MALTA MEDICINES AUTHORITY

Adverse Drug Reaction Reporting & Pharmacovigilance Guidance Notes For Healthcare Professionals

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Post Licensing Directorate

TABLE OF CONTENTS

1. Introduction

The mission of the Malta Medicines Authority is to protect and enhance public health through the regulation of medicinal products and pharmaceutical activities.

The Malta Medicines Authority hereby also referred to as the Authority, is continually monitoring the safety of medicinal products which have a marketing authorisation in Malta. The national system for adverse drug reaction (ADR) reporting is key for the Authority to be able to carry out this function. Healthcare professionals (HCPs) play a pivotal role in supporting the Authority to carry out its mission to protect patient and public health by reporting ADRs which they may encounter in their daily practice. HCPs are in fact regarded as the main contributors for ADR reporting.

To this effect it is important that all HCPs are aware of the ADR reporting mechanisms which are in place in Malta so that they can report ADRs experienced by patients under their care.

Furthermore, HCPs are encouraged to understand the implications and effects of reporting of ADRs and how the ADR reporting system contributes to the overall regulatory system for medicines in Malta and the EU, as mandated by EU legislation.

2. Scope

This document aims to provide guidance and support to healthcare professionals in following the local ADR reporting process as established by the Malta Medicines Authority.

Furthermore, the scope of this document is to provide understanding into the importance of ADR reporting and the vital role that healthcare professionals play in protecting individual patient safety and the overall public health in Malta through the reporting of adverse drug reactions.

3. Abbreviations and Definitions

3.1 Abbreviations

AE:	Adverse Event
ADR:	Adverse Drug Reaction
DHPC:	Direct healthcare Professional Communication
EMA:	European Medicines Agency
EV:	EudraVigilance
HCP:	Healthcare Professional
ICSR:	Individual Case Safety Report
MA:	Marketing Authorisation
MAH:	Marketing Authorisation Holder
ME	Medication Error
PRAC:	Pharmacovigilance Risk assessment committee
RMP:	Risk Management Plan
RMM:	Risk Minimisation Measure
SmPC:	Summary of Product Characteristics
WHO:	World Health Organisation

3.2 Definitions

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 [Dir 2001/20/EC Art 2(m)].

An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (see GVP Annex IV, ICH-E2D Guideline).

Adverse reaction; synonyms: Adverse drug reaction (ADR), Suspected adverse (drug) reaction, Adverse effect, Undesirable effect

A response[a] to a medicinal product which is noxious and unintended [DIR 2001/83/EC Art 1(11)]

[a]*Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (see GVP Annex IV, ICH-E2A Guideline). An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated by the by healthcare professional or consumer as primary source, it meets the definition of an adverse reaction (see GVP Annex IV, ICH-E2D). Therefore, all spontaneous reports notified by healthcare professionals or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the primary source specifically state that they believe the event to be unrelated or that a*

causal relationship can be excluded. Adverse reactions may arise from use of the product within or outside[b] the terms of the marketing authorisation or from occupational exposure [DIR 2001/83/EC Art 101(1)]

[b]Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

Medication error

For the scope of this reporting system, medication errors that require reporting to the Malta Medicines Authority are those which are related to the use of medicinal products. The adopted definition of a medication error is: Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in control of the health-care professional, patient or consumer. (National Coordinating Council for Medication Error Reporting and Prevention[1]).

It may also be referred to as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient (see EMA-PRAC Good Practice Guide on Recording, Coding, Reporting and Assessment of Medication Errors).

Off-label use

Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation. Examples include the intentional use of a product in situations other than the ones described in the authorised product information, such as a different indication in terms of medical condition, a different group of patients (e.g. a different age group), a different route or method of administration or a different posology. The reference terms for off-label use are the terms of marketing authorisation in the country where the product is used.

Risk management system

A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions [DIR 2001/83/EC Art 1(28b)].

