TYPICAL POST-MARKETING PHARMACOVIGILANCE CASES IN THE MEDICAL GASES INDUSTRY

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Amendments from 203/18

Section	Change
General	Include Definitions aligned with the current definitions in the Pharmacovigilance Legislation
Appendix A	General review of the entire Appendix with more examples in the gas industry

Note: Technical changes from the previous edition are underlined

1. Introduction

EIGA members are supplying medicinal gases under marketing authorizations and CE certification respectively for which pharmacovigilance activities are legally required to be performed.

These gases have been used for many decades and there is a long experience of their safe use, however gases are used in many combinations and therefore the pharmacovigilance remains important.

This publication aims to harmonize the approach EIGA members have to these typical post-marketing cases. This is by classifying them in the same manner and therefore fulfilling the same reporting requirements to EU authorities if necessary. This list of typical post marketing cases is not exhaustive.

Additionally, the administration of medicinal gases requires the use of medical devices, and it is sometimes difficult to define incidents and differentiate between medical device vigilance and pharmacovigilance. This publication also gives guidance for these typical cases if they shall be classified as medical device vigilance and/or pharmacovigilance cases.

By having harmonized practices and a consistent approach throughout industry regarding the classification and reporting of typical post-marketing cases, this will help facilitate product safety profile follow up or updates for the benefit of patients.

2. Scope and purpose

2.1 Scope

This publication serves the interest of all who could in any way be associated or concerned with pharmacovigilance reporting as part of the post-marketing obligations of the marketing authorisation holders.

This publication is a guideline for classification of pharmacovigilance cases but, as required by the regulation, the final classification is provided by the qualified person responsible for pharmacovigilance (QPPV) with the assistance of a medically trained person in case the QPPV is not medically trained.

Local regulations shall take precedent.

2.2 Purpose

The purpose of this publication is to have a harmonised approach to the classification of post marketing cases.

3. Definitions

3.1 Publications terminology

3.1.1 Shall

Indicates that the procedure is mandatory. It is used wherever the criterion for conformance to specific recommendations allows no deviation.

3.1.2 Should

Indicates that a procedure is recommended.

3.1.3 May and need not

Indicate that the procedure is optional.

3.1.4 Will

Is used only to indicate the future, not a degree of requirement.

3.1.5 Can

Indicates a possibility or ability.

3.2 Technical definitions

3.2.1 Adverse event (AE)

Synonym: Adverse experience

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:

(Source: Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, Art 2(m) [1] [1].)

An adverse event can therefore be any unfavourable and unintended sign, for example 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.

3.2.2 Adverse reaction (AR)

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

Response to a medicinal product which is noxious and unintended.

(Source: Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use Art 1(11) [2]. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, see ICH- Clinical Safety Data Management, Definitions and Standards for Expedited Reporting E2A Annex IV [3]. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure, 2001/83/EC Art 101[2]. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.)

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 authorisation or from occupational exposure. Use outside the marketing authorisation includes off-label use, overdose, misuse, abuse and medication errors.

3.2.3 Individual case safety report (ICSR)

Format and content for the reporting of one or several suspected adverse reactions to a medicinal product that occur in a single patient at a specific point of time. [based on IR 520/2012 Art 25-29]

[1] References are shown by bracketed numbers and are listed in order of appearance in the reference section.

3.2.4 Minimum criteria for reporting

For the purpose of regulatory reporting, the minimum data elements for a suspected adverse reaction case are:

- an identifiable reporter,
- an identifiable patient,
- an adverse reaction and
- a suspect medicinal product

Without the four minimum data elements, this cannot be considered a valid ICSR and therefore, should not be reported to the Competent Authority.

3.2.5 Periodic safety update report (PSUR)

Format and content for providing an evaluation of the risk-benefit balance of a medicinal product for submission by the marketing authorisation holder at defined time points during the post-authorisation phase.

In the EU, periodic safety update reports should follow the format described in Module VII [4].

3.2.6 Pharmacovigilance Case

The commonly agreed definition of a pharmacovigilance case by the competent authorities is any of the following situations when associated with a designated medicinal product:

Individual reports of suspected adverse reactions

- **Adverse reaction**
- **Suspected adverse reactions related to quality defect or falsified medicinal products**
- **Suspected transmission via a medicinal product of an infectious agent**
- **Suspected ADR related to quality defect or falsified medicinal product**
- **Interaction:** reaction between two (or more) drugs or between a drug and a food, beverage, or supplement.

