal product is intentionally used in a manner that deviates from the prescribed pattern, which can have serious medical consequences. The morbidity and mortality associated with non-therapeutic use of medicines are rising and there is a need to implement strategies to cope with this growing health problem.

- **Overdose**
  This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgement should always be applied.

- **Antimicrobial resistance** is the ability of microorganisms to survive in the presence of antimicrobials. New resistance mechanisms are emerging and spreading, threatening the ability to treat common infectious diseases. This is a major threat to global health that requires global collaboration and action. Without effective antimicrobials, medical procedures such as organ transplantation, cancer chemotherapy and major surgery become very risky.

- **Occupational exposure** this refers to adverse outcome occur due to the exposure to a medicinal product, as a result of one's professional or non-professional occupation.

- ***Quality of Medicines*** scope of pharmacovigilance includes the monitoring of safety problems related to the quality of medicines which includes poor manufacturing practice, substandard and falsified medical products and lack of efficacy.

- **Poor manufacturing**, storage or distribution practice is when the quality standards specified are not met. In addition to Good Manufacturing Practice, there are also guidelines on best practices for storage, transportation and distribution of pharmaceuticals to ensure that medicines remain of high quality all the way to the patient. If these quality standards are not met, it may lead to product contamination, wrong amount of active ingredient or incorrect labels, resulting in ineffective treatment, adverse effects or even death.
- **Falsified medicinal products** deliberately misrepresent their identity, composition or source, for example by containing the wrong amount of the active ingredient, no active ingredient at all or other ingredients.
- **Lack of efficacy** is defined as unexpected failure of a medicine to produce the intended effect as determined by previous scientific investigation. Since lack of efficacy may be a consequence of poor manufacturing practice or substandard and falsified medicines, it could indicate a quality problem. Lack of efficacy may have serious implications for the patient.

- ***The Broader Scope of Products***

Another aspect to consider is the broad scope of products that fall under the pharmacovigilance umbrella including:

- Medicinal products
- Biotherapeutics and vaccines
- Medical devices
- Dietary supplements
- Traditional medicines
- Cosmetics
- Veterinary medicines

Classification of adverse drug reactions

Type A (augmented) reactions: result from an exaggeration of a medicinal product's normal pharmacological actions and are normally dose-dependent. Examples include respiratory depression with opioids or bleeding with warfarin. Type A reactions also include those that are not directly related to the desired pharmacological action of the medicinal product, for example dry mouth that is associated with tricyclic antidepressants.

Type B (bizarre) reactions are novel responses that are not expected from the known pharmacological actions of the medicinal product. These are less common, and so may only be discovered for the first time after a medicinal product has already been made available for general use. Examples include anaphylaxis with penicillin or skin rashes with antibiotics.

Type C, or 'continuing' reactions, persist for a relatively long time. An example is osteonecrosis of the jaw with bisphosphonates.

Type D, or 'delayed' reactions, become apparent sometime after the use of a medicinal product. The timing of these may make them more difficult to detect. An example is leucopoenia, which can occur up to six weeks after a dose of lomustine.

Type E, or 'end-of-use' reactions, are associated with the withdrawal of a medicinal product. An example is insomnia, anxiety and perceptual disturbances following the withdrawal of benzodiazepines.

Type F 'Failure of therapy' reaction

The National Pharmacovigilance system in Sri Lanka

The National Pharmacovigilance Center in Sri Lanka is based in the National Medicines Regulatory Authority. It is responsible for the safety monitoring of medicines in Sri Lanka and is taking all the appropriate measures to:

- Maintaining the national reporting system as well as the relevant regulatory framework;
- Raise awareness about pharmacovigilance and encourage healthcare professionals and patients to report the suspected adverse reactions and other medicines related problems;
- Collect, manage & analyze national ICSRs to identify new medicines risks, furthermore, report these ICSRs to the global database as appropriate;
- Ensure introduction of risk minimization measures and providing effective communication on aspects related to medicines safety;
- Apply resulting information from pharmacovigilance and take the appropriate regulatory actions for the benefit of public health programs, individual patients and national policies related to medicine and treatment guidelines;
- Monitor compliance of the pharmaceutical companies to ensure the fulfillments of their pharmacovigilance obligations of their medicines for the sake of patient safety.

Approaches for medicines safety surveillance

Passive surveillance (of spontaneous reports)

A surveillance method that relies on healthcare providers and consumers to take the initiative in communicating suspicions of adverse drug reactions that may have occurred in individual patients to a spontaneous reporting system.

Active surveillance

A system for the collection of case safety information as a continuous pre-organized process. Active surveillance can be:

1. Drug based: identifying adverse events in patients taking certain products;
2. identifying adverse events in certain healthcare settings where they are likely to present for Treatment
3. Event based: identifying adverse events that are likely to be associated with medicinal products, e.g., liver failure.

National reporting system

Spontaneous reports are the most common source of information in the pharmacovigilance system of Sri Lanka. In line with this general scope of pharmacovigilance the reporting system in Sri Lanka is not limited to the adverse drug reactions. It also includes lack of efficacy, medication errors, quality defects, counterfeit medicines, abuse or misuse interactions of medicines, off-label use and occupational exposure. On some occasions there may be an inter relation among these elements. For example, complaint received as an incident of lack of efficacy may be due to a counterfeit product. Cluster of adverse reactions may reveal a serious quality defect of a particular product. Irrespective of the type of the problem it affects the safety of medicinal products.