Risk minimisation measure; synonym: Risk minimisation activity

Interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur. These activities may consist of routine risk minimisation measures (the summary of product characteristics, the package leaflet, the labelling, the pack size, the legal status of the product, and its formulation) or additional risk minimisation measures (educational programmes, controlled access programmes, other additional risk minimisation measures). Risks related to use of a medicinal product Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment [DIR 2001/83/EC Art 1(28)].

[1] National Coordinating Council for Medication Error Reporting and Prevention. About Medication Errors. Accessed 14/05/2020. Available at: http://www.nccmerp.org/about-medication-errors.

Serious adverse reaction

An adverse reaction which results in death, is life-threatening[a], requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect [DIR 2001/83/EC Art 1(12)].

[a.]*Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see GVP Annex IV).*

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse (see GVP Annex IV)

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Unexpected adverse reaction

An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics [DIR 2001/83/EC Art 1(13)]. This includes class-related reactions which are mentioned in the summary of product characteristics (SmPC) but which are not specifically described as occurring with this product. For products authorised nationally, the relevant SmPC is that authorised by the competent authority in the Member State to whom the reaction is being reported. For centrally authorised products, the relevant SmPC is the SmPC authorised by the European Commission. During the time period between a CHMP opinion in favour of granting a marketing authorisation and the Commission decision granting the marketing authorisation, the relevant SmPC is the SmPC annexed to the CHMP opinion.

4. Background

Before medicinal products are marketed in Malta or in any European Member State, a marketing authorisation needs to be granted for that product.

The authorisation is granted based on an independent assessment of the product's quality safety and efficacy which is submitted by the manufacturer (or the company wishing to market the drug) to the competent authority. Prospective applicants derive premarketing efficacy and provisional safety data from pre-clinical / laboratory studies and clinical studies.

Premarketing studies of drugs, although well-designed and large enough to demonstrate efficacy and detect common adverse events, may not reliably detect an increased incidence of rare adverse events or events with significant latency. Apart from the latency of the occurrence of an adverse event, clinical trial conditions, do not necessarily reflect the real-

world use of the medicinal product once it is licensed. Variations in patient population (healthy patients vs those with confounding factors) or treatment conditions and the way the drug is used, may affect a drug's efficacy and result in new and unknown adverse reactions. The above and other limitations listed below are reasons why at the time of first marketing the safety profile is incomplete.

- Toxicological (pre-clinical) studies in animals are not always predictive of human safety
- Data from clinical trials is limited by the sample size and trial duration
- Exclusion criteria create a trial population which might in the end not be representative of the general population. Patients who are at a higher risk of experiencing adverse events are usually omitted from clinical trials. Such examples of these populations are the elderly or paediatric patients, and patients with chronic disease or terminal illness. Eliminating these populations from clinical trials will not give the full profile of a drug's safety and efficacy when this is in turn used in such patients.
- 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 and will only manifest after the drug is released for widespread use, maybe after several years.

For these reasons it is recognized that products require ongoing monitoring throughout their lifecycle as the widespread real-world use of a medicinal product gives a more complete safety profile over time. Regulators and marketing authorisation holders are thus legally bound to maintain vigilance for safety issues.

This process of continuous surveillance is known as **Pharmacovigilance**.

The impact of the occurrence of ADRs

The risk of ADRs is an inherent risk of all drug therapy and is modulated by several factors, including dose and frequency of administration, genotype, and pharmacokinetic characteristics within special populations, such as paediatric and geriatric patients and those with hepatic or renal impairment (Sultana J et al, 2013). Particularly within the geriatric patient population there are multiple co-morbidities with a higher chance of polypharmacy and altered physiological states e.g. renal or hepatic impairment which further increase the chances of drug interactions and resultant ADRs.

