



**Guidance Notes for Pharmaceutical Companies on  
Pharmacovigilance Obligations &  
Adverse Drug Reaction (ADR) Reporting Requirements  
for Medicinal Products for Human Use**

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**Issue 3**

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**1. Introduction**

In line with the Medicines Act 2003, pharmaceutical companies have specific obligations with regards to pharmacovigilance. The information contained in this document is directed to pharmaceutical companies that hold marketing authorisations and to applicants for marketing authorisations for medicinal products on the Maltese market. It gives background information on the pharmacovigilance obligations of potential applicants and marketing authorisation holders (MAHs). The legal framework for these obligations is described in the following legislation:

1. Medicines Act 2003
2. Pharmacovigilance Regulations 2006 (L.N. 61 of 2006)
3. Codified Directive 2001/83/EC
4. Directive 2001/20/EC
5. Clinical Trials Regulations 2004 (L.N. 490 of 2004)

Throughout this document, frequent reference is made to the Notice to Marketing Authorisation Holders (NtMAHs) included in Volume 9A of the Rules Governing Medicinal Products in the European Union (Pharmacovigilance for Medicinal Products for Human Use), which provides further detail on the collection, verification and presentation of ADR reports, Periodic Safety Update Reports (PSURs), Post-Authorisation Safety Studies (PASS) and ongoing benefit/risk evaluation. It is essential that these European guidelines are referred to and thoroughly consulted. Additional information can also be found in Volume 2A of the Rules Governing Medicinal Products in the European Union (Procedures for Marketing Authorisation). Volumes 2A and 9A of the Rules Governing Medicinal Products in the European Union can be downloaded from this website:

[http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm)

## **2. Roles and Responsibilities of Pharmaceutical Companies**

In accordance with Article 5 of Pharmacovigilance Regulations 2006, the MAH should have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance. The person responsible for pharmacovigilance will have the following responsibilities:

- To establish and maintain a pharmacovigilance system to ensure that any information about suspected adverse drug reactions reported to the personnel of the company and to medical representatives, is collected and collated in order to be made available to the Medicines Authority;
- To prepare necessary reports in accordance with the NtMAH;
- To reply fully and promptly to any request made by the Medicines Authority, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned;
- To provide any other information to the Medicines Authority in relation to the evaluation of the risk-benefit balance of a medicinal product, including appropriate information on PASS.

According to Article 6 of Pharmacovigilance Regulations 2006, the MAH shall be legally obliged to carry out the following activities:

- To maintain detailed records of all suspected adverse drug reactions occurring either in Member States or in a third country;
- To immediately record and report to the Medicines Authority all suspected serious ADRs (both expected and unexpected) occurring in Malta not later than 15 calendar days from receiving the information;
- To immediately record and report to the Medicines Authority all suspected serious and unexpected ADRs occurring in the territory of a third country (i.e. outside the EU/EEA) not later than 15 calendar days from receiving the information;

- To report serious ADRs occurring outside Malta but within other EU/EEA Member States to the competent authority of the Member State in whose territory the adverse reaction occurred within 15 calendar days following receipt;
- To ensure that the Reference Member State (RMS) has access to any suspected serious ADRs which have occurred within the EU/EEA in the case of medicinal products authorised via mutual recognition or decentralised procedures;
- To submit a record of all ADRs including a scientific evaluation of the benefits and risks afforded by the medicinal product in the form of PSURs in accordance with the agreed timetable, as described in the NtMAH. (For further information on PSURs refer to section 5 of these guidance notes.)

In accordance with Volume 9A of the Rules Governing Medicinal Products in the European Union, MAHs shall use internationally agreed medical terminology e.g. MedDRA for the reporting of ADRs. Further information on MedDRA can be obtained from the following website: [www.meddransso.com](http://www.meddransso.com)

### **3. ADR Reports**

The following requirements apply to **all** medicinal products for human use available in Malta, including products that have a marketing authorisation, products that do not have a marketing authorisation but have a licence to be placed on the market (qualified licence) and unlicensed medicinal products.

For further information on medicinal products that do not have a marketing authorisation but have a licence to be placed on the market (qualified licence), refer to Article 4 of Medicines (Marketing Authorisation) Regulations, 2007 (Legal Notice 324 of 2007), which can be downloaded from the following website:

<http://www.doi.gov.mt/EN/legalnotices/2007>

Unlicensed medicinal products for human use include products which:

- (i) are obtained from a hospital or a commercial supplier with a “specials” manufacturing licence;
- (ii) have a licence in another country but are being imported and used on a “named patient basis”.

