Pursuant to articles 75 and 127 of the Law on Medicines („Official Gazette of Montenegro“ No 56/11 and 6/13), the Ministry of Health hereby issues the

RULEBOOK
ON THE MANNER OF COLLECTING DATA AND REPORTING AND MONITORING ADVERSE REACTIONS TO MEDICINES FOR HUMAN USE

("Official Gazette of Montenegro", No 46/14 from 31 October 2014)

I GENERAL PROVISIONS

Article 1

In order to ensure safe use of medicines in Montenegro, marketing authorisation holder, health institution, healthcare professional, clinical trial sponsor, legal entities participating in marketing of medicines (hereinafter: participants in the system of pharmacovigilance), shall, according to the manner defined in this Rulebook, collect, submit and monitor data on adverse reactions to medicines for human use.

Article 2

The terms from this Rulebook used for natural persons in the masculine gender shall include the same terms in the feminine gender.

Article 3

The terms used in the Rulebook shall have the following meaning:

1) serious adverse event shall mean an undesirable experience occurred during the use of a medicine and for which the causal link with the use of the medicine does not have to be proved and which results in death, is life-threatening, requires hospitalization or prolonged impatient hospitalization, results in persistent or significant incapacity/disability, congenital anomalies or disorders during breastfeeding or other significant medical condition;
2) interaction shall mean a change in the pharmacokinetic or pharmacodynamic properties of a medicine caused by concurrent use of another medicine, food, or any other substance;
3) abuse of a medicine shall mean permanent or occasional, intentional excessive use of a medicine followed by harmful physical or psychological effects;
4) medical error shall mean an unintentional error in prescribing, dispensing or use of a medicine by a healthcare professional or patient;
5) off-label use of a medicine shall mean use of a
medicine which is not in accordance with approved summary of product characteristics;
6) misuse of a medicine shall mean unintentional, inappropriate use which is not in accordance with the approved documents on a medicine;
7) suspected medicine shall mean a medicine which is suspected to cause adverse reaction or interaction;
8) Data Lock Point (hereinafter: DLP) shall mean the cut-off date for new data to be included in a Periodic Safety Update Report (hereinafter: PSUR), except for important subsequently received information;
9) Development Safety Update Report (hereinafter: DSUR) Development Safety Update Report (DSUR) is an annual report and assessment of relevant safety information collected during the reporting period for the investigational medicine, regardless of whether the marketing authorisation has been granted, which is submitted by the sponsor, i.e. the applicant of a clinical trial;
10) The “pharmacovigilance system” shall mean a system established by the marketing authorization holder and the Agency for Medicines and Medical Devices (hereinafter:

Agency) for the purpose of monitoring safety of marketed medicines and detecting any change in the benefit-risk ratio of their use;
11) Risk Management System (hereinafter: RMS) is a set of activities and intervention measures in pharmacovigilance which should provide identification, characterization, prevention or minimization of the risk in the use of a medicine, as well as to evaluate the effectiveness of those actions and measures;
12) Detailed description of pharmacovigilance system (hereinafter: DDPS) shall mean a description of the pharmacovigilance system which the marketing authorization holder shall use for monitoring of one or more medicines;
13) Pharmacovigilance System Master File (hereinafter: PSMF) shall mean a description of the pharmacovigilance system used by marketing authorization holder;
14) good practice in the pharmacovigilance is a system of quality assurance in planning, organizing and implementing procedures related to collecting, processing and evaluating data on medicines safety in order to protect health of the population;
15) Company Core Safety Information (hereinafter: CCSI) shall mean a document containing all relevant safety information contained in the Company Core Data Sheet prepared by the marketing authorisation holder, or the manufacturer, and which is required to be listed in the information about a medicine (Summary of Product Characteristics and Patient Information Leaflet) in all countries where the medicine is marketed, except when the local regulatory authority specifically requires a modification;
16) Company Core Data Sheet (hereinafter: CCDS) shall mean a document prepared by the marketing authorisation holder, or the manufacturer, containing, in addition to all relevant safety information, material relating to indications, dosing, pharmacology and other data on a medicine;
17) Medical Dictionary for Regulatory Activities (hereinafter: MEDDRA) is a dictionary that the Agency and participants in the pharmacovigilance system use when processing data on adverse reactions to medicines;
18) adverse reaction report is a document that contains most possible data about the particular case of one or more adverse reactions in the use of one or more medicines in one patient;
19) The Council for International Organizations of Medical Sciences (hereinafter: CIOMS I) is standardized, international form for reporting issued in 1990 by the Council for International Organizations of Medical Sciences (CIOMS) Working Group I.