Information needed for adverse reaction reporting

Reporting forms have been designed to collect the essential information required for proper assessment of the ADR case report. Information to be filled in the ICSR forms can be categorized under the following headings.

1. Patient information	2. Suspected medicine(s) Information	3. Adverse reactions Description	4. Reporter Information
– patient identifier – age at time of event or date of birth – gender – weight	– name (INN and brand name) – dose, frequency & route used – therapy date – diagnosis for use – batch number – expiration date – concomitant medical products and therapy dates	– description of event or problem – date of event – date of this report – relevant tests/laboratory data, clinical measurements (if available) – other relevant patient information/history – event abated after use stopped or dose reduced – event reappeared after reintroduction of the treatment – Information on management of the adverse reactions and final outcome.	– name, address and telephone number – specialty and occupation

In order to overcome high level of missing data in the ADR reports on suspected anaphylactic reactions PV division has introduced a separate form for reporting of anaphylaxis which would capture all the important data.

Seriousness of Adverse drug reactions

A serious adverse reaction is any untoward medical occurrence associated with the use of a medicinal product in a patient that at any dose, the patient outcome is one of the following:

1. **Death**

   Report if the patient's death is suspected as being a direct outcome of the adverse reaction.

2. **Life-Threatening**

   Report if the patient was at substantial risk of dying at the time of the adverse reaction or it is suspected that the use or continued use of the product would result in the patient's death.

   Examples: Pacemaker failure; gastrointestinal hemorrhage; bone marrow suppression; infusion pump failure which permits uncontrolled free flow resulting in excessive medicine dosing.

3. **Hospitalization (initial or prolonged)**

   Report if admission to the hospital or prolongation of a hospital stay results because of the suspected adverse reaction.

   Examples: Anaphylaxis; pseudomembranous colitis; or bleeding causing/ prolonging the existing hospitalization.

4. **Disability**

   Report if the adverse reaction resulted in a significant, persistent, or permanent disability/ incapacity; (change, impairment, damage, or disruption in the patient's body function/structure, physical activities, or quality of life).

   Examples: Cerebrovascular accident due to medicine-induced hypercoagulability; toxicity; peripheral neuropathy.

5. **Congenital Anomaly**

   Report if there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child (birth defect).

   Examples: Vaginal cancer in female offspring from diethylstilbestrol during pregnancy; malformation in the offspring caused by thalidomide.

6. **Medically important event or reaction**

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might NOT be immediately life-threatening or result in death or hospitalization but might cause danger to the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

Examples:

- Acetaminophen overdose-induced hepatotoxicity requiring treatment with acetylcysteine to prevent permanent damage;
- Burns from radiation equipment requiring medicine therapy;
- Breakage of a screw requiring replacement of hardware to prevent in appropriate healing of a fractured long bone.
- **Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction**.
- Intensive treatment in an emergency room or at home for allergic bronchospasm,
- Convulsions that do not result in hospitalization,
- Development of medicine dependency or medicine abuse

Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). i.e. expected and unexpected ADR can refer to labeled vs unlabeled (for official data sheets/package inserts for marketed products)

The concept of "expectedness" refers to events which may or may not have been previously observed and documented. It does not refer to what might have been anticipated (expected in a different sense) from the known pharmacological properties of the medicine.

Priorities for reporting

Pharmacovigilance Division encourage to report even seemingly insignificant or common adverse drug events as it is required to establish a reporting culture in Sri Lanka. However, more emphasis should be made on the following categories.

- All suspected reactions for new medicines
- All serious or unexpected suspected reactions for established or well-known medicines
- Increased frequency of a given reaction

- All suspected ADRs associated with medicine– medicine, medicine – food or medicine – food supplements
- ADR on special field of interests such as medicine abuse, misuse
- Medicines used during pregnancy and during lactation resulting in harmful effect to the fetus or infant
- Teratogenicity due to medicinal product
- Suspected ADRs associated with medicine withdrawals
- ADRs due to overdose or medication error
- Lack of efficacy or pharmaceutical defects
- ADRs due to use of medicinal products in children under the age of 18
- Any ADR for medicinal products under the Black triangle scheme ▼

Black triangle scheme (intensified spontaneous reporting)

New medicines and vaccines that are under additional monitoring have an inverted black triangle symbol (▼) displayed in their package leaflet and summary of product characteristic, together with a short sentence explaining what the triangle means – it does not mean the medicine is unsafe. All suspected ADRs for these products should be reported.

How to recognize ADRs in patients

ADRs are difficult and sometimes impossible to distinguish from the disease being treated since they may act through the same physiological and pathological pathways. However, the following approach is helpful in assessing possible drug-related ADRs:

1. Ensure that the medicine ordered is the medicine received and actually taken by the patient at the dose advised.
2. Take a proper history of patient
   - A full medicine and medical history should be taken
   - An ADR should be the first differential diagnosis at all times
3. Establish time relationships by answering the following question: *Did the ADR occur immediately following the medicine administration?*

   Some reactions occur immediately after the medicine has been given while others take time to develop. The time from start of therapy to the time of onset of the suspected reaction must be logical.
4. Carry out a thorough physical examination with appropriate laboratory investigations if necessary:

- Remember: only a few medicines produce distinctive physical signs
- Exceptions include fixed medicine eruptions, steroid-induced dermal atrophy, acute extra-pyramidal reactions
- Laboratory tests are important if the medicine is considered essential in improving patient care or if the laboratory tests results will improve management of the patient.
- Try to describe the reaction as clearly as possible- Where possible, provide an accurate diagnosis