Individual reports of events or patterns of use, that should be monitored even when do not result in suspected adverse reactions (also called Special Situations)

- **Pregnancy (drug exposure during pregnancy):** Reports, where the embryo or foetus may have been exposed to medicinal products (either through maternal exposure and/or if the suspected medicinal product was taken by the father), should be followed-up in order to collect information on the outcome of the pregnancy and the development of the child after birth.
- **Breastfeeding (drug exposure during breastfeeding):** Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk should be submitted.
- **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.
- **Misuse:** Situations where a medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation.

- **Overdose:** Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorised product information.

- **Abuse:** Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects [DIR 2001/83/EC Art 1(16)].

- **Lack or loss of therapeutic efficacy:** Reports of lack of therapeutic efficacy should be collected and recorded when notified and followed-up if incomplete. They should normally not be submitted as ICSRs if there is no associated suspected adverse reaction, but they should be discussed in periodic safety update reports as applicable. In certain circumstances, reports of lack of therapeutic efficacy with no suspected adverse reactions may require to be submitted within a 15-day time frame.

- **Medication error:** An unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.

- **Accidental exposure, occupational exposure:** For the purpose of reporting cases of suspected adverse reactions, an exposure to a medicinal product as a result of one's professional or non-professional occupation.

- **Paediatric or Elderly population exposure:** The collection of safety information in the paediatric or elderly population is important

Some also include unexpected therapeutic benefits that are considered as a possible source of off-label use.

When there is a pharmacovigilance case that do not result in a suspected adverse reaction, it will be integrated and discussed in a periodic safety update report (PSUR).

If the case is associated with an adverse reaction, it might be subject to expedited reporting according to the local regulation. For some countries, the submission of non-serious case reports are mandatory, while for other countries only the submission of serious reports are required.

The administration of the drug can be associated with the use of devices, for example ventilator, wall outlet. In this situation, a medical device vigilance case should be considered for this separate device.

4. References

Unless otherwise stated the latest edition shall apply.

[1] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, Art 2(m) www.ema.europa.eu

[2] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use www.ema.europa.eu

[3] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Clinical Safety Data Management, Definitions and Standards for Expedited Reporting E2A, Annex IV www.ema.europa.eu

[4] Guideline on good pharmacovigilance practices (GVP) www.ema.europa.eu

Appendix 1 – Examples of Report Classification

Reported typical case	Pharmaco vigilance case	Medical device vigilance* impact	To be internally reported to the EU QPPV	External PSUR reporting	External expedited ICSR reporting	Rationale
Patient presenting burns while treated with medicinal gas (Burning caused by defect of medical device, directly associated with the medicinal gas treatment e.g. pressure regulator or cryogenic vessel portable unit, or VIPR even included as part of the speciality of the gas	YES	YES if it is a medical device failure and to report to the legal manufactu rer	YES	YES	YES	Side effect associated with a quality defect (GVP VI.C.2.2.4) [4]
Caregiver presenting burns. Burning of the caregiver while administering medicinal gas to the patient (Caused by rich oxygen environment combined with other sources for a fire) (e.g., high flow oxygen therapy in COVID)	YES	YES, if there was a failure of a medical device involved	YES	YES	YES	Suspected adverse reactions related to occupational exposure (GVP VI.C.6.2.3.3.)[4]
Patient presenting burns while treated with medicinal gas (Burning caused by patient e.g. smoking)	YES	NO	YES	YES	YES	Spontaneous reports (incorrect use of the product) (GVP VI.C.2.2.1) [4]
Fatal or other serious AR of patient during therapy with a medicinal gas including nitric oxide therapy (Gas reasonably possibly caused the fatal outcome or serious AR)	YES	NO	YES	YES	YES	Spontaneous reports (Serious adverse reactions) (GVP VI.C.2.2.1) [4]
Fatal or other serious AE of patient during hospitalization with a medicinal gas including nitric oxide therapy (The healthcare professional identified an issue with the delivery system of Nitric Oxide and confirmed the gas did not cause the AE)	YES	YES, if there was a failure of a medical device involved	YES	YES	YES	Special Requirement for Nitric Oxide The Competent Authorities requested the submission of all issues regarding the Delivery System of the medicinal gas even if there is no causal relationship between the gas and the AE.

