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Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use

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1. Introduction

This document sets out guidance on the collection, verification and presentation and decoding procedures of adverse event/reaction reports arising from clinical trials on medicinal products for human use.

2 Legal Basis

Article 18 of Directive 2001/20/EC requires the Commission to publish detailed guidance on the collection, verification and presentation of adverse event/reaction reports, together with decoding procedures for unexpected serious adverse reactions. The present guideline fulfils the obligations laid down in this Article.

3 Scope

This guideline applies to all clinical trials on medicinal products for human use conducted within the EU, with the exception of non-interventional trials. It describes the reporting requirements and procedures, including timelines, for different levels of adverse event arising from such trials. In addition it sets out the responsibilities of the various interested parties. It applies to all investigational medicinal products for human use, independently from their marketing authorisation status in any Member State.

4 Definitions

The definitions of Directive 2001/20/EC are applicable. These are further supplemented by terms from the following Community guidelines where they are related to collection, verification decoding and presentation of adverse reaction reports arising from clinical trials: Note for Guidance on Good Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95), Note for Guidance on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (CPMP/ICH/287/95 modification) and Note for Guidance on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (CPMP/ICH/288/95).

5 Responsibilities

5.1 Investigator

The responsibilities of the investigator in relation to the notification of adverse events are set out in Directive 2001/20/EC.

a) The investigator is responsible for reporting all serious adverse events immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report is to be followed by detailed, written reports. The subjects are to be identified in the immediate and follow-up reports by unique code numbers.

b) Adverse events and/or laboratory abnormalities identified in the protocol as critical to the evaluation of safety must be reported to the sponsor by the investigator according to the reporting requirements within the time periods specified in the protocol.

c) The investigator must supply the sponsor and the ethics committee with any additional requested further information in relation to the death of any study subject.

5.2 Sponsor

5.2.1 General remarks

The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

The sponsor should notify promptly all concerned investigator(s), ethics committees and competent authority/ies of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC .

Quality control and quality assurance standards are to be observed in every step of the case report documentation, collection, validation, evaluation, storage and reporting. Quality control and quality assurance should be ensured by the sponsor who should devise and implement the necessary structures and procedures.

5.2.2 Adverse events (AEs)

The sponsors are to keep detailed records of all adverse events reported to them by the investigator/s. All records are to be submitted on request of the competent authority of the member states in whose territory the clinical trial is being conducted.

5.2.3 Suspected unexpected serious adverse reactions (SUSARs)

(a) The sponsor is to ensure that all relevant information about SUSARs that are fatal or life-threatening is appropriately recorded and reported as soon as possible to the concerned competent authorities and to the concerned ethics committee(s) in all Member States. Such reports shall be received no later than seven calendar days after first knowledge of such a case by the sponsor. The relevant follow-up information is subsequently communicated within an additional eight calendar days.

(b) All other SUSARs are to be reported to the competent authorities and to the ethics committee(s) concerned as soon as possible within a maximum of fifteen calendar days of first knowledge by the sponsor.

(c) The sponsor must also inform about SUSARs all investigators concerned by the investigational medicinal product.

5.2.4 Listing of all suspected serious adverse reactions (SSARs) and report of the subject's safety

Once a year throughout the clinical trial or immediately on request, the sponsor is to provide the competent authority of the Member States in whose territory the clinical trial is being conducted and the ethics committee of this Member States with a listing of all individual case reports on suspected serious adverse reactions which have occurred over this period and an overview report of the subject´s safety. The report should discuss the implications of the findings presented.

The anniversary date for annual reports is one year after the first authorisation date by a competent authority in a Member State of a clinical trial involving the tested investigational medicinal product.

6 Case Report Processing

6.1 Initial individual case safety reports

Information for the final description and evaluation of a SUSAR case report may not be available within the required time frames for reporting. For regulatory purposes, initial reports should be submitted within the time limits as long as minimum criteria are met. Completeness of initial case reports should be validated according to these criteria.