5. Analyze the alternative causes (other than the drug) that could on their own have caused the reaction;
6. Effect of Dechallenge and Rechallenge should be determined
   - Dechallenge (withdrawal of the suspected medicine):

     Positive dechallenge is the improvement / resolution of ADR when the suspected medicine is withdrawn in a strong, though not conclusive indication of medicine-induced reaction.
   - Rechallenge (re-introducing the suspected medicine after a dechallenge)

     Rechallenge is only justifiable when the benefit of reintroducing the suspected medicine to the patient overweighs the risk of recurrence of the reaction, which is rare. In some cases, the reaction may be more severe on repeated exposure. Rechallenge requires serious ethical considerations**.**
7. Report any suspected ADR or safety incident to the Pharmacovigilance Division or the pharmaceutical company relevant to the suspected medicinal product.

Who can report?

All Medical Professionals Preferably Doctors, Dentists, Pharmacists, Nurses and Family practitioners, Traditional medicine practitioners can submit ADR reports to the PV division. Also patients & their relatives are encouraged to report.

How to report

- **Online**:

  An online ICSR reporting portal has been enabled to facilitate the reporting of adverse reaction and collecting all relevant information in a structured way. Upon submitting the report, a confirmation message with Report ID will appear. **This report ID should be saved** by the reporter and used when case follow up information is to be reported later.

This online reporting can be accessed through the National Medicines Regulatory Authority (NMRA) website on the following link (https://nmra.gov.lk/index.php?option=com_contact&view=reporting&Itemid=191&lang=en)

QR Code

- **Reporting form:**

  ICSR forms for reporting ADRs is available on the web site of the NMRA (https://nmra.gov.lk/images/PDF/suspected_adverse_reaction_to_medicinesborderline_products.pdf) for download. In addition, printed copies of the forms have been distributed among the pharmacy departments/sections of the government health care institutes. Requests from the health care professionals or institutes for reporting forms should be made to the Pharmacovigilance Division of the NMRA. Fill in this form & send it back to the NMRA on contact details included in the reporting form.

Timelines for reporting

Any suspected ADR should be reported as soon as possible. In case of serious adverse events reporting should be done within 24 hours. Delay in reporting will make reporting inaccurate and unreliable. If possible, report while the patient is still in the health facility this gives a chance to reporter to clear any ambiguity by re-questioning or examining the patient.

Q&A

Must I be sure that a reaction was caused by the medicine before reporting it?

No, it can be hard to tell whether a medicine caused a possible adverse effect.

To report, you only need **to suspect** that the reaction was related to the medicine.

Reporting Follow up information

Information may become available to the reporter after sending the initial report upon follow up of the case e.g. clinical management of the adverse event or patient **final outcome** regarding whether the event resolved or not, in this case the reporter should report this follow-up information as "follow up report" and quote the unique reference number from the previous report generated by the online reporting portal.

Will reporting have any negative consequences on the reporter?

- The adverse drug reaction report does not constitute an admission that the reporter or any other health professional or the medicine contributed to or caused the reaction in any way.
- The outcome of the report, together with any important or relevant information relating to the reported reaction, will be communicated to the reporter as appropriate.
- The details of the report are stored in a confidential database at the PV division and the analyzed report will be sent to the Uppsala Monitoring Center (UMC).
- The names of the reporters or any other health professionals named on the report and the patient will be removed before any details about a specific adverse drug reaction is used or communicated to others.
- The information obtained from the report will not be used for commercial purposes. It is only meant to improve our understanding and use of medicines.

What are the benefits of reporting on Healthcare professionals and patients?

The health care professional and patient stand to benefit as follows:

- Improvement on the quality of care offered to patients
- Reduction of medicines-related problems leading to better treatment outcome
- Improved patient confidence in the professional's practice and consequently professional growth
- Improved knowledge, access to feedback information on drug related problems reported within the country and internationally
- Satisfaction for the fulfillment of moral and professional obligation

What Happens after reporting ADRs

Upon reporting, it is crucial that reporters fill in all the fields on the reporting form and provide full description of the adverse reaction(s) as well as the circumstances that led to them- all the information is important.

All reports sent by healthcare professionals or patients are collected by the pharmacovigilance division, where the responsible pharmacovigilance specialist would ensure that the form has all the essential information before proceeding to perform case assessment. All received reports are entered in the national database (Vigiflow)

In some cases, the pharmacovigilance division will need to learn more about what happened or to collect missing information, so they contact back the reporter for follow up. This follow-up information can be obtained, via one or more of the following email, telephone call, message on WhatsApp or similar application, and/or site visit and/or a written request. It is important to continue follow-up and report new information until the outcome has been established or the condition is stabilized.

In specific situations where the product quality is suspected, the reporter/reporting institute may be asked by the pharmacovigilance specialist to submit the samples of the suspected medicinal product for laboratory testing directly to the National Medicines Quality Assurance Laboratory (NMQAL). If it is required to do so, samples should always be submitted with the required information.

Complaints received from medical professionals, patients, mass media and the data base of the Medical Supplies Division (MSD) may also trigger collection of further details.

All the collected reports will be analyzed at the national level, serious adverse effects will be processed and analyzed in priority. Furthermore, all national report will also be sent to the global database (Vigibase) where reports from all over the world are stored and analyzed.