DH Circular 137/2004 concerning the “Guidelines Governing the Use of Medicinal Products for Human Use without a Marketing Authorisation” should be consulted for further information on unlicensed medicinal products. The circular can be accessed at the following website: <http://www.sahha.gov.mt/pages.aspx>

In keeping with the Pharmacovigilance Regulations, 2006, the MAH should submit the following ADR reports to the Medicines Authority:

- (i) all suspected serious ADRs (expected and unexpected) occurring in Malta;
- (ii) all suspected serious and unexpected ADRs occurring in the territory of a third country (i.e. outside the EU/EEA, e.g. Switzerland, USA, Canada, Malaysia).

All the above reports should be sent on an expedited basis i.e. within 15 calendar days of first notification of any personnel within the company.

Serious ADRs occurring outside Malta but within other EU/EEA Member States do **not** require reporting to the Medicines Authority. They should, nevertheless, be reported within 15 calendar days following receipt to the competent authority of the Member State in whose territory the adverse reaction occurred. They should also be available for review upon request by the Medicines Authority.

The flowchart in Appendix 1 summarises the requirements for serious ADR reporting.

ADR reports from pharmaceutical companies may be submitted to the Medicines Authority either in paper format or in electronic format via EudraVigilance.

**(i) Paper format**

ADR reports being submitted in paper format can be presented on the company's own reporting form or, preferably, on a CIOMS form (Appendix 2) which can be downloaded from the following website: <http://www.cioms.ch/cioms.pdf>

ADR reports submitted in paper format should be accompanied by a cover letter clearly identifying them as cases occurring in Malta or in a third country (non-EU/EEA). All correspondence should include the brand name(s) and marketing authorization number(s) of the suspect product(s) and the type of report (i.e. initial or follow-up). The company should additionally inform the Medicines Authority if it is aware that Maltese reports have been separately reported to the Medicines Authority by a healthcare professional. This information would help facilitate identification of duplicate cases.

Reports should be addressed to:

Pharmacovigilance Section,  
Post-Licensing Directorate,  
Medicines Authority,  
203 level 3 Rue D'Argens,  
Gzira. GZR 1368.

Malta.

Tel: (+356) 23439000

Fax: (+356) 23439161

Email address: [postlicensing.mru@gov.mt](mailto:postlicensing.mru@gov.mt)

**(ii) Electronic format**

ADRs may be submitted electronically via EudraVigilance as Individual Case Safety Reports (ICSRs) in E2B(M) format. Information regarding electronic report submission via this European data-processing network and ICSR database system can be obtained from the following website:

<http://eudravigilance.emea.europa.eu/human/>

ICSRs concerning suspected serious adverse reactions originating in Malta should be transmitted electronically to the Medicines Authority with the message receiver identifier ADM. Parallel reporting of ICSRs in paper format would not be required. ICSRs concerning suspected serious and unexpected adverse reactions occurring in the territory of a third country (non-EU/EEA) should be submitted to EudraVigilance only with the message receiver identifier EVHUMAN. It is worth noting that ICSR submission to EVHUMAN encompasses reporting to the Agency and to all the Member State authorities (including the Medicines Authority) in line with the requirements of Directive 2001/83/EC and Pharmacovigilance Regulations 2006.

The Medicines Authority also accepts reports sent via EudraLink. EudraLink is a highly secure email system designed by the EMEA for the transmission of confidential scientific data. Pharmaceutical companies can apply for a EudraLink account by contacting the EudraLink helpdesk at the EMEA on telephone number +44 20 74 18 8680 or on the following email address: [eudralink@emea.eu.int](mailto:eudralink@emea.eu.int)

The responsibility of ADR reports submitted via email and not using EudraLink rests with the pharmaceutical company.

#### **4. Criteria for a Valid ADR Report**

The following minimum criteria are required for an ADR report to be considered valid:

1. An identifiable reporter (profession, name, contact details)
2. Patient identifier i.e. initials or age or date of birth or sex
3. Name of the suspected medicinal product(s)
4. Details of the suspected reaction(s)

It should be stressed that these are the **minimum** criteria for a valid ADR report and that ADR reports should provide as much information as possible in order to facilitate evaluation by the Medicines Authority. The Medicines Authority may request further information regarding individual ADR reports, as appropriate.