II PHARMACOVIGILANCE OF A MARKETED MEDICINE

Article 4

The Agency shall establish and organize the system of pharmacovigilance, in order to monitor the safety of medicines on the market and identify each change in the benefit-risk ratio of their use and to take appropriate measures.

The Agency is involved in the monitoring program for safe use of medicines of World Health Organization and works with its collaborative center (The Uppsala Monitoring Centre - UMC).

The Agency cooperates with the European Medicines Agency (EMA) and other professional and regulatory bodies of the European Union and other countries in order to exchange information in the field of pharmacovigilance.

Article 5

The establishment and organization of the pharmacovigilance system includes the following:
1) collection and analysis of adverse reaction reports in Montenegro;

2) maintaining a database of adverse reaction reports in Montenegro;
3) encouraging healthcare professionals to report adverse reactions to medicines;
4) collection, processing and evaluation of data from clinical trials conducted in Montenegro;
5) intensive monitoring of certain medicines because of risks associated with their use, according to a list which may be determined by the Agency;
6) evaluation of the documents relating to the safety of the medicine in order to establish new risks relating to safety profile of the medicine, changes of these risks or changes in the benefit-risk ratio of the medicine;
7) proposing or taking regulatory measures in accordance with the Law, based on the information concerning safe use of medicines in Montenegro;
8) preparation of annual reports about adverse reactions to medicines;
9) providing information to the public on safety of medicines.

In performing activities referred to in paragraph 1 of this Article, the Agency may require that marketing authorisation holder takes appropriate measures in the risk management system.

Article 6

Adverse reactions to medicines reporting may be spontaneous and solicited.

Spontaneous reporting shall mean a causal relationship between the use of a medicine and adverse reaction to it. Spontaneous reporting is each voluntary adverse reactions to medicines reporting by healthcare professionals to the marketing authorisation holder and to the Agency, by which one or more adverse reactions occurred in patients using one or more medicines are described and which is not the result of a clinical trial or any other organized data collection.

Solicited reporting shall mean an evaluation of a causal relationship between the medicine and adverse reaction by a healthcare professional or marketing authorisation holder. Solicited reporting is each reporting of adverse reactions obtained through organized data collection (clinical trials, registers, post-marketing trials, surveys, etc.). These reports are listed as clinical trial reports.

Article 7

Participants in the system of pharmacovigilance report suspected adverse reaction on the CIOMS I form for adverse reaction reporting or on the form of the Agency.

Reporting of adverse reactions to vaccines is adapted to specific characteristics of the use of vaccines and, in part referring to the description of an adverse reactions, provides an overview of the most common local and general reactions that occur after the use of vaccines.

In order to be considered valid, the report on suspected adverse reaction to a vaccine/medicine shall contain at least the information about the following:
- reporter;
- patient;
- manifested adverse reaction to a medicine;
- suspected medicine.

Article 8

Healthcare professionals report suspected adverse reaction to a medicine/vaccine to the Agency by submitting reports referred to in Article 7 paragraph 1 and 2 of this Rulebook.

Healthcare professionals may report suspected adverse reaction to a medicine/vaccine through the information system of the Health Insurance Fund of Montenegro, which is connected to the information system of the Agency.

In accordance with applicable regulations, healthcare professionals report adverse reactions to vaccines marketed in Montenegro to the Agency and the Institute for Public Health.

Article 9

Data on healthcare professional who report suspected adverse reaction are considered confidential and are only used by the Agency for the purpose of pharmacovigilance and protection of health of the population. Agency must not forward the information about the identity of healthcare professional to third parties, except in cases with written approval of the healthcare professional.

Article 10

If a healthcare professional participates as an investigator in the non-interventional clinical trial of the medicine, all suspected adverse reactions are reported to the applicant of the clinical trial, in accordance with the Law.

Article 11

If significant changes in the safety profile of a medicine occur, the Agency shall inform healthcare professionals on it via letter to healthcare professionals.

If a letter to healthcare professional is sent by marketing authorisation holder, the text of the letter and its distribution plan should be approved by the Agency.

Letter to healthcare professionals must not contain any form of advertising of a medicine.