Upon data analysis experts will discuss the following points:

- Is the report about something which is already known about the medicinal product? Or is it new?
- Is the report isolated? Or have other patients/healthcare professionals reported similar events?
- How frequent is this? How many patients are concerned, out of the total number of patients treated?
- Is the adverse event likely to be caused by the medicinal product, or not?
- If it is confirmed that this is a new effect caused by the medicinal product, which measures should be taken?

One or more regulatory action may be taken as detailed below

Every report counts

A single case report should be seen as a piece of a jigsaw puzzle, where further data and more reports are usually needed to complete the picture.

Taking regulatory action to minimize risk

Upon analyzing the reported adverse reaction reports, once it has become clear that an adverse effect results from the use of medicinal product, steps are taken to publicize the new information and to minimize the risk of the adverse effect.

Actions might include:

- adding the new adverse effect to the existing list of adverse effect in the package insert of the medicinal product
- restricting the uses of the medicinal product, revising the dosage recommendations, issuing advice on precautions (e.g. by introducing special monitoring), or contraindicating the medicinal product in some circumstances
- changing the arrangements for supplying the medicinal product (e.g. making a previously over the-counter medicinal product to one that can be supplied only on a prescription)
- encouraging the reporting of all suspected adverse effects by placing the medicinal product on a list of more intensively monitored medicines or black triangle scheme
- rarely, removal of the medicinal product from the market if the risks outweigh the its benefits
- for important medicinal products found to have serious adverse effects, introducing special measures such as registering all patients taking the medicinal product and supplying the medicinal product only on the condition that the patient undergoes specific screening

Patients and health professionals reporting suspected adverse drug reactions help contribute to these important processes.

Safety and Risk Evaluation Sub Committee (SAFRESC)

There would be an expert committee appointed by the NMRA which shall be named as Safety and Risk Evaluation Sub Committee (SAFRESC). The Committee provides advices and technical assistance to the division pertaining to the subject.

Members of the SAFRESC

1. Head of the PV Division
2. Two Pharmacologists from two different recognized universities in Sri Lanka
3. Two pharmacists attached to the PV unit
4. Immunologist, Medical Research Institute
5. Consultant Physician, NHSL
6. Director, NMQAL
7. Chief Pharmacist Technical Unit of NMQAL
8. Representative from the FHB
9. Representative from the Epidemiology Unit
10. A pharmacist representing MSD

Members of the SAFRESC would be appointed according to an approved procedure. Each appointment would be valid for a period of 3 years.

Pharmacovigilance and the role of pharmaceutical companies

It is mandatory for pharmaceutical companies (including manufacturers and importers) in order to register products for use in Sri Lanka to have a pharmacovigilance system capable of monitoring the safety of their medicinal products. This include collection, management and submission of ADRs & other safety incidents to the Pharmacovigilance Division at the NMRA, analyze the collected safety data to identify new risks, and bring to the attention of the NMRA to any foreign regulatory decisions taken in relation to the safety of their medicinal products.

Furthermore, as a part of their pharmacovigilance practice, pharmaceutical companies shall adopt the appropriate risk management measures to ensure the safe & effective use of their medicinal products. In specific circumstances they may be requested by the NMRA to conduct post-authorization safety/ efficacy studies when needed.

Pharmacovigilance in Public Health Programmes

The objective of the Public Health Programmes is to promote health and reduce morbidity and mortality due to major common diseases e.g immunization programmes, Anti- HIV, Anti-tuberculosis, Anti- malaria, Anti- filariasis and Anti- Leprosy programs. It is common to expose

large populations to medicines to prevent a disease, although only a small proportion of the population is affected. The goal is to eliminate the disease as a public health problem.

Since the medicinal products used in Public Health Programmes may be new and have limited safety information for the specific target population, it is important to have a system in place to monitor safety.

Accordingly, it is very important to integrate Pharmacovigilance in Public Health Programmes for better capturing, recording and reporting of adverse drug reactions and other safety incidents.

APPENDIX: (01) ADR REPORTING FORMS

	SUSPECTED ADVERSE REACTION CASE REPORTING FORM TO MEDICINES/BORDERLINE PRODUCTS	To be filled in by the NMRA REPORT NO: STATE SECTOR: PRIVATE SECTOR:

If you suspect an adverse event, please complete this white card. Do not put off reporting because some details are not known. Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the adverse reaction. Identity of the patient and or/the reporter is kept strictly confidential.

A. PATIENT INFORMATION

BHT/ Record no.	Name & address (optional):	Age /DOB	Weight	Sex ☐M ☐F	Ethnicity

B. SUSPECTED MEDICINE:

Generic name:	Dose	Route	Therapy Dates (dd/mm/yyyy)
Trade name		☐ ORAL ☐ IV ☐ IM	Begun:
Batch no			
Expiry date:			
Diagnosis for use	Frequency	OTHER SPECIFY	Stopped:
Manufacturers name	Address (if available)		

C. ADVERSE REACTION OR PRODUCT PROBLEM

☐Adverse event and/or ☐Product problem e.g. quality, defects. If product problem also fill green form

Date of onset of event dd/mm/yyyy:	Date of this report:
Describe event:	LAB INVESTIGATIONS IF ANY:

Do you consider the reaction to be serious ☐ Yes ☐ No If yes please tick "✓" why the outcome of the adverse event is serious

Death ☐ Date	Life threatening ☐	Hospitalisation ☐ Hospitalisation prolonged ☐	Congenital anomaly / Birth defect (specify): ☐	Disability/ Permanent damage ☐	Required intervention to prevent permanent damage/ Medically significant (specify) ☐ .....