## 5. Periodic Safety Update Reports (PSURs)

In keeping with their legal requirements, MAHs should submit PSURs in accordance with an agreed timetable defined at the time of granting of a **full** Marketing Authorisation for a medicinal product.

Until a full Marketing Authorisation is granted, companies are **not** required to submit PSURs on a regular basis to the Medicines Authority. However, if the Medicines Authority requests a company to submit an interim PSUR, such a PSUR should be submitted to the Medicines Authority immediately upon request.

The format and content for a PSUR is outlined in the NtMAH, together with details of reporting requirements and circumstances where the PSUR cycle may be considered for amendment. The requirements for submission of PSURs are also specified in national legislation. Article 6(3) of Pharmacovigilance Regulations, 2006 (L.N. 61 of 2006), stipulates the following cycle for submission of PSURs:

- Immediately upon request
- 6-monthly after authorisation and until the placing on the market
- 6-monthly during the first 2 years after initial placing on the market
- Annually for the subsequent 2 years
- Thereafter at 3-yearly intervals

For those products that were initially granted a provisional Marketing Authorisation (PMA) prior to a full Marketing Authorisation, PSURs should be submitted by the MAH to the Medicines Authority in accordance with the MAH's established cycle of PSUR submission for the authorised medicinal products. Therefore, it will not be necessary to start a new six-monthly reporting cycle for products following the granting of a full Marketing Authorisation by the Medicines Authority.

For those products that were **not** initially granted a PMA, it will be necessary to start a new six-monthly reporting cycle for products following the granting of a full Marketing Authorisation by the Medicines Authority.

The following are the Medicines Authority's submission requirements for PSURs:

1. For products authorised via the national procedure, 1 electronic copy on CD-ROM accompanied by a relevant cover letter should be submitted;
2. For products authorised via the centralised, mutual recognition and decentralised procedures, 1 electronic copy on CD-ROM accompanied by a relevant cover letter should be submitted if Malta is a Concerned Member State (CMS);
3. For products authorised via the centralised, mutual recognition and decentralised procedures, 1 paper copy and 1 electronic copy on CD-ROM should be submitted if Malta is Rapporteur, Co-Rapporteur or Reference Member State (RMS).

The Medicines Authority's requirements for PSUR submission, and the relevant postage contact details are further outlined in Appendix 3.

## **6. Variations**

Prior to marketing, the numbers of patients exposed to a medicinal product are extremely limited and the full safety profile of a product only becomes known when it is used in large numbers of patients over long periods of time. As a result of new information, changes to the product information will be required. Such changes may be initiated by the MAH or requested by the Medicines Authority and require the MAH to submit a variation application to the Medicines Authority to amend the marketing authorisation documents. For further guidance on the regulations governing variations and their respective submission requirements consult the following website:  
<http://www.medicinesauthority.gov.mt/psvariations.htm>

## 7. Clinical Trials and ADR Reporting

The legal obligations of the sponsors of clinical trials are specified in Directive 2001/20/EC and the Clinical Trials Regulations 2004 (Legal Notice 490 of 2004). Further guidance on the requirements of sponsors and investigators is outlined in the “Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use” issued by the European Commission. This guidance can be obtained from the following website:

[http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

The Medicines Authority only requires expedited reporting of reactions arising from clinical trials conducted in Malta and from multi-centre clinical trials which also include Maltese centres. The requirements for clinical trial sponsors are as follows:

- To keep detailed records of all adverse events, and submit them upon request to the Medicines Authority and to the other competent regulatory authorities in whose territory the clinical trial is being conducted.
- To report all fatal or life-threatening Suspected Unexpected Serious Adverse Reactions (SUSARs) as soon as possible to the Medicines Authority, to the other competent regulatory authorities in whose territory the clinical trial is being conducted, and to the Health Ethics Committee in Malta. Such fatal or life-threatening SUSARs should be reported not later than 7 calendar days after knowledge by the sponsor of such a case. Relevant follow-up information should be subsequently communicated within an additional 8 calendar days.
- To report all other SUSARs to the Medicines Authority, to the other competent regulatory authorities in whose territory the clinical trial is being conducted, and to the Health Ethics Committee in Malta, not later than 15 calendar days of first knowledge by the sponsor.
- To provide the Medicines Authority, the other competent regulatory authorities in whose territory the clinical trial is being conducted, and the Health Ethics Committee, with an annual listing of all suspected serious adverse reactions and a corresponding report on the safety of the subjects participating in the clinical trial.