- In a study by Kumar et al published in 2019, it was estimated that 10% of hospital admissions were a result of patients experiencing ADRs. (Kumar et al, 2019)
- It was also stated that around 5-20% of these hospitalized patients are afflicted by a serious ADR. (Kumar et al, 2019)
- The more vulnerable population who experienced drug related ADRs were geriatric patients and those who received multiple medication. This was stated a separate literature review by Ayalew et al, published in 2019, where it was also concluded that there was a link between these patients and an increase in hospital admissions resulting from a drug related ADR. (Ayalew et al, 2019)
- Ayalew et al, estimated that drug related hospital admissions accounted for 15.4% of admissions, 2.7% of resulted in a fatality. (Ayalew et al, 2019)

- Another paper published in 2013, it was suggested that ADRs cause 2.5-10.6% of hospital admissions in Europe (Sultana J et al, 2013).

Sultana et al also revealed that between 2.1% and 5.2% of ADRs in children lead to hospitalization, and up to 39% of ADRs in paediatric patients can be life-threatening or fatal. (Sultana J et al, 2013)

Due to the high frequency and potentially serious consequences, ADRs may have a dramatic impact in clinical practice both from a clinical and economic perspective. Furthermore, ADRs may also have an effect on the patient's health-related quality of life (HR-QOL). (Rolfes et al, 2016)

5 Pharmacovigilance and the European Medicines Agency

The European Medicines Agency (EMA) is the regulatory body which oversees the scientific assessment and safety monitoring of medicines across the European Union (EU) and is responsible for the marketing authorisation of medicinal products which are placed on the European market. It shares in the Malta Medicines Authority's view to "foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health"[2] across the European market.

The Malta Medicines Authority is an active member of the EMA along with other medicines regulatory authorities of other EU Member States. Scientific and medical experts from these medicines regulatory authorities form part of the EMA's scientific committees and working parties with the purpose of creating a regulatory network for medicinal products. This collaboration brings together resources and allows the EMA to coordinate across the whole of the EU Member States thus regulating medicines more efficiently and effectively.

The function of the EMA (in terms of pharmacovigilance) is:

- Protect patients form harmful effects as a result of adverse reactions arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and
- Promote the safe and effective use of medicinal products, specifically by providing timely information about the safety of medicinal products to patients, healthcare professionals and the public[3].

This forms the basis of pharmacovigilance also known as drug safety monitoring and is intended to protect patient and public health. The spontaneous reporting of suspected adverse drug reactions is a core data-generating activity for medicinal products both locally and globally.

[2] European Medicines Agency. About us. Accessed 22/06/2020. Available at: https://www.ema.europa.eu/en/about-us/what-we-do.

[3] European Medicines Agency and Heads of Medicines Agencies. Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev 3). 2014; EMA/876333/2011. Accessed 22/06/2020. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf.

5.1 Legal basis for National ADR Reporting

The Malta Medicines Authority was set up in 2003, in order to implement provision in Maltese (Medicines Act of 2003) and European Laws (EU Directive 2001/83/EC). This included the setting up of a national pharmacovigilance system and a system for local ADR reporting.

National Pharmacovigilance was strengthened and rationalised with the national implementation of new EU Pharmacovigilance legislation published in 2010 (Directive 2010/84/EU) and 2012 (Directive 2012/26/EU) and Commission Implementing Regulation (EU) 520/2012. These new laws brought new tasks (e.g mandatory reporting of medication errors) into force and other existing task were further streamlined for both regulators and the pharmaceutical industry across the EU.

According to the Pharmacovigilance Regulations set out in S.L.458.35, doctors and healthcare professionals are duty bound to "immediately report to the Authority any suspected adverse reaction to a medicinal product in Malta"[4]

This system remains the primary means of data collection for post-authorisation safety surveillance of medicinal products in Malta.

5.2 Additional Monitoring

Following the implementation of the pharmacovigilance legislation in 2012, the concept of additional monitoring was introduced. Drugs requiring additional monitoring are marked with an inverted black triangle to denote this requirement. ▼

After authorisation, all medicinal products are subject to continuous monitoring. In the case of drugs which are newly approved or where limited data is available on their long-term use, it might be required to have additional monitoring in place. This does not mean that the medicine is unsafe but rather to boost reporting of adverse drug reactions and collect information early in the lifecycle of this product. Subsequently this will lead to safer and more effective use of these medicines when used in everyday medical practice.