Result on discontinuation of suspect drug:√ ☐ Recovered ☐ Improved/ recovering ☐ Persisted ☐ Recovered/ resolved with sequelae ☐ Not Known	Result on reintroduction of drug Reappeared: Yes / No / Not known	Alternative diagnosis

Risk factors present: ✓

Renal dysfunction ☐	Cardiac Dysfunction ☐	Hepatic Dysfunction ☐	Previous Allergies ☐	Smoking ☐	Alcohol ☐	Drug addict ☐	Pregnant ☐	Other (name) .....

D. OTHER MEDICINES TAKEN AT TIME OF REACTION WITH THERAPY DATES (EXCLUDE TREATMENT OF EVENT):

E. REPORTER (doctor/ pharmacist/ nurse/dentist/ other HCP or the patient)

Name..... Specialty:.....

Address:..... Email: .....

Telephone number:..... Hospital & Ward No:.....

Signature:..... Date of reporting: ..... / ...../....

Send the filled form to the Pharmacovigilance Division, National Medicines Regulatory Authority, 120, Norris Canal Road Colombo 10. Fax: +94112523385. Tel: +94112698896/7 Email: vigilance@nmra.gov.lk

APPENDIX: ANAPHYLAXIS REPORTING FORMS

	ANAPHYLAXIS CASE REPORTING FORM **PINK FORM** *(To be completed by a Medical officer)* **Identity of the patient and the reporter is kept strictly confidential.**	**REPORT NO:** **To be filled in by the NMRA** **STATE SECTOR:** **PRIVATE SECTOR:**

If you suspect an allergic reaction (see definition of anaphylaxis at the end of page 2) related to a pharmaceutical product please complete this PINK FORM. Do not put off reporting because some details are not known. Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the anaphylactic reaction

PATIENT IDENTIFICATION DETAILS				
Name:	Address:		Tel.No:	
Date of birth dd/mm/yyyy (age) Sex ☐ M ☐ F	Ethnicity: specify	BHT number:	MOH Area	RDHS Area:
Past allergic history: Has patient had previous allergic reactions? ☐ Yes ☐ No If 'Yes', Allergen is a ☐Drug ☐Vaccine (specify) ☐ Food ☐ Other Specify details?				

Part I: Clinical features						
Onset of first symptom: Date (dd/mm/yy) Time: am/pm ☐ Unknown						
Skin & Mucosa	☐ Urticaria ☐ Erythema ☐ Pruritus ☐ Prickle sensation				Specify the site of skin reaction:	
	Eye	☐ Red bilateral ☐ Red unilateral ☐ Itchy				
	Angioedema	☐ Tongue ☐ Throat ☐ Uvula ☐ Larynx ☐ Lip ☐ Face ☐ Limbs ☐ Other				
Respiratory system	☐ Sneezing ☐ Rhinorrhoea ☐ Sore throat	☐ Hoarse voice ☐ Stridor	☐ Sensation of throat closure ☐ Cough	☐ Tachypnoea ☐ Difficulty in swallowing	☐ Wheezing ☐ Indrawing / retractions ☐ Chest tightness	☐ Grunting ☐ Cyanosis ☐ Difficulty in Breathing
Circulatory System	☐ Measured hypotension (specify BP)		☐ Decreased central venous pulse		☐ Capillary refill time >3secs	☐ Tachycardia (specify rate)
CNS	☐ Loss of consciousness		☐ Distress	☐ Other(specify):		
GIT	☐ Diarrhoea	☐ Nausea		☐ Abdominal pain/cramp		☐ Vomiting
Diagnostic Criteria for anaphylaxis	☐ **Rapid onset of occurrence of above sign & symptoms**			☐ **Two or more systems are affected**		

PART 2: SUSPECTED PRODUCT AND EXPOSURE INFORMATION			
Date & Time of drug/vaccine administration: Date(dd/mm/yy) Time : am/pm			
Drug ☐ Oral ☐ Parenteral	☐ Vaccine	☐ Serum	☐1st dose ☐2nd dose ☐3rd dose ☐4th dose ☐Other
Generic name :	Trade name :		Dose (specify units,, mg, ml, mg/kg) and regimen
Batch/Lot number :	Expiry date :		For vaccine: VVM status I II III IV
If diluents used, specify batch number & expiry date:			
If parenteral medicine/vaccine: ☐ Single dose ☐ Multi dose			☐ Liquid ☐ Lyophilised
Route of administration: ☐ Oral ☐ IV ☐ IM ☐ SC ☐ ID ☐ Other(specify)			
Site of Administration: ☐ Deltoid ☐ Thigh ☐ Buttock ☐ Other (specify)			
Person who administered: ☐ Doctor ☐ Nurse ☐ PHI ☐ PHM ☐ Other (specify)			

Part 3: Management

Was Adrenaline administered? ☐ Yes ☐ No

If 'Yes', Route : ☐ IM ☐ SC ☐ IV ☐ Other (Specify) Dose:……ml

Place: ☐ Clinic ☐ Hospital ☐ Other (specify) Time:……am/pm

Person who administered adrenaline: ☐ Doctor ☐ Sister/Nurse ☐ PHI/PHM ☐ Other

Was a repeat dose of adrenaline given? ☐ Yes ☐ No	If 'Yes', describe
Were other medicines administered? ☐ Yes ☐ No	

Any other details concerning medicines/management (Including CPR)?