The Medicines Authority does **not** require:

- reporting of ADRs arising from clinical trials conducted outside Malta and which do not involve Maltese centres.
- reporting of SUSARs arising from foreign clinical trials which involve products authorised in Malta.

SUSAR reports may be submitted to the Medicines Authority either in paper format or in electronic format via EudraVigilance.

**(i) Paper format**

SUSAR reports being submitted in paper format can be presented on the company's own reporting form or, preferably, on a CIOMS form which can be downloaded from the following website: <http://www.cioms.ch/cioms.pdf>

SUSAR reports together with a cover letter which clearly identifies them as clinical trial cases, should be addressed to the Pharmacovigilance Section within the Post-Licensing Directorate using the contact details as given under Section 3 of these Guidance Notes.

**(ii) Electronic format**

SUSARs may be submitted electronically via EudraVigilance in E2B(M) format. Information regarding the testing of such electronic submission can be obtained from the website: <http://eudravigilance.emea.europa.eu/human>

SUSARs arising from clinical trials conducted in Malta and from multi-centre clinical trials which include Maltese centres, should be submitted electronically by the sponsor to the EudraVigilance Clinical Trial Module (EVCTM) using message receiver identifier EVCTMPROD. It is worth noting that SUSAR submission to EVCTM encompasses reporting to the Agency and to all the concerned Member State authorities (including the Medicines Authority) as per the requirements of Directive 2001/20/EC.

## **8. Further information**

Further information can be obtained from the document titled “Frequently Asked Questions (FAQs) by Pharmaceutical Companies regarding Pharmacovigilance Obligations & Adverse Drug Reaction (ADR) Reporting Requirements” also available on the Pharmacovigilance Section of the Medicines Authority website at:

<http://www.medicinesauthority.gov.mt/phvigilance.htm>

In case of additional queries, the staff of the Pharmacovigilance Section may be contacted at:

Pharmacovigilance Section,  
Post-Licensing Directorate,  
Medicines Authority,  
203, level 3 Rue D’Argens,  
Gzira. GZR 1368.

Malta.

Tel: (+356) 23439000

Fax: (+356) 23439161

Email address: [postlicensing.mru@gov.mt](mailto:postlicensing.mru@gov.mt)

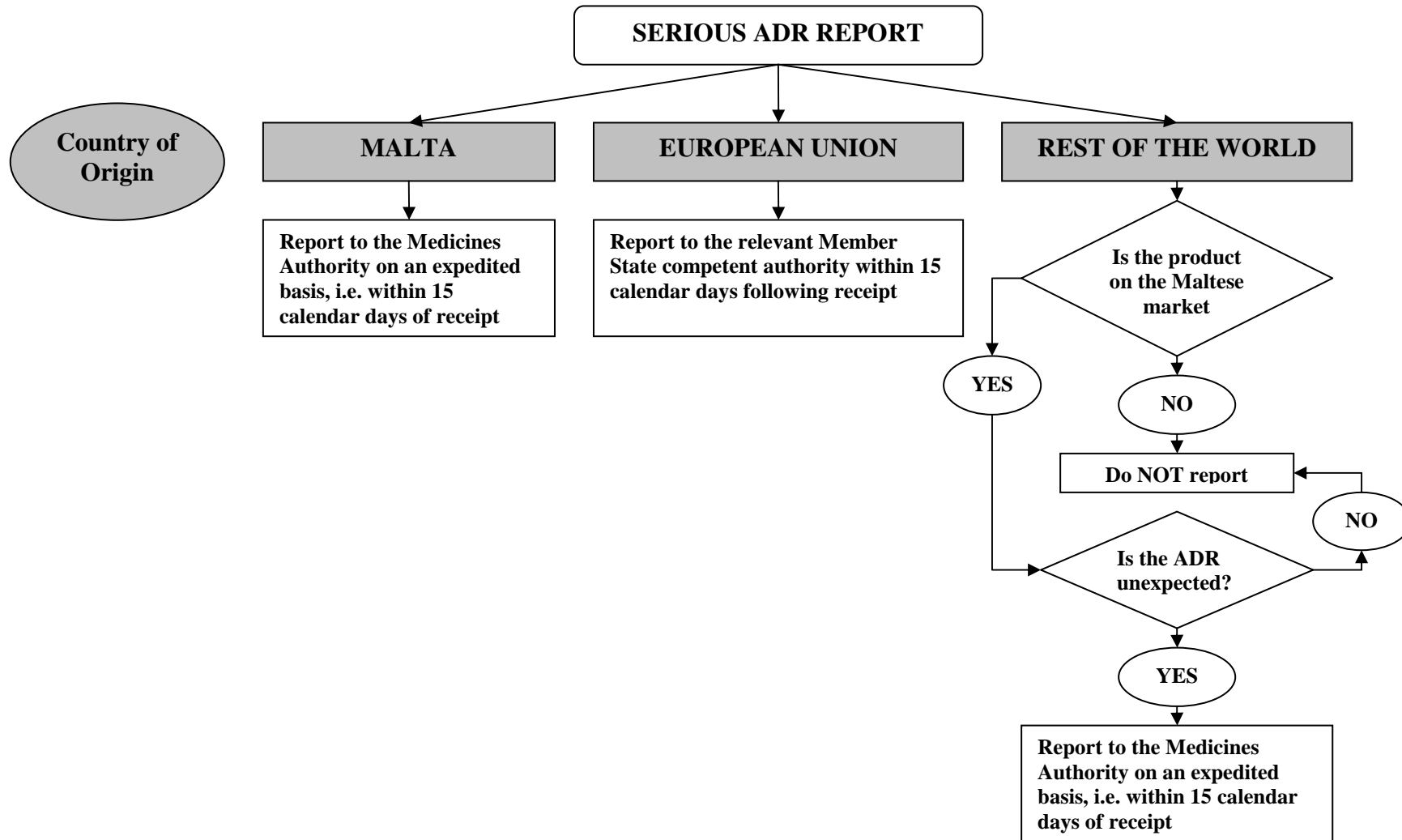
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Appendix 3 Requirements for PSUR submission

Appendix 1 Flowchart for serious ADR report submission to the Medicines Authority



## Appendix 2 CIOMS Form

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT												

### I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE Years	3. SEX	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										<input type="checkbox"/> PATIENT DIED <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING

### II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)		19. THERAPY DURATION

### III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

### IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE <input type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input type="checkbox"/> HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP	

### Appendix 3 Requirements for PSUR submission

PSURs should be submitted to the Medicines Authority in the format and reporting frequencies as outlined below:

Report format and copies required	Addressee(s)
<p><u>Products authorised via the National Procedure:</u> <b>1 electronic copy on CD-ROM</b></p> <p><u>Products authorized via the Mutual Recognition Procedure OR Decentralised Procedure:</u></p> <p>If Malta is RMS: <b>1 paper copy + 1 electronic copy on CD-ROM</b></p> <p>If Malta is CMS: <b>1 electronic copy only on CD-ROM</b></p> <p><u>Products authorised via the Centralised Procedure:</u></p> <p>If Malta is Rapporteur/Co-Rapporteur: <b>1 paper copy + 1 electronic copy on CD-ROM</b></p> <p>If Malta is <b>not</b> Rapporteur/Co-Rapporteur: <b>1 electronic copy only on CD-ROM</b></p>	<p><u>For ALL products:</u></p> <p><u>Six monthly and annual PSURs:</u> Pharmacovigilance Section, Post-Licensing Directorate, Medicines Authority, 203, level 3 Rue D'Argens, Gzira. GZR 1368. Malta. Tel: (+356) 23439000 Fax: (+356) 23439161 Email address: <a href="mailto:postlicensing.mru@gov.mt">postlicensing.mru@gov.mt</a></p> <p><u>Subsequent 3-yearly PSURs:</u> Pharmacovigilance Section, Post-Licensing Directorate, Medicines Authority, 203, level 3 Rue D'Argens, Gzira. GZR 1368. Malta. Tel: (+356) 23439000 Fax: (+356) 23439161 Email address: <a href="mailto:postlicensing.mru@gov.mt">postlicensing.mru@gov.mt</a></p> <p><u>Interim PSURs:</u> To the person from the Post-Licensing Directorate making the request.</p>