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INSTRUCTIONS FOR MARKETING AUTHORISATION HOLDERS REGARDING ELECTRONIC (E2B) REPORTING OF ADVERSE DRUG REACTIONS

Establishment of electronic (E2B) reporting

Pursuant to the Rules on pharmacovigilance of medicinal products for human use (Official Gazette of the Republic of Slovenia no. 53/2006) a Marketing Authorisation Holder (hereinafter: MAH) shall report adverse reactions directly to the JAZMP. Reporting in electronic form, taking into account the ICH standards and guidelines for electronic reporting, is mandatory. Since 20 November 2005, pursuant to legislation, electronic reporting is mandatory for all authorised medicinal products in the EU. Exceptionally, the Marketing Authorisation Holder may agree with the JAZMP on a different method of reporting.

These instructions describe reporting of adverse drug reactions as part of the pharmacovigilance obligations (the *ICSRs-Individual Case Safety Reports*):

- reports of adverse reactions to authorised medicinal products (regardless of the type of procedure used for obtaining the marketing authorisation) and
- reports from post-marketing non-intervention clinical trials.

The requirements for reporting on non-intervention clinical trials (*SUSARs - Suspected Unexpected Serious Adverse Reactions* reports) are regulated by the Rules on clinical trials of medicinal products (Official Gazette of the Republic of Slovenia no. 54/06). *SUSARs* are sent in the E2B format to EVCTM only, in accordance with the Rules. For any other information related to *SUSAR* electronic reporting please contact the person in charge of clinical trials. Information provided hereinafter relates to *ICSR* electronic reporting only.

For electronic reporting, the MAH must be registered with the EudraVigilance system. Further information on registration is available at <http://eudravigilance.emea.europa.eu/highres.htm>.

The standards for electronic reporting are defined in the framework of the ICH (International Conference of Harmonisation of Technical requirements for registration of Pharmaceuticals for Human Use). ICH guidelines and standards are published on the website <http://www.ich.org>.

The list of relevant guidelines and standards is provided in Vol. 9A - Guidelines on Pharmacovigilance for Medicinal Products for Human Use, available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol9_en.htm.

The use of MedDRA (Medical Dictionary for Regulatory Activities) terminology is mandatory. For further information see <http://www.meddrasso.com>.

Detailed information regarding electronic reporting and related documents are available at the above-mentioned EudraVigilance website.

JAZMP uses the EudraVigilance WEB Trader (EVWEB) as electronic reporting system which allows the sending and receiving of E2B reports. Consequently there are no additional requirements, besides those of the EMA, regarding electronic reporting.

The agency's ID in the EudraVigilance production environment is: ARSZMP.

Expedited (15-days) reporting requirements

Pursuant to legislation, MAH reports to the JAZMP:

- Serious adverse reactions (expected and non-expected) that occurred in Slovenia. Reports are sent to the agency's ID (ARSZMP). **As of the publication of these instructions, sending reports to EVHUMAN is no longer necessary – the JAZMP**

will forward the reports received from Marketing Authorisation Holders to EVHUMAN.

- Unexpected serious adverse reactions from third countries. These reports do not need to be sent to the agency's ID but to EVHUMAN only.

Reports on serious adverse reactions from other EU Member States: The MAH sends to the agency's ID only the reports for those medicinal products for which Slovenia is the Reference Member State. These reports are sent to the agency's ID to ascertain the MAH that the JAZMP was informed of these ADRs. The JAZMP anticipates that, pursuant to legislation, these reports will be sent to EV by the agency of the country in which the adverse reaction occurred and will therefore not forward these reports to EV. If the MAH provides a (written) statement that all reports from the EU Member States are available in EV (i.e. that they have established E2B reporting with the EEA agencies which forward the reports to EV), an agreement may be made with the JAZMP stating that sending reports to the agency's ID is not necessary.

Reports received by MAH from patients and other consumers shall be sent to the JAZMP within 15 days (expedited reporting) only if medically confirmed.

Reporting requirements in individual Member States are provided in Annex 6 of the Guidelines: Volume 9A - The Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Human Use. They are published on: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol9_en.htm

ACK - Acknowledgement message

JAZMP shall send an acknowledgement message to the MAH about received ICSR in accordance with the ICH standard for acknowledging messages (ACK) within two business days. If MAH does not receive the ACK a notification should be sent to JAZMP pharmacovigilance h-farmakovigilanca@jazmp.si. See instructions below on failed transmission cases and errors in data transmission.

Forwarding reports to the Marketing Authorisation Holder

Reports received by the JAZMP from Poison Control Centre or directly from patients, other consumers or from other sources, shall be forwarded to the MAH, namely:

- If electronic reporting is already established, the JAZMP shall send a report on a serious adverse reaction in the E2B format to the MAH. The report sent by the JAZMP shall be marked SI-JAZMP-xxxx in the field A 1.0.1.
- If the JAZMP does not receive the ACK from the MAH within two business days, the MAH (or the local representative) shall be contacted and questioned about receiving the report.
- The JAZMP also sends the report to the EudraVigilance base (EVHUMAN).
- If electronic reporting has not yet been established, the MAH is obliged to inform the JAZMP of this fact and reach an agreement on the method of reporting.
- Reports of adverse reactions that are not considered serious shall be sent by the JAZMP to the MAH via the usual communication channels (e-mail, fax or mail).

Reports sent to EVHUMAN by the JAZMP do not need to be re-sent by MAH. A courtesy copy of the report sent to the principal EEA and to EVHUMAN is usually sent to Marketing Authorisation Holders with a representative in Slovenia. In practice the report is then resent to the agency's ID and EVHUMAN. Please consider that reports need not be re-sent. This is to avoid unnecessary duplication of reports in the database, which is important for further evaluation of reports and data processing with the aim of signal detection.