Part 4 Investigations (All relevant reports)

Blood for mast cell tryptase: ☐Yes ☐No If 'Yes' specify the time interval after event:

(Note:Serum Tryptase levels peak 60-90 min after the onset of anaphylaxis and persist to 6h. Blood should be taken between 1 and 2 after the initiation of symptoms)

Part 5: Outcome

☐Full recovery ☐Recovering ☐ Not recovered ☐ Recovered with sequelae ☐Unknown ☐ Death (date)

Specify details:

Highest impact of Adverse drug event/Adverse Event Following Immunization:

☐ Did not interfere with daily activities ☐ Interfered, but did not prevent daily activities ☐ Prevented daily activities

Part 6: Immunisation errors: Did this AEFI occur follow an incorrect immunization ☐Yes ☐No ☐Unknown

If yes choose all that apply: ☐Given outside recommended age group ☐Product expired ☐Wrong dose ☐Wrong vaccine g ☐ Incorrect route ☐ Other Give details

Part 7: Reporter Information

Name: Specialty: Institute:

Signature Date: Telephone:

Place of administration: ☐ Hospital ☐ MOH ☐ Clinic ☐ Private Hospital ☐ GP ☐ Other(specify)

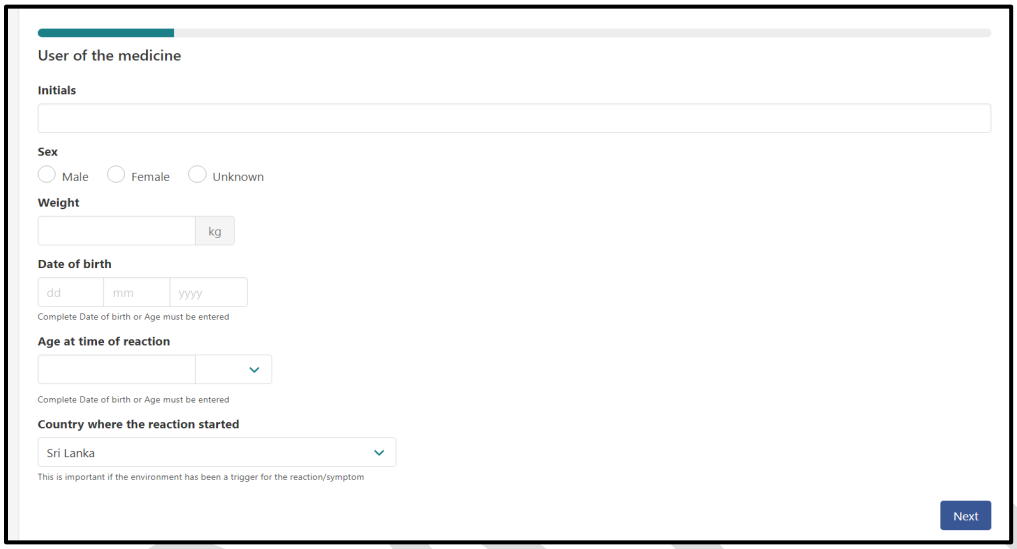
Send the filled form to Secretary, Safety of Medicines and Risk Evaluation Subcommittee (SAFRESC), National Medicines Regulatory Authority, 120, Norris Canal Road Colombo 10. Fax: +940112689704. Tel: +940112698896/7.
Email ……

Definition: Anaphylaxis is defined as a severe, life-threatening, generalized or systemic hypersensitivity reaction, characterized by rapidly developing life-threatening airway and/or breathing and/or circulation and or gastrointestinal problems usually (not always) associated with skin and mucosal changes.