Every initial SUSAR report must contain the following information:

- an unequivocal clinical trial identification
  (Eudract number for the clinical trial involved or where the trial is not being conducted in the EU by the sponsor clinical trial code)
- an unequivocal report identification
  (sponsor´s case identification number)
- suspected investigational medicinal product(s)
- an identifiable study subject/patient
  (initials of the names or the case´s code in the clinical trial, birth date or age, gender, country)
- an event or outcome that can be identified as a SUSAR.
- an identifiable reporting source

This is the minimum information which allows the case to be entered into the European database. It will then be available for signal generation and facilitate the evaluation by competent authorities of cases related to a clinical trial. Every effort should be made by each concerned investigator and the sponsor to obtain complete information where appropriate.

6.2 Follow-up individual case safety reports

In a case where complete information is not available at the time of initial reporting, the sponsor should provide further information promptly in the form of follow-up reports to improve the quality and validity of the data available and facilitate causality assessment. Follow-up information should be actively sought and submitted promptly. This may be from the initial reporter or other available sources. In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

If considered appropriate, copies of the most important and relevant original documents (e.g. hospital discharge forms, specialist reports, laboratory tests, prescriptions and post-mortem reports etc.) may be transmitted.

6.3 Identification and management of follow-up and duplicate individual case safety reports

Each individual case report should contain enough information to allow identification of duplicate reports. After identification follow-up reports and duplicates should be flagged as such. No report should be deleted from the European database because of duplication, but identification of follow-up reports or duplicate reports should lead to the creation of an identifiable “master report”, combining information from all reports, to give assurance that it can be considered as one case only.

6.4 Evaluation of individual case safety reports

Case report processing concerns evaluation of data in individual cases, identification of individual cases requiring specific handling, recognition and processing of alerts, and any other data processing of aggregated cases.
Each individual SUSAR should be evaluated primarily by the investigator and secondarily by the sponsor. This includes the evaluation of the causality between the investigational medicinal product(s) and the suspected adverse reaction(s), its seriousness, and expectedness. All methods used to evaluate these parameters should be appropriately documented.
Evaluators should have adequate knowledge in the pharmacology and toxicology of the investigational medicinal product and in the differential diagnoses likely to be associated with adverse reactions. They should be trained in the relevant methodology. Such training should, whenever possible, be appropriately verified by the sponsor.

6.4.1 Suspectedness - causality

A suspected adverse drug reaction is by definition possibly related to the medicinal product which caused it. Therefore, for each adverse event an assessment should be made of the probability that it was caused by an investigational medicinal product. The expression reasonable causal relationship means that there is evidence of reasonable arguments which might suggest a causal relationship.

Currently there is no standard international nomenclature for a classification of the degree of causality for a suggested causal relationship between an adverse event and an investigational medicinal product.

All cases judged by either the reporting physician (investigator) or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as suspected adverse reactions. The classification which is given by the physician (investigator) should not be overruled by the sponsor. If the sponsor disagrees with the causality classification of the investigator a comment from the sponsor should be provided. Both, the opinion of the investigator and the sponsor should always appear on the declaration form.

6.4.2 Seriousness

A serious adverse event and a serious adverse reaction occurring in the context of a clinical trial are defined in Directive 2001/20/EC. The Community guideline CPMP/ICH/377/95 provides additional clarification of what is understood by “seriousness”.

6.4.3 Expectedness

An unexpected adverse reaction occurring in the context of a clinical trial is defined in Directive 2001/20/EC. The Community guideline CPMP/ICH/377/95 provides additional clarification of what is understood by “expectedness”.

The expectedness of an adverse reaction may be product or product-use specific, and separate investigator´s brochures may be used accordingly in different clinical trials. However, such documents should cover all information on adverse drug reactions that applies to all affected product presentations and uses. When relevant, separate discussions of pertinent product-specific or use-specific safety information should also be included in the investigator´s brochure. It is recommended that any adverse drug reaction that qualifies for special attention and is observed with one product dosage form or use should be cross-referenced in the investigator´s brochures for all dosage forms and uses during the clinical development of an investigational medicinal product.

Reports which add significant information on specificity or severity or evolution of a known, already documented serious adverse reaction, also constitute unexpected events. Severity should take into account the population and the disease concerned by the trial. For example, a reaction more specific or more serious than described in the source document should be considered ”unexpected”.