The Agency shall publish on its portal content of the letter referred to in paragraph 1 of this Article.

Article 12

In order to ensure safe use of medicines, marketing authorisation holder shall establish, maintain, improve and manage the pharmacovigilance system in Montenegro.

The responsible person for pharmacovigilance shall follow safety profile and all safety issues related to medicines for which marketing authorisation holder obtained marketing authorisation in Montenegro.

For the purpose of establishing the system of pharmacovigilance and taking measures in a timely manner, the marketing authorisation holder shall:

- establish and manage the system that provides information about all suspected adverse reactions and events related to the use of a medicine that were reported to marketing authorisation holder, persons promoting medicines, or that were obtained from the literature;
- propose to the Agency measures to be conducted for safety reasons, provide complete and timely responses and information necessary to assess safety of a medicine and risk relating to its use;
- report to the Agency all adverse reactions to a medicine or a suspicions of them, including any suspected transmission of an infectious agent through a medicine that has occurred on the territory of Montenegro, in accordance with the Law, on CIOMS I form, or on the form of the Agency, immediately or not later than 15 days from the day of receipt of the information from Article 7 paragraph 3 of this Rulebook by any employee of marketing authorisation holder. Day of receipt of the information from Article 7 paragraph 3 of this Rulebook is considered day zero. Same time period referred to in paragraph 3, indent 3 of this Article shall apply to sending additional information, and the day 0 (zero) is the day of receipt of new information on adverse reaction;
- at the request of the Agency, report suspected serious and unexpected adverse reactions to a medicine, or transmission of an infectious agent through a medicine that has occurred on the territory of European Union, or some other country, in accordance with the Law, on CIOMS I

form or on the form of the Agency, immediately or not later than 15 days from the day of receipt of the request;
- in accordance with paragraph 3, indents 3 and 4 of this Article, report suspected adverse reactions to a medicine during the post-marketing non-interventional clinical trial of a medicine where marketing authorization holder is applicant for this trial ;
- submit to the Agency the following documents on safety: PSUR, RMP, DDPS, PSMF, report on the results of non-interventional clinical trials of a medicine and other documents containing information on safety;
- provide complete and timely answers to all questions of the Agency and submit to the Agency all information relating to the evaluation of the benefit-risk ratio of the medicine, as well as information on the sales or prescription volume of medicines on the territory of Montenegro.

MEDDRA shall be used when processing data on manifested adverse reactions to a medicine referred to in paragraph 3, indents 3, 4 and 5 of this Article.

If the marketing authorisation holder receives a report on adverse reactions listed only under international non-proprietary name of suspected medicine (INN), it shall assume that the report concerns its medicine and is thus obliged to report the adverse reaction to the Agency pursuant to paragraph 3, indents 3, 4 and 5 of this Article.

Article 13

Marketing authorisation holder shall protect the identity of the healthcare professional who reported adverse reactions to a medicine in the manner that the information on the reporter is submitted exclusively to the Agency and may not be disclosed to third persons.

Article 14

Marketing authorisation holder shall collect and monitor data relevant to the evaluation of the benefit-risk ratio particularly in the following cases:
- in the period from submitting the application for marketing authorisation to the Agency until obtaining it;
- after temporary suspension or recall of a medicine from the market;
- using a medicine during pregnancy;
- using a medicine during breastfeeding;
- using a medicine in children and elderly;
- lack of efficacy of a medicine;
- transimission of infectious agents through a medicine;
- overdose, abuse and off-label use of a medicine;
- medical error.

When using a medicine referred to in paragraph 1 of this Article has resulted in suspicion of adverse reaction, marketing authorisation holder shall report it to the Agency in accordance with Article 12 of this Rulebook.

When using a medicine referred to in paragraph 1 of this Article has not resulted in suspicion of adverse reaction, marketing authorisation holder shall submit the collected data to the Agency in the form of periodic update safety report, or immediately at the request of the Agency.

Article 15

In case that public health is endangered, regular manner of reporting adverse reactions may be amended according to the guidelines and recommendations given by the Agency for individual cases, which the marketing authorisation holder is obliged to comply with.

Article 16

Marketing authorisation holder shall submit to the Agency Risk Management Plan (hereinafter: RMP) which describes the system of risk management.