If the representative does not wish to receive the courtesy copy of the report it should inform the JAZMP.

Follow-up reports

If the MAH has obtained additional information important for the assessment of the report (considering the criteria for follow-up reports), an amended report must be sent to the JAZMP, which will be forwarded to EVHUMAN.

Electronic reporting testing

The JAZMP makes use of the EVWEB application. Consequently there are no additional requirements, besides those of the EMA, regarding electronic reporting. If the MAH has tested its system with the EMA and is logged in the production environment, the JAZMP expects no complications in sending and receiving of reports.

The Marketing Authorisation Holder must submit the following information to (which can be sent to h-farmakovigilanca@jazmp.si):

- name and contact data of the person responsible for the E2B reporting,
- ID in the production environment,
- data regarding the establishment of the E2B reporting, including the information whether both sending and receiving of E2B reports are foreseen,
- proposed date of test reporting.

For the purpose of testing, one report from the Marketing Authorisation Holder's production environment, namely the report on an adverse reaction that occurred in Slovenia, sent to the agency's ID ARSZMP (there is no special test environment for this purpose), is sufficient. If a MAH wishes to have the test performed before the local report is available it may also send a report on an ADR from a third country. Together with the E2B report the report should also be sent in the CIOMS form (including the sender's report reference data in the E2B format (*Safety report ID*: ICH A 1.0.1) and the message number (*Message Number*: ICH M.1.4.) to the e-mail address: h-farmakovigilanca@jazmp.si. The JAZMP shall check if the data in the CIOMS report was correctly transferred also in the E2B report and will send an acknowledgement message to the MAH about received ICSR in accordance with the ICH standard for acknowledging messages (ACK) within two business days. Furthermore, the MAH will be informed (via an electronic message) whether it can proceed with regular E2B reporting. After the establishment of E2B reporting other forms of report sending (paper or electronic form) are no longer necessary. In the received ACK the MAH should check the "transmissionacknowledgmentcode" – mark 01 meaning the report has been accepted and there are no major errors – re-sending is not needed, while marks 02 or 03 mean there are significant errors present – a report marked in such a way must be adequately corrected by the MAH and sent again within two business days from receiving the ACK (detailed information regarding the request for re-sending is included in the instructions for E2B electronic reporting, Vol. 9).

The MAHs that have not yet set up the E2B reporting system shall send local reports either in paper form, via mail or to the following e-mail address: h-farmakovigilanca@jazmp.si. Reports from third countries shall also be sent to the e-mail address: h-farmakovigilanca@jazmp.si, periodically if desired but taking into account the requirements for the 15-day reporting.

Personal data protection

Member States have different requirements in the area of personal data protection and there are no uniform standards for entering such data in EV. The JAZMP does not forward the sender data to the MAH or to EV. The patient's personal identifiers are coded (initials only) or the information is marked as "PRIVACY".

Procedure to be followed in case E2B reporting system is not working

If the E2B reporting system is not working and the MAH would thereby miss the 15-days reporting deadline, the message should be sent on the CIOMS form to h-farmakovigilanca@jazmp.si. Once the system is re-established, the message must also be sent as an E2B report. In addition, if the E2B reporting system is not running, the JAZMP sends the MAH a report in the agreed way and later also sends the report in the E2B format.

Reports that have not yet been sent to EV (Backlog reports)

All reports on serious adverse reactions received by JAZMP directly from healthcare professionals (through Poison Control Centre or directly) and have not yet been sent to EV after 1 May 2004 shall be sent to EV by the JAZMP. Reports in the E2B format shall also be sent to the MAH on a CD-ROM or on previous notice in another agreed manner. All other reports on serious adverse reactions that occurred in Slovenia and of which the MAH has been informed (pursuant to the Vol. 9A guidelines since 1 January 1995) shall be sent to EV by the MAH. Reports in the E2B format shall be sent to the JAZMP on a CD-ROM or on previous notice in another agreed manner. For detailed instructions regarding the marking and sending of backlog reports see Vol. 9A.

EVMPD (EudraVigilance Medicinal Product Dictionary)

To ensure adequate identification of medicinal products in relation to reports on adverse reactions, we ask the Marketing Authorisation Holders to enter the medicinal product data for which marketing authorisation has been obtained in the above medicinal products code list in accordance with the specifications and guidelines stated in Vol. 9A.

Additional information:

The Marketing Authorisation Holder must inform the JAZMP of any changes to the Qualified Person Responsible for Pharmacovigilance (QPPV). The notification is sent to the Legal, Personnel and General Affairs Department (including evidence) and a copy of the notification to the Pharmacovigilance Department. The Pharmacovigilance Department keeps a record of QPPV (and local QPPV) for implementing pharmacovigilance activities.

Literature reports: The entire article used as a source for compiling the report shall be sent by the MAH to the JAZMP only upon request, to the general e-mail address h-farmakovigilanca@jazmp.si, stating the E2B format identification number of the sent report. The JAZMP shall send an e-mail requesting the MAH to submit the article.

The list of national literature to be examined by the Marketing Authorisation Holder for compiling literature reports:

- Slovenian Medical Journal (Slovenian Medical Association)
- Slovenian Pharmaceutical Journal (Slovenian Pharmaceutical Society)
- the journal Medicinski razgledi ("Medicinski razgledi" Society)
- "Tavčarjevi dnevi" – journal (Faculty of Medicine, University of Ljubljana)
- Emergency Medicine Symposium – journal (Slovenian Society for Emergency Medicine)
- "Derčevi dnevi" – journal (Faculty of Medicine, University of Ljubljana)

If you have any questions regarding the reporting of adverse reactions, please address them to: h-farmakovigilanca@jazmp.si.