The following source documents or circumstances will be used to determine whether an adverse reaction is expected; they are to be appended to the request for the ethics committee opinion and the competent authority authorisation :

6.4.3.1 In the case of investigational medicinal products not yet approved for marketing authorisation in any Member State

The actual version of the sponsors Investigator´s Brochure will serve as the source document.

6.4.3.2 In the case of investigational medicinal products approved for marketing authorisation in some, but not in all Member States in which the clinical trial is performed

The actual version of the sponsor’s Investigator´s Brochure should provide all adverse drug reactions given in the current SPC of the Member State/s supplemented by any additional adverse reactions which may be suspected. This may be dependent upon any special treatment conditions foreseen in the trial protocol. This Investigator´s Brochure will serve as the source document.

6.4.3.3 In the case of investigational medicinal products approved for marketing authorisation in all member states in which the clinical trial is performed and used in the clinical trial according to the approved conditions

In the case of multiple national marketing authorisations with multiple SPCs the source document is the investigator´s brochure taking into account the SPCs available in the Member States concerned and proposing a sponsor core safety information.

6.4.3.4 In the case of investigational medicinal products approved for marketing authorisation by centralised procedure in the European Union

The European SPC is the source document.

6.5 Listings of all suspected serious adverse reactions (SSARs) and report of the subject´s safety

According to Directive 2001/820/EC, once a year through the clinical trial the sponsor must provide the Member States in whose territory the clinical trial is being conducted and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred in the clinical trial over this period and a report of the subjects safety according to. The time frame should be determined by the anniversary date for the clinical trials with the tested investigational medicinal product.

6.5.1 Listings

Listings of suspected serious adverse reactions occurring in the clinical trial should be validated by the sponsor. The sponsor should consider the completeness of the reports, exclusion of duplicates, the minimum reporting criteria, the nature of the adverse reactions and the terminology used.

Comments should be made if relevant (e.g. causality assessment if the sponsor disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect medicinal product(s); dechallenge/rechallenge results if available). Usually there should be one listing, but separate listings may be made if appropriate, for example for different formulations, indications, or routes of administration, or adverse reaction listings for different target organs/systems, if such differentiation facilitates the presentation and interpretation of the data.

The following headings should usually be included in the line listing.

a) Clinical trial identification (EU trial protocol number, national trial protocol number if applicable)
b) sponsor´s listing reference number
c) case reference number in the sponsor´s adverse reaction database
d) case reference number in the clinical trial
e) country in which case occurred
f) age and sex
g) daily dose of suspected investigational medicinal, and when relevant, dosage form or route
h) Date of onset of the reaction. If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible (may go in Comments section).
i) Dates of treatment. If not available, best estimate of treatment duration.
j) Description of reaction as reported, and when necessary as interpreted by the sponsor (English translation when necessary).
k) Subject outcome (at case level) (e.g. resolved, fatal, improved, sequelae, unknown). This field does not refer to the criteria used to define a "serious" ADR. It should indicate the consequences of the reaction(s) for the subject, using the worst of the different outcomes for multiple reactions.
l) comments, if relevant (e.g. causality assessment if the sponsor disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge / rechallenge results if available)
m) blinding code broken (yes, no, not applicable, results)

6.5.2 Aggregate summary tabulations

Aggregate summary tabulations for each of the line listings of the clinical trial should be presented. These tabulations ordinarily contain more terms than subjects. It would be useful to have separate columns for SUSARs and SSARs. When the number of cases is very small, a narrative description should be more suitable.

A concise safety analysis of the trial should be finally given together with other relevant information (i.e. Drug Safety Monitoring Board conclusions).

6.5.3 Report of the subject's safety

The sponsor should provide a critical analysis and opinion on the risk/benefit profile of the tested investigational medicinal product taking in account all the safety information available.