APPENDIX: ADR Electronic Reporting

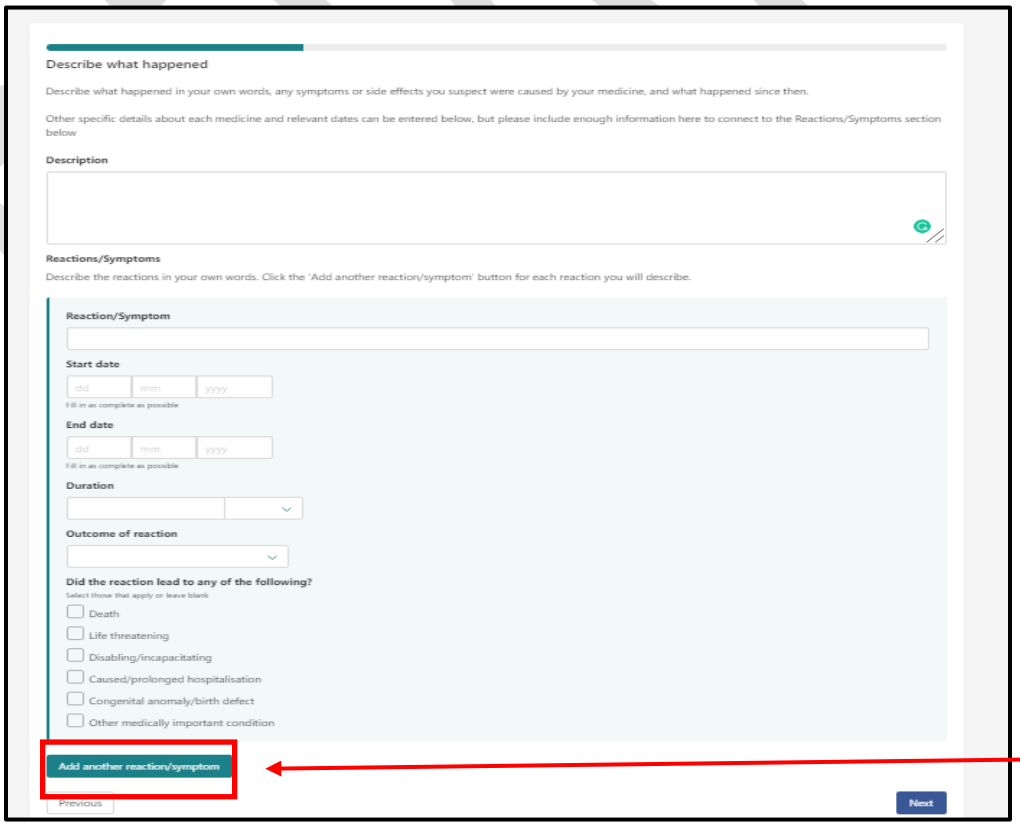
0

Select patient or Healthcare professional reporting



1

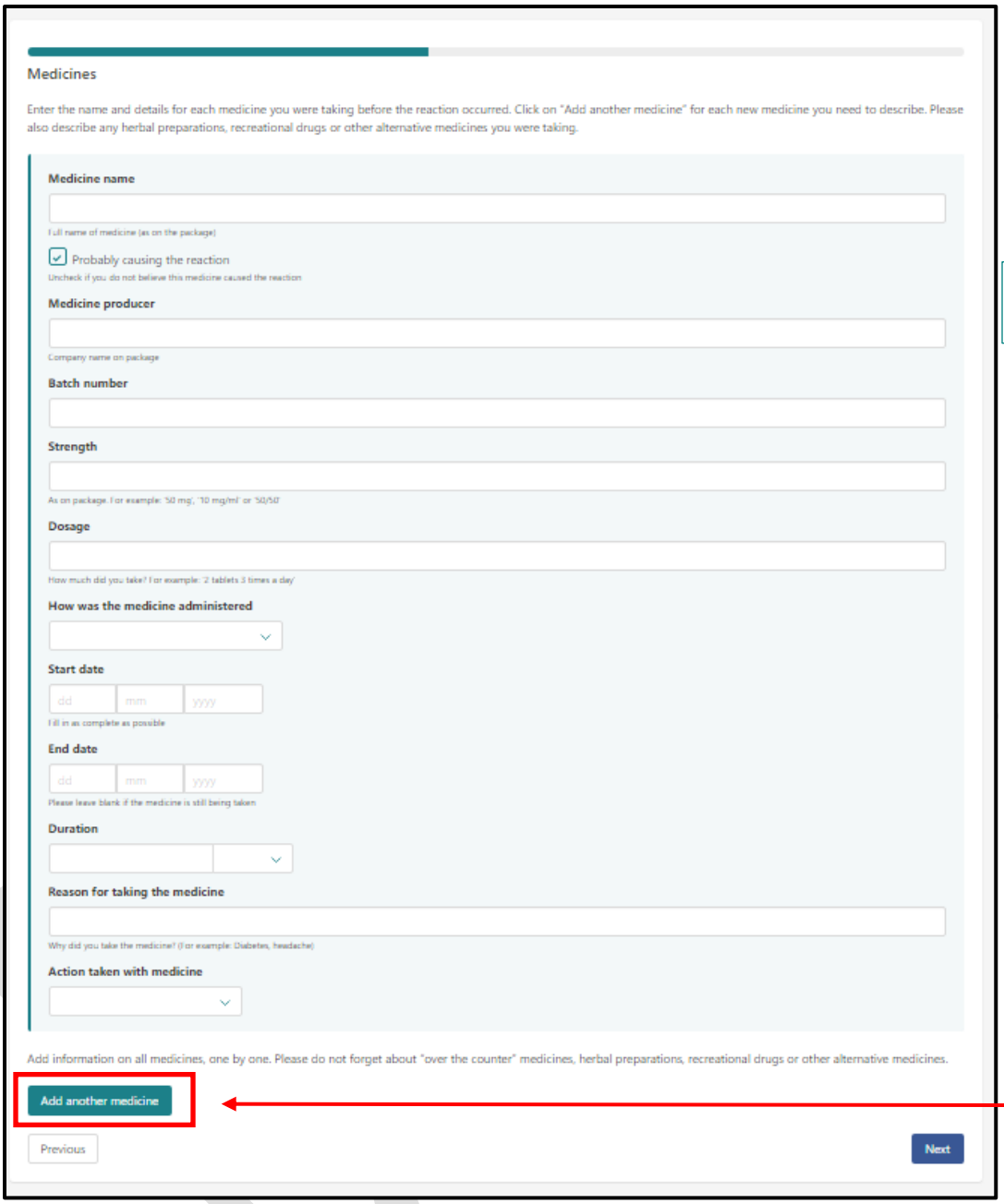
Enter Patient information



2

Enter in details the adverse reaction(s) and the circumstances leading to this harmful effect

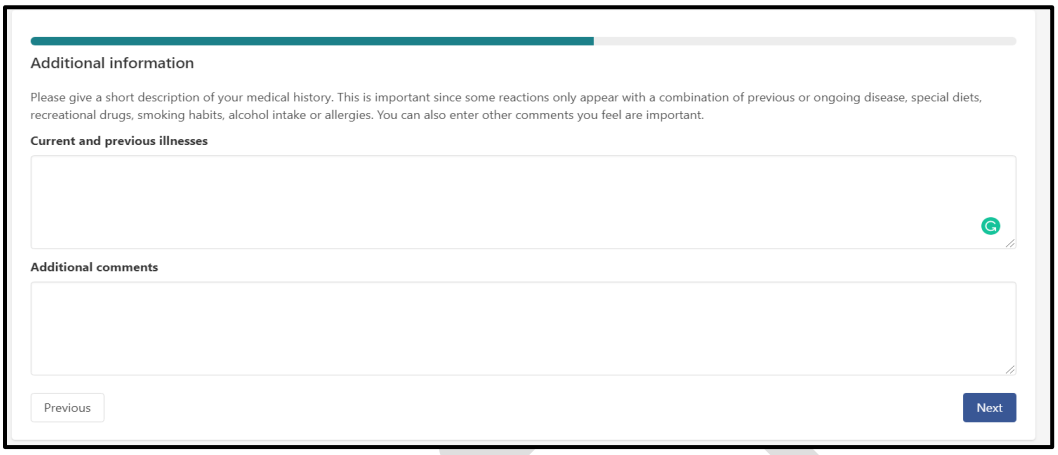
Press here if there are other adverse reactions for the same case



3

Enter details of Suspected medicine

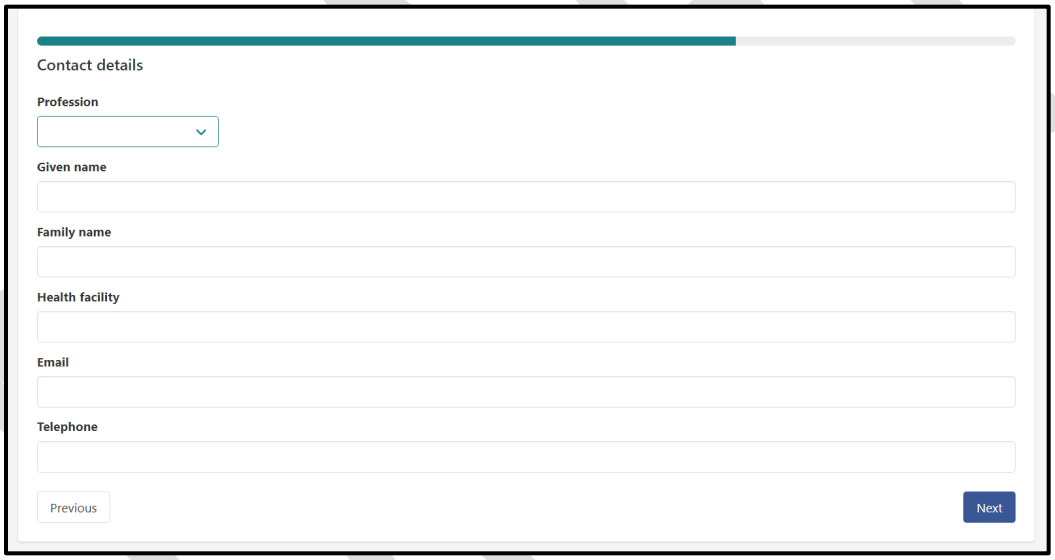
Press here if there are other suspected medicines for the same case



4

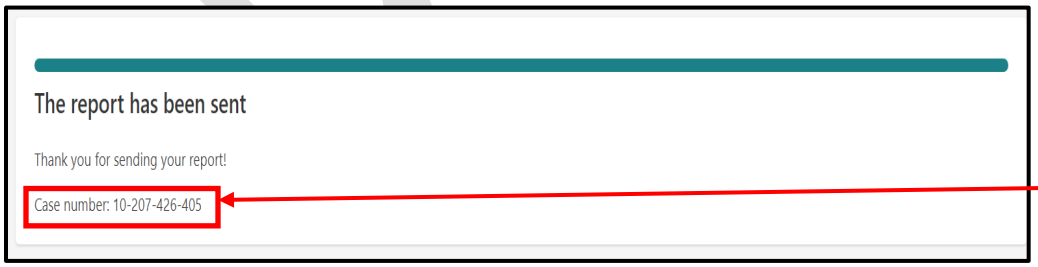
Enter description of medical history, special diets, recreational drugs, smoking habits, alcohol intake or allergies

Pregnancy status for women



5

Enter the reporter details



6

Save your report ID & use it when reporting follow-up information for the same report

References

- CIOMS Cumulative Pharmacovigilance Glossary: Version 1.0, Council for International Organizations of Medical Sciences, 2021
- Safety of Medicines, A guide to detecting and reporting adverse drug reactions. World Health Organization (WHO) Geneva 2002
- Safety monitoring of medical products: reporting system for the general public. World Health Organization (WHO), 2012
- Safety Monitoring of Medicinal Products, Guidelines for setting up and running a Pharmacovigilance Centre. the Uppsala Monitoring Centre (the UMC), WHO Collaborating Centre for International Drug Monitoring, 2000
- Guidance on adverse drug reactions, YellowCard, Medicines and Healthcare Products Regulatory Agency, UK