Reported typical case	Pharmaco vigilance case	Medical device vigilance* impact	To be internally reported to the EU QPPV	External PSUR reporting	External expedited ICSR reporting	Rationale
Fatal or other serious AR of patient during HOMECARE therapy with medicinal OXYGEN	YES (unless it is clear gas did not cause the fatal or other serious AE)	YES, if there was a failure of a medical device involved	YES	YES	YES	Spontaneous reports (Serious adverse reactions) (GVP VI.C.2.2.1) [4]
Healthcare professional (or patient) injury coming from the package (Without quality defect, e.g. tripping, cylinder slipping)	NO	NO	NO	NO	NO	The medicinal product was not administered (GVP VI.A.1.1) [4]
Healthcare professional or patient injury coming from the package (excluding the valve) (With quality defect, e.g. breaking of handle)	NO	YES if it is a medical device failure of a separated device	YES	NO	NO	
Off-Label use (e.g. COVID Patient treated with Nitric Oxide)	YES	NO	YES	YES	YES If adverse reaction	Off-Label Use (GVP VI.A.1.2.) [4]
Pregnancy or breastfeeding (e.g. Patient received medicinal gas oxygen during baby delivery)	YES	NO	YES	YES	YES If adverse reaction	Use of a medicinal product during pregnancy or breastfeeding (GVP VI.B.6.1. and VI.C.6.2.3.1.) [4]
Overdose (e.g. Patient on NO treatment received 80 ppm instead of the recommended dose in the authorised product information)	YES	YES, if it is due to medical device defect	YES	YES	YES If adverse reaction	Overdose (GVP VI.B.6.3. and VI.C.6.2.3.3.) [4] Side effect associated with a quality defect (GVP VI.C.2.2.4) [4]
Lack of therapeutic efficacy (e.g. Leakage empty cylinder, blocked valve, device failure)	YES	YES, if it is due to separate medical device defect	YES	YES	YES If adverse reaction	Lack of therapeutic efficacy (GVP VI.B.6.4.) [4]
Occupational and accidental exposure (e.g. A healthcare professional (HCP) tried to open a valve on the side of the cylinder which caused a nitrous oxide/oxygen mixture leak, exposing the HCP to the gas).	YES	YES, if it is due to a separate medical device defect	YES	YES	YES If adverse reaction	Occupational and accidental exposure (GVP VI.B.6.3. and VI.C.6.2.3.3.) [4]

Reported typical case	Pharmaco vigilance case	Medical device vigilance* impact	To be internally reported to the EU QPPV	External PSUR reporting	External expedited ICSR reporting	Rationale
Medication Error (e.g. Hospitalized patient needed to be transferred to another department under some medicinal gas. Due to a confusion with the colour of cylinders and regulator the administered medicinal gas was different)	YES	NO	YES	YES	YES If adverse reaction	Medication Error (GVP VI.B.6.3. and VI.C.6.2.3.3.) [4]
Abuse (e.g. Patient started using the medicinal gas nitrous oxide for recreational use)	YES	NO	YES	YES	YES If adverse reaction	Abuse (GVP VI.B.6.3. and VI.C.6.2.3.3.) [4]
Misuse (e.g. Patient with chronic respiratory insufficiency was prescribed medicinal gas oxygen 2 litres/min, however patient intentionally increases the flow to 4 litres/min because he/she decided that the oxygen flow was not enough to improve oxygen saturation)	YES	NO	YES	YES	YES If adverse reaction	Misuse (GVP VI.B.6.3. and VI.C.6.2.3.3.) [4]
Patient complains about bad smell of the gas (Not associated with an adverse reaction)	NO	NO	NO	NO	NO	Quality complaint
Patient complains about bad smell of the gas (Associated with an adverse reaction, like headache)	YES	NO	YES	YES	YES	Spontaneous report (GVP VI C.2.2.1) [4]

*Usually a pharmacovigilance notification does not require a second notification as a medical device vigilance case unless specified by the national authorities.