Observed risks should be specially evaluated with regard to relevant information about:

a) relation with dose, duration, time course of the treatment
b) reversibility
c) evidence of previously unidentified toxicity in the trial subjects
d) increased frequency of toxicity
e) overdose and its treatment
f) drug interactions or other cofactors of risks
g) any specific safety issues relating to the treatment of special subject groups, such as the elderly, the very young or any other at risk group.
h) positive and negative experiences during pregnancy or lactation
i) drug abuse
j) special risks which may be caused by the special methodology of the clinical study

Supporting results of other nonclinical or clinical studies or experiences with the investigational medicinal product that are likely to affect the subjects safety shall be described in a clearly separate part of the report.

7 Adverse Reaction Reporting

The rapid and secure exchange of information about adverse reactions observed in clinical trials is of great importance to guarantee the protection of volunteers and patients participating in clinical trials. To minimise preparation time and costs of processing submitted reports and to achieve a high quality of submission content and format between involved parties it is it necessary to move away from a paper based reporting system towards electronic transmission of the information to be reported in accordance with Directive 2001/20/EC.

7.1 Expedited Reporting

The purpose of expedited reporting is to make regulators, investigators and other appropriate parties aware of new, important information on serious unexpected adverse reactions. Sponsors are therefore required to report only SUSARs in an expedited manner, using the definitions and standards for expedited reporting in the Community guideline CPMP/ICH/377/95. The key data elements for inclusion in expedited reports of serious adverse reactions are given at Annex 2.

All reports of SUSARs which occur in a clinical trial within or outside the EU should be transmitted to the Member State(s), in which a trial on the tested investigational medicinal product concerned is taking place.

Expedited reporting of reactions which are serious but expected is not usually required. It is also inappropriate for events that are considered unrelated to the study product, whether the event is unexpected or not. The same applies for non-serious adverse reactions whether unexpected or not.

7.2 Non-Expedited Reporting

7.2.1 Annual listing of all suspected serious adverse reactions in clinical trials and the subject´s safety report

The anniversary date for annual reports is one year after the first authorisation date by a competent authority in the EU of the first clinical trial with the tested investigational medicinal product.

7.2.2 Listing of adverse events at the request of the competent authority

Serious adverse events that are notified to the sponsor should be submitted at the request of the competent authority in whose territory the trial is being conducted.

If the competent authority does not request another format, this listing may be submitted on form B at Annex 5.

7.3 Managing blinded treatment cases

Treatment codes should always be broken before a serious unexpected adverse reaction is reported to a competent authority. The time frame for each single case report begins at the time point when the individual code is broken. As a rule, single case codes in blinded studies should be broken only by an independent pharmacovigilance representative or by an independent safety committee according to the trial protocol. The unblinding of single cases by investigators in the course of a clinical trial should be reserved for emergency situations only.

7.4 Adverse reactions associated with an active comparator or placebo

It is the sponsor´s responsibility to report all serious and unexpected adverse reactions associated with a comparator product in a clinical trial. However, the sponsor may decide whether they should be reported directly to the competent authority and/or to the marketing authorisation holder/manufacturer.

SUSARs with placebo will not usually satisfy the criteria for severe adverse reactions. However, if they occur these cases should be reported according to the reporting requirements for investigational medicinal products.

7.5 Reports from High Morbidity and High Mortality Diseases

In clinical trials in high morbidity and/or high mortality disease states, sponsors are encouraged to appoint an Independent Safety Data Monitoring Committee which would decode the trialist's reports, construct the group sequential analysis and report directly to the competent authority at agreed time intervals. Arrangements for establishing and reporting these adverse reactions should be set out in the protocol. Procedures for this form of reporting can be discussed with the competent authority. Individual case reports may be presented by body system in the format of a line listing such as appears in Annex 5.

7.6 Other Observations

The availability of information that might materially influence the benefit-risk assessment of a medicinal product or that would be sufficient to suggest changes to the way a medicinal product was administered or to the way a clinical investigation was conducted may prompt the sponsor to make an expedited report. Appropriate medical and scientific judgement should be applied in each case.