When RMP envisages additional pharmacovigilance activities in order to minimize the risk of use of a medicine (e.g. educational material, patient card), marketing authorisation holder is required to prepare and submit the documentation to healthcare professionals, i.e. patients.

Marketing authorisation holder is responsible for the accuracy and timeliness of data.

Article 17

Marketing authorisation holder shall submit PSUR to the Agency, which contains comprehensive information on safety of a medicine that were collected in the period after placement of a medicine onto the market, with expert assessments of the benefit-risk ratio, at the request of the Agency immediately, or in the form of regular reports, in accordance with the guidelines of the European Medicines Agency on good practice in pharmacovigilance (Guideline on good pharmacovigilance practices GVP, Module VII - Periodic safety update report).

Article 18

With PSUR marketing authorisation holder shall also submit a cover letter.

Cover letter shall contain:

- information on the medicine that submitted PSUR referrs to (name, pharmaceutical form, strength, marketing authorisation number);
- period which PSUR referrs to;
- main differences between CCSI and approved summary of product characteristics of a medicine for Montenegro.

Cover letter should be signed by the person responsible for pharmacovigilance of the marketing authorisation holder.

PSUR should contain expert evaluation of the benefit-risk ratio of a certain medicine in relation to the information collected during the reporting period, in line with previous findings on safety of the medicine, as well as the need for changes to the summary of product characteristics, patient information leaflet, or RMP.

Article 19

If PSUR is submitted upon the request of the Agency, it shall contain data for the period from submitting last report until the day of the request of the Agency.

Article 20

All legal entities that participate in marketing of medicines shall submit to the Agency all the information available to them which are important for the evaluation of the benefit-risk ratio of marketed medicines.

III PHARMACOVIGILANCE IN A CLINICAL TRIAL OF A MEDICINE

Article 21

Sponsor of a clinical trial (hereinafter: sponsor) shall timely inform the Agency about serious and unexpected adverse reaction in the clinical trial of a medicine.

A health care professional participating in a clinical trial as an investigator shall be responsible to immediately report all serious adverse reactions/events to the sponsor, except those that are not required by the trial protocol or investigator's brochure.

The sponsor shall immediately make assessment of the reports referred to in paragraph 2 of this Article and inform all the investigators, Ethics Committee and Agency about all findings that could adversely affect health of trial participants, conducting of a trial or suspension of a clinical trial.

The sponsor shall keep detailed records of all adverse reactions/events reported to him or her by the investigator, and assess their seriousness, causal link and expectancy.

The sponsor shall not reduce the level of causal link assessed by the investigator. If the sponsor does not agree with the assessment of the causal link made by the investigator, both assessments should be stated in the case report that shall be submitted to the Agency.

Article 22

The sponsor of the clinical trial of a medicine shall report to the Agency the following adverse reactions manifested in Montenegro:

1) serious, unexpected adverse reactions which occurred in a clinical trial;
2) serious, expected adverse reactions which occurred in a clinical trial of a medicine, but with an increased frequency of occurrence (clinically significant);
3) serious risks for patients which occurred in a clinical trial of a medicine (e.g. lack of efficacy of a medicine for patients in a life-threatening condition);
4) serious, unexpected adverse reactions which occurred in patients after completion of a clinical study, which the investigator reported to the sponsor;
5) serious, unexpected adverse reactions to a medicine used as active control, which the sponsor shall notify the marketing authorization holder on the territory of Montenegro.

Sponsor shall submit to the Agency adverse reactions referred to in paragraph 1 of this Article directly if it has main office in Montenegro, or through a legal representative which is situated in Montenegro.

Article 23

The sponsor shall report to the Agency serious, unexpected adverse reactions to a medicine that occurred in a clinical trial of a medicine or that are fatal or life-threatening, immediately or not later than seven days from the date the sponsor obtained the first information (initial report).

The sponsor shall submit to the Agency follow-up information for the reporting referred to in paragraph 1 of the Article, not later than eight days from the day of submission of the first, initial report.

The sponsor shall submit to the Agency serious, unexpected adverse reactions to a medicine that are not fatal or life-threatening immediately or not later than 15 days from the day the sponsor was first informed about this adverse reaction (initial report), and then submit the follow-up report as soon as additional information becomes available.

Article 24

The sponsor shall submit to the Agency the following:

1) list of all suspected serious unexpected adverse reactions to a medicine (hereinafter: SUSAR) from all countries where clinical trial is conducted at least once in six months, or more often at the request of the Agency;
2) Development safety update report at least once a year and final safety report of an investigated medicine after the completion of the trial.