6. How to report ADRs in Malta

All healthcare professionals are encouraged to report suspected Adverse Drug Reactions and Medication Errors. The ADR reporting form for HCPs may be downloaded from the MMA website.

HCPs may either:

- Fill in the form in ink and scan it, or fill it out in MS Word and then send to the Malta Medicines Authority via email on postlicensing.medicinesauthority@gov.mt

[4] Malta Government. Subsidiary Legislation 458.35 Pharmacovigilance (Amendment) Regulations. Laws of Malta. Legal Notice 352 of 2013; Government Gazette of Malta (No. 19,157): B 4266-B 4268.

OR

- Fill it in and send it via free postage to:

Malta Medicines Authority
Sir Temi Żammit Buildings
Malta LifeSciences Park
San Ġwann SĠN 3000

The paper ADR form may alternatively be sent to the marketing authorization holder (MAH) or its local representative, the address of whom is found on the medicine's package insert.

It is important not to send the form simultaneously to both parties so as to avoid creation of duplicate cases.

The MMA web portal provides direct reporting in a simplified manner for public consumer use. The ADR reporting form for HCPS is a more detailed and medically oriented form for use by HCPs.

The minimum criteria required for a valid ADR report are:

- An identifiable and contactable reporter (e.g. doctor, pharmacist, dentist)
- An identifiable patient (i.e. initials, age and gender)
- A suspected medicinal product
- A suspected adverse drug reaction

Healthcare professional are encouraged to read and follow the instructions for reporting adverse drug reactions and medication errors or other causative events found on page 3 of the ADR paper form.

Healthcare professionals should not be discouraged to forward the report if some ADR details are unknown or if in doubt about the causality i.e. whether the reaction observed was due to the drug or not. Reporters need only suspect that a medicinal product may have caused the adverse reaction. Even if in doubt, the ADR should always be reported.

HCPs should send in reports for:

- All suspected adverse drug reactions for medicines (prescription only medicine (POM) and over the counter (OTC) medicines), vaccines, biological medicines and blood products [include batch number for vaccines, biological medicines and blood products].
- All serious and expected and/or unexpected adverse drug reactions (see Section 3 for definition) i.e. irrespective of whether they are listed in the summary of product characteristics.
- All suspected adverse drug reactions for new medicines and medicines under additional monitoring.
- All suspected adverse drug reactions which occur in special populations including children, pregnant women and the elderly.
- All medication errors (ME) that cause harm (an actual Adverse Drug Reaction) or MEs that may have the potential to cause an ADR – this is also termed as a near miss.

- For reports with vaccines, biologicals, biosimilars, and blood products it is required to include the batch number in the ADR report.

The information submitted in ADR reports will be entered into a database in an anonymised and secure manner. All personal data will be treated as confidential in conformity with local and EU data protection laws and regulations.

HCPs are asked to fill in the ADR report form to the best of their ability, in clear and legible handwriting to minimise the risk of error when coding the information in the database. HCPs are kindly asked to avoid using ambiguous terms and abbreviations which can be open to various interpretations.

Having accurate and good quality reports will also enable better causality assessment and timely decisions on regulatory actions. This includes information on the ADR start/stop date, the suspect drug treatment start/stop date, the indication of the suspect drug, the patient outcome and the reaction's seriousness, as well as de-challenge and re-challenge information (if known) and pertinent patient details such as medical history and concomitant drugs.

Causality assessment refers to the evaluation of a connection between a drug treatment and the manifestation of an adverse event. It is used to assess whether a medicine is the cause of an observed adverse event or not

7 ADR Reporting Outcomes

7.1 Processing of ADR reports by the Malta Medicines Authority

Once an ADR report is received by the Authority it is validated against the 4 minimum criteria for a valid ADR report and if any further information is required, follow up information may be requested. As part of the ADR process, the report is assessed for causality and registered in an EU wide database known as Eudravigilance. This database receives suspected adverse reactions which arise from the use of medicinal products that have either been authorised for use or are being used in clinical trials within the European Economic Area (EEA). This data collection makes it possible to detect and analyse signals that provide further insights and detect safety issues with medicinal products. EudraVigilance is operated by the European Medicines Agency (EMA) on behalf of the European Union (EU) medicines regulatory network.

Through the identification of a potential safety issue a regulatory process is triggered. Such safety issues are investigated by specific EMA committees such as the Pharmacovigilance Risk Assessment Committee (PRAC), and recommendations are made on regulatory action if any. PRAC is the EMA committee responsible for assessing and monitoring the safety of human medicines. Regulatory action may include direct labelling change to the product information, or less frequently, the suspension or even withdrawal of a marketing authorisation where necessary.

The post marketing analysis of data may also prompt actions such as changes to a drug's therapeutic dose, changes to warnings in the product's summary of characteristics or patient information leaflet, changes to the indications for use of the drug, and changes to the prescribing status of a drug e.g. from over the counter to prescription only medicine.

Occasionally a drug may even be withdrawn from the market when its risks to patients outweigh the benefits of the drug's treatment.

7.2 Safety Communication

The Malta Medicines Authority publishes safety circulars to keep stakeholders informed of ongoing EMA reviews and their outcomes and of emerging safety issues with marketed medicinal products.

Archived safety circulars are available on the Malta Medicines Authority website here.

The Malta Medicines Authority also facilitates safety communication to stakeholders by collaborating with MAHs when they need to issue safety instructions on the use of a medicinal product via direct healthcare professional communications (DHPCs). If multiple MAHs need to send out a DHPC with the same product, the Malta Medicines issues a joint DHPC. This MMA initiative avoids information overload and alert fatigue since MAHs are grouped and one letter may be issued on their behalf.

Archived DHPCs are also available on the Malta Medicines Authority website here.

Safety circulars and direct healthcare professional communications (DHPCs) are ways of communicating regulatory actions with medicinal products to HCPs. Such regulatory actions may be the result of safety signals which arise from the collective reporting of adverse drug reactions.

Regulatory actions include changes to the risk minimisation measures (RMMs) (see Section 3 for definition) for a given drug product. PRAC communicates these RMMs to MAHs which are then bound to implement them accordingly. Changes include highlighting risks associated with a medicinal product and which require further information to characterise them or the issuing of educational materials for patients or HCPs in order to counter the occurrence of ADRs.

Archived RMMs are also available on the Malta Medicines Authority website here.

The reporting of adverse events has a positive impact on patient safety and the overall public health system. The timely identification of signals from ADR reports contribute to making medicines safer and preventing future harm to patients as well as allowing patient and HCPs to make better informed choices on the use of medicines

The role of HCPs in the reporting of ADRs is crucial to ensuring the proper function of this system.

8. Further guidance

Should you require any further guidance or detail on any of the above do not hesitate to contact the Malta Medicines Authority by phone on +356 2343 9000/9111 or by email on postlicensing.medicinesauthority@gov.mt

9. References

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10. Revision History

Issue No.	Effective date	Reason for revision
01	01.11.2004	Initial Publication
02	01.07.2008	Legal Notice 61 of 2006 replaces Legal Notice 22 of 2004 New website URL for downloading ADR for Minor changes in text
03	01.02.2010	No major changes observed
04	24.08.2020	Update as per QIF102-2019 such that the whole document was formatted in line with SOP QM010-05 Appendix 4 Template for Guidelines. MMA logo changed to the current MMA Logo/Branding and inclusion of a revision table. Content updated to reflect current PhV and GVP guidelines, as well as Malta Medicines Authority activities. Included Directives 2010/84/EU and 2012/26/EU and SL 450.35 in the legal basis of ADR reporting

		Added list of definitions Hyperlinks added throughout document. Updated list of references according to update within the content of the guidelines.

Signatures on file