Examples of such information include:

- for an expected serious ADR, an increase in the rate of occurrence which is judged to be clinically important,
- a significant hazard to the subject population such as lack of efficacy with a investigational medicinal product used in treating a life-threatening disease,
- serious and unexpected adverse events which,

  (i) occur during trials conducted in third countries with the tested investigational medicinal product,

  (ii) are identified by spontaneous reporting or publication,

  (iii) are transmitted by another regulatory authority,
- serious adverse events which could potentially be due to the research conditions [eg : investigations performed (exercise ECG), wash-out period (eg : suicide attempt occurring

during a wash-out period of an antidepressive agent)], and, generally, any new information that could lead to reassessment (in an unfavourable way) of the benefit/risk ratio of the clinical trial research**.**

7.7 SUSAR reporting forms

Sponsors are encouraged to send reports of SUSARs occurring in a clinical trial performed in the EU or elsewhere electronically wherever possible. It is important that certain information/data elements be included in the SUSAR report. The listing in Annex 4 addresses these key elements. If electronic reporting is impossible reports may be submitted by sponsors in written form using the form in Annex 4.

7.8 Subject confidentiality

The highest possible standards of confidentiality must always be maintained and any relevant national legislation on data protection must be followed. The subject's right to confidentiality is paramount. The subject's identity in the report forms should be codified and only authorised persons should have access to identifiable personal details if data verification procedures demand inspection of such details. Identifiable personal details must always be kept confidential.

Annex 1: Additional guidance on Definitions and Abbreviations

The definitions are given in italics and are taken from Directive 2001/20/EC. Additional guidance is given beneath each definition.

Adverse event (AE): *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.*

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product

Adverse reaction of an investigational medicinal product (AR): *all untoward and unintended responses to an investigational medicinal product related to any dose administered.*

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship, i.e. the relationship cannot be ruled out.

Serious adverse event or serious adverse reaction (SAE , SAR) : *any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.*

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgement should be exercised in deciding whether a reaction is serious in other situations. Important adverse reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered as serious.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations for example, drug abuse, drug dependency, severe effect without hospitalisation.

Suspected adverse reaction (SAR):

All cases judged by either the reporting investigator (physician) or the sponsor as having a 'reasonable' suspected causal relationship to the investigational medicinal product qualify as adverse drug reactions. The expression 'reasonable causal relationship' is meant to convey in general that there is evidence or argument to suggest that a causal relationship with the use of the investigational medicinal product cannot be ruled out.

Unexpected adverse reaction (UAR): *an adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).*

When the outcome of the adverse reaction is not consistent with the applicable product information, this adverse reaction should be considered as unexpected .

Additional clarifications

Marketing Authorisation holder (Sponsor) core safety information: The core data sheet prepared by the marketing authorisation holder of a marketed product represents the core safety information for the product when it is used as an investigational medicinal product in a clinical trial, except when the local regulatory authority specifically requires a modification.

Anniversary date for annual reports: The anniversary date for annual reports is one year after the first authorisation date by a competent authority in a member state of a clinical trial involving the test product.

Concerned Ethics Committee: Ethics Committee which gave the favourable opinion for the clinical trial in the Member State concerned.

Concerned Competent authority and Concerned Member State: Competent authority and Member State in whose territory the clinical trial is being performed.

Annex 2: SUMMARY OF REPORTING REQUIREMENTS FOR ADVERSE REACTION REPORTING BY SPONSORS

Expedited reporting

- individual cases of **serious unexpected reactions** as expedited (15 calendar days) reports.

- fatal or life-threatening unexpected reactions within 7 days, followed by as complete a report as possible within 8 additional calendar days

- all cases must be judged by the reporting health professional or the sponsor as having a suspected causal relationship to the study drug.
- for written reporting use the reporting form shown in appendix 5
- reports should be sent to concerned competent authority and concerned Ethics Committee

Non-expedited reporting

- details of all adverse events reported during the trial should be recorded and reported to the competent authority concerned at its request
- all serious suspected adverse reactions should be provided in an annual listing to the competent authority in whose territory the trial is being conducted and to the Ethics Committee(s) concerned
- a report of the subject´s safety should be transmitted annually to the competent authority concerned and to the Ethics Committee concerned

The Member States' contact points for reports of adverse reactions occurring in clinical trials on human medicinal products are as follows:

Member state	**Contact point**

What constitutes a valid report

The following are the minimum requirements for expediting an initial report:

- clinical trial identification
  (Eudract number or clinical trial code where the clinical trial is not being conducted in the EU by the sponsor)
- report identification
  (sponsor´s case report reference number)
- an event or outcome that can be identified as a suspected unexpected serious adverse reaction
- suspected investigational medicinal product
  (product name)
- an identifiable study subject/patient
- an identifiable reporting source

All cases should be **unblinded** before submission. Cases involving placebo do not meet the criteria for expedited reporting. But if they occur, then such cases should be reported if they are serious events that are likely to influence the overall conduct of the trial as described in section 7.6.

Reports with insufficient information may be returned to the company for completion and resubmission.

Annex 3 Key data elements for inclusion in expedited reports of unexpected serious adverse drug reactions

[Taken from the Community guideline on Good Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) supplemented by key data elements necessary for the clinical trial identification]

1. Clinical Trial Identification

1.1 Clinical Trial Identification/Authorisation) Number of the Competent Authority
1.2 Clinical Trial Identification Code of the Sponsor

2. Study subject's/patient's details

- Sponsor´s Case Identification Number
  (this number must be the same for the initial and follow-up reports on the same case)
- Initials (of names if allowed)
- Gender
- Age and/or date of birth
- Weight
- Height

3. Suspected Medicinal Product(s)

- Brand name as reported
- International non-proprietary name (INN)
- Batch number
- Indication(s) for which suspect medicinal product was prescribed or tested
- Dosage form and strength
- Daily dose and regimen (specify units e.g. mg, ml, mg/kg)
- Route of administration
- Starting date and time of day
- Stopping date and time, or duration of treatment

4. Other treatments

- For concomitant medicinal products (including non-prescription/OTC medicinal products) and non-medicinal product therapies, provide the same information as for the suspected product.

5. Details of suspected Adverse Drug Reaction(s)

- Full description of reaction(s) including body site and severity, as well as the criterion (or criteria)for regarding the report as serious should be given. In addition to a description of the reported signs and symptoms, whenever possible attempts should be made to establish a specific diagnosis for the reaction.
- Start date (and time) of onset of reaction
- Stop date (and time) or duration of reaction
- Dechallenge and rechallenge information
- Setting (eg hospital, out-patient clinic, home, nursing home)
- **Outcome:** information on recovery and any sequelae; what specific tests and/or treatment may have been required and their results; for a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction should be provided. Any autopsy or other post-mortem findings (including a coroner's report) should also be provided when available. Other information: anything relevant to facilitate assessment of

the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations.

6. Details on Reporter of event (Suspected ADR)

- Name
- Address
- Telephone number
- Profession (speciality)

6 Administrative and Sponsor/Company details

- Source of report: from a clinical trial (provide details), other
- Date event report was first received by sponsor/manufacturer
- Country in which event occurred
- Type of report filed to authorities: initial or follow-up (first, second, etc)
- Name and address of sponsor/manufacturer/company
- Name, address, telephone number, and fax number of contact person in reporting company or institution
- Identifying regulatory code or number for marketing authorisation dossier or clinical investigation process for the suspected product (for example IND or CTX number, NDA number)

Annex 4 REPORT ON SERIOUS UNEXPECTED ADVERSE REACTIONS

1. Report only serious unexpected adverse reactions.
2. Record all other drugs, including self-medication, taken in the previous 3 months. With congenital abnormalities, record all drugs taken during pregnancy.
3. Please do not be deterred from reporting because some details are not known.
4. Has this subject's reaction been reported to us previously [YES/NO].
5. To show the clinical trial approval under which the drug reaction occurred please tick the relevant box and provide identifying number and protocol number.
6. 'Country' refers to the country where the reaction occurred.

EU TRIAL PROTOCOL REGISTRATION NO: ☐☐☐☐☐☐☐☐☐☐☐☐

NATIONAL TRIAL PROTOCOL REGISTRATION NO: ☐☐☐☐☐☐☐☐☐☐☐☐ (Number assigned by the Competent Authority of the Member State to which this adverse reaction is notified)

CAS-IND NO. OF SPONSOR | **DATE SPONSOR RECEIVED** | **TRIAL PROTOCOL CODE OF SPONSOR**

CAS-IND No. OF COMPETENT AUTHORITY | ***DATE RECEIVED***

(Sponsor signs in, if it is a follow-up report.)