By derogation of paragraph 1 of this Article, an individual SUSAR from all countries in which the same clinical trial is conducted shall be submitted to the Agency, at its request only.

Article 25

The report referred to in Article 23 of this Rulebook contains at least the following information:

1) The identification code of a patient (trial participant);
2) The information about an investigational medicine and which is suspected to have caused an adverse reaction;
3) Manifested adverse reaction which is assessed to be serious and unexpected;
4) The identification number of a clinical trial;
5) The name and address of the sponsor.

Article 26

In case of incomplete information referred to in Article 23 of this Rulebook, the sponsor shall gather from the investigator all relevant information required for the assessment of the causal link and submit them in the follow-up report referred to in Article 23 this Rulebook.

The follow-up report shall contain all relevant information on the following:

1) clinical trial: identification number of the clinical trial (protocol number), the most significant information about the clinical trial (e.g. stage and purpose of the trial, investigational medicine, indication), authorization number;
2) patient and/or trial participant: initials, identification code, age, gender, weight, height, country;
3) medicine which is suspected to have caused an adverse reaction: international non-proprietary name (INN) and/or trade name of a medicine, batch number, indication, pharmaceutical form and strength, dosage regime, route of administration, date and time of commencement and completion of use of a medicine;
4) adverse reactions;
5) concurrent medicines, including non-prescription medicines (traditional and homeopathic medicines), dietary products etc., with the same information as for the medicine suspected to have caused an adverse reaction;
6) reporter: name and surname, phone number, occupation, signature and date of the report.

Article 27

The information on adverse reactions referred to in Article 26, item 4 of this Rulebook, shall contain the following:

1) detailed description of all reactions (signs and symptoms), seriousness and criteria on the basis of which a case shall be considered serious and, whenever possible, specific diagnoses (MKB-10) for exhibited reactions shall be stated;
2) date and time of the commencement and cessation of reactions;
3) given therapy and measures taken due to occurred adverse reactions;
4) information on the presence or absence of adverse reactions after stopping with the use of a medicine and after re-introduction of a medicine;
5) information about the outcome of manifested reactions (fatal outcome with the information about the cause of death, comment about the causal link with the medicine suspected to have caused an adverse reaction and post-mortem findings, if available, persistent incapacity, included or prolonged impatient hospitalization, threat to life or recovery without consequences);
6) information significant for the assessment of adverse reactions (e.g. case history, laboratory findings and diagnostic trial results, allergies, pregnancy, abuse of medicines or alcohol, family medical history).

Article 28

The sponsor shall report to the Agency on serious, unexpected adverse reactions to a medicine by submitting a standardized international report form (CIOMS-I form).

Article 29

In case of a serious, unexpected adverse reaction to a medicine that may have a causal link with the investigational medicine, the sponsor shall disclose a therapy code only for the trial participant with manifested adverse reaction, before submitting a report to the Agency.

If with disclosing a therapy code is determined that the investigational medicine or placebo have been administered to the trial participant, suspected serious and unexpected adverse reactions to a medicine shall be reported to the Agency. If with disclosing a therapy code is determined that a medicine, which is active control, has been administered to the trial participant, the expectancy of an adverse reaction shall be re-assessed according to the summary of product characteristics determined in the trial protocol. If a serious adverse reaction is assessed as unexpected, it shall be reported to the Agency.

Article 30

The Agency shall organize and monitor collection and assessment of information on safety of the medicines included in a clinical trial in Montenegro and, if necessary, take appropriate measures.

Article 31

Based on collected information on adverse reactions/events to medicines in a clinical trial, the Agency may:

1) amend the protocol of a clinical trial of a medicine;
2) conduct control of a clinical trial of a medicine;
3) propose to the competent health authority to suspend or prohibit a clinical trial of a medicine.

Article 32

Agency's forms for reporting adverse reactions to a medicine and vaccine, CIOMS I form, instructions on the content and structure of the description of the system of pharmacovigilance and risk management plan shall be published on the portal of the Agency.

IV FINAL PROVISION

Article 33

This Rulebook shall enter into force on the eighth day of its publication in the "Official Gazette of Montenegro".

Number: 011-228/2014
Podgorica, 24 October 2014
Minister,
prof. dr Miodrag Radunović, m.p.