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Patient Health Protection

Guide on the interpretation of spontaneous case reports of suspected adverse reactions to medicines

Introduction

This document provides guidance on how to interpret information on spontaneously reported cases of suspected adverse reactions to medicines. It also gives an overview of current pharmacovigilance systems put in place to monitor the safety of medicinal products.

Definition of adverse reaction

An adverse reaction is a response to a medicinal product which is noxious and unintended [1]. Commonly, this is referred to as a “side effect”.

Key considerations

- Case reports of suspected adverse reactions alone are rarely sufficient to confirm that a certain effect in a patient has been caused by a specific medicine.
- The fact that a suspected adverse reaction has been reported does not necessarily mean that the medicine has caused the observed effect as this could have also been caused by the disease being treated, a new disease the patient developed, or by another medicine that the patient is taking. Case reports need therefore to be assessed by an expert.
- A single case report should be seen as a piece of a jigsaw puzzle, where further data are usually needed to complete the picture. These include data from worldwide spontaneous case reports, clinical trials and epidemiological studies.
- The number of case reports for a particular medicine or suspected adverse reaction does not only depend on the real frequency of the adverse reaction but also on the extent and conditions of use of the medicine, the nature of the reaction as well as public awareness. Therefore comparing numbers of case reports between medicines may give a misleading picture of their safety profiles.



Monitoring the safety of medicines

No medicine is completely free of risks. All medicines, including vaccines, are authorised on the basis that the likely benefit outweighs the potential harm.

To come to this conclusion for a marketing authorisation, data from clinical trials conducted during the development of a medicine are assessed. However, adverse reactions which occur rarely or after a long time may become apparent only once the product is used in a wider population. In addition, the benefits and risks of a medicine used in normal healthcare where patients may have more than one disease or treatment can usually not be studied before authorisation. Therefore, after a medicine is placed on the market, its use in the wider population requires continuous monitoring. The evaluation of the benefit-risk balance of a medicine may change over time with the increase in knowledge gained from its use by many people and the availability of new therapeutic alternatives.

The monitoring of the safety of medicines is called pharmacovigilance, which has been defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem [2].

Reporting of suspected adverse reactions

The reporting of cases of suspected adverse reactions seen in individual patients outside clinical trials is a fundamental process underpinning pharmacovigilance. This spontaneous reporting is triggered by a suspicion of a healthcare professional or a patient that observed signs and symptoms could have been caused by a medicine.

Reporting adverse reactions is usually part of the codes of conduct for healthcare professionals. Competent authorities in Member States encourage healthcare professionals to report their suspicions and observations of adverse reactions to medicines through national reporting systems.

Patients are also prompted by the information in the package leaflets to talk to their healthcare professional about any adverse experience associated with their treatment, and in some Member States national reporting systems also exist for patients. New European legislation will require systems for reporting by patients across the whole European Union (EU).

The national reporting systems ensure that reported cases are brought to the attention of the competent authority and the marketing authorisation holder (i.e. the company marketing the medicine).

Most important is the spontaneous reporting of **serious** or **previously unknown** suspected adverse reactions. An adverse reaction is considered serious if it

- is life-threatening or has a fatal outcome;
- requires in-patient hospitalisation or extended existing hospitalisation;
- results in persistent or significant disability or incapacity; or
- is a congenital anomaly/birth defect.

Spontaneous reporting for newly marketed medicinal products is also a priority, given the limited experience with such medicine.

Sources and assessment of safety signals

New information on a possible risk is called a signal [3]. Signals of possible so far unknown adverse reactions or changes in the severity, characteristics or frequency of known reactions may arise from various data sources, including spontaneous reports, clinical trials and epidemiological studies (including registry studies). Once a signal has been identified, investigations are necessary to refute or confirm and quantify the risk. These investigations consider the likelihood that the medicine caused or contributed to the effect, try to identify risk factors and estimate the frequency of occurrence. Assessment of signals takes into account possible errors in the use of the medicine or manufacturing defects.

Possible regulatory actions after assessment

Following the assessment of a safety signal, a decision on the most appropriate regulatory action is taken by the competent authorities. The decision may include:

- a request for (an) additional study(ies) from the marketing authorisation holder to gain further evidence on the matter;
- a change to the product information¹ to promote the safe use of the product, e.g. by changing the dose recommendations or including new restrictions on the use of the medicine in a certain patient population;
- the suspension of the marketing of a medicine while investigations are ongoing;
- the withdrawal of the marketing authorisation for the medicine.

The regulatory action is communicated to healthcare professionals, patients and the general public through established channels and timelines reflect the degree of urgency. The established channels include publications on websites, information provided to patient and healthcare professional organisations and the media as well as direct mailing of healthcare professionals.

Public access to case reports

Reporting systems at national and EU level comply with data protection legislation, and therefore the data contained in the databases of national competent authorities and EudraVigilance are anonymised appropriately and are not available in full to the public. EudraVigilance [4] is a database maintained by the European Medicines Agency which brings together all serious adverse reactions reported within the EU as well as reports from outside the EU submitted by marketing authorisation holders in accordance with EU legislation. A EudraVigilance Access Policy is in place on public access to these data without jeopardising data privacy. Implementation of this policy is ongoing.

Anonymised case reports or a report on a series of anonymised observed cases are also sometimes published in the scientific literature by healthcare professionals.

Further information

Details on the processes for the conduct of pharmacovigilance in the EU can be found in the guidelines contained in Volume 9A of the Rules Governing Medicinal Products in the EU [5].

¹ The product information consists of the summary of product characteristics, the package leaflet for the patient and the label on the packaging.

References

- [1] Article 1 of Directive 2001/83/EC as amended by Directive 2010/84/EU of the European Parliament and the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Brussels: Official Journal of the European Union; 2010: pp L 348/74- L348/99. Available under http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm.
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- [3] CIOMS Working Group VIII. Practical aspects of signal detection in pharmacovigilance. Geneva: Council for International Organizations of Medical Sciences; 2010.
- [4] European Medicines Agency. EudraVigilance. Available under <http://eudravigilance.emea.europa.eu/highres.htm>.
- [5] European Commission. Volume 9A of the Rules Governing Medicinal Products in the European Union. Available under http://ec.europa.eu/health/documents/eudralex/vol-9/index_en.htm.