COUNTRY IN WHICH ADR OCCURRED | **TYPE OF REPORT** | **(INITIAL/FOLLOW-UP)** | **SUBJECT´S REFERENCE** | ***NO. IN THE TRIAL, GIVEN BY SPONSOR***

SUBJECT´s FIRST NAME (INITIALS) | **LAST NAME** (INITIALS) | **SEX** | **DATE OF BIRTH OR AGE** | **WEIGHT** (KG) | **HEIGHT** (CMS)

NAME AND ADDRESS OF THE SPONSOR	NAME AND ADDRESS OF CLINICAL INVESTIGATOR	**NAME OF SUBJECT´S OWN DOCTOR**

Subjects reference number (to allow for linkage with other reports for same subject.) (Please give record number for hospital patients)

DRUGS, VACCINES (Including Batch No) DEVICES, MATERIALS etc. (Please give Brand Name if known)	**ROUTE**	**DAILY DOSE**	**DATE STARTED**	**DATE ENDED**	**INDICATION**
SUSPECTED DRUG (inclusive Dosage Form and Strength)					
OTHER DRUGS (Inclusive non-prescription/OTC medicinal products; please state if no other drug given).					

SUSPECTED REACTIONS	**STARTED**	**ENDED**	**OUTCOME (eg fatal, recovered)**

ADDITIONAL NOTES

Investigator´s Causality Classification | **Signed** (Reporting Investigator) | **Date**

Sponsor´s Causality Classification | **Signed** (Reporting Representative of Sponsor) | **Date**

Annex 5

Form A: Line Listing of Serious Suspected Adverse Reactions, Listing of all Serious Suspected Adverse Reactions which occured in all Clinical Trials which are also performed in the Member State

EU Trial Protocol Registration Number	☐☐☐☐☐☐☐☐
National Trial Protocol Registration Number	☐☐☐☐☐☐☐☐ (Number assigned by the Competent Authority of the Member State which will receive this Line Listing)
Sponsor's Line Listing Reference Number	☐☐☐☐☐☐☐☐☐☐

Subject Ref No in the Clinical Trial	Reaction Description	Country	Source	Age	Sex	Total Dose mg/day route and form	Date of onset of reaction[1]	Dates of treatment[2]	Outcome[3]	Comment[4]

[1] If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible (may go in Comments section).
[2] If not available, best estimate of treatment duration.
[3] e.g. resolved, fatal, improved, sequelae, unknown. This field does not refer to the criteria used to define a "serious" ADR. It should indicate the consequences of the reaction(s) for the subject, using the worst of the different outcomes for multiple reactions.
[4] e.g. causality assessment if the manufacturer disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge/rechallenge results if available.

Date:

Form B: Line Listing of Serious Suspected Adverse Reactions
Summary of all Serious Suspected Adverse Reactions which are observed in all Clinical Trials performed with the Test Product

Time period coverd by this report:
Investigational Medicinal Products:
Test product::
Comparator/s:

EU Trial Proto-col Regi-stration No.	Subject Ref No in the Clinical Trial	Reaction Description	Coun-try	Source	Age	Sex	Total Dose mg/day route and form	Date of onset of reaction[5]	Dates of treatment[6]	Outcome[7]	Comment[8]

[5] If not available, best estimate of time to onset from therapy initiation. For an ADR known to occur after cessation of therapy, estimate of time lag if possible (may go in Comments section).
[6] If not available, best estimate of treatment duration.
[7] e.g. resolved, fatal, improved, sequelae, unknown. This field does not refer to the criteria used to define a "serious" ADR. It should indicate the consequences of the reaction(s) for the subject, using the worst of the different outcomes for multiple reactions.
[8] e.g. causality assessment if the manufacturer disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect drug(s); dechallenge/rechallenge results if available.

Date: