

Pursuant to Article 161, paragraph 8 of the Law on Medicines and Medical Devices ("Official Gazette of RS", No. 30/10),  
the Minister of Health hereby adopts

## Rulebook on the method of reporting, collecting and monitoring adverse reactions to medicines

*The Rulebook was published in the "Official Gazette of RS", No. 64/2011 of 31 August 2011*

### I. INTRODUCTORY PROVISIONS

#### 1. Contents of the Rulebook

##### Article 1

The Rulebook shall prescribe the method of reporting, collecting and monitoring adverse reactions to medicines in human use (hereinafter referred to as the "pharmacovigilance"), as well as the method of submission of information by health care institutions to regional pharmacovigilance centers and/or the Medicines and Medical Devices Agency of Serbia (hereinafter referred to as the "Agency").

#### 2. Definitions

##### Article 2

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

1) "Pharmacovigilance" shall mean a set of activities related to the collection, detection, assessment, understanding and prevention of adverse reactions to a medicine, and other medicine-related issues;

2) An "adverse reaction" shall mean any harmful and unintended reaction to a medicine occurring during the administration of the normal dose of a medicine to human subjects (for treatment, disease prevention, diagnosis, rehabilitation, improvement or alternation of the physiological function), or during the administration of any dose of a medicine in a clinical trial;

3) A "serious adverse reaction" shall mean a harmful and unintended reaction to a medicine which shall:

- result in death;
- is life-threatening;
- result in persistent or significant incapacity/disability;
- requires hospitalization or prolonged inpatient hospitalization;
- is a congenial anomaly/birth defect;
- result in other medically significant condition;

4) An "unexpected adverse reaction" shall mean a reaction to a medicine whose nature, severity or outcome are not described in the summary of product characteristics and/or investigator's brochure for investigational medicines;

5) An "adverse event" shall mean an undesirable experience occurring during the administration of a medicine and for which the causal link with the administration of the medicine does not have to be proved;

An adverse event shall mean any unintended and undesirable signal (e.g. abnormal laboratory findings), a symptom or a disease related to the administration of a medicine;

6) A "serious adverse event" shall mean an undesirable event with the following results:

- death;
- is life-threatening;
- result in permanent or significant disability/incapacity;
- requires hospitalization or prolonged inpatient hospitalization;

- is a congenial anomaly/birth defect;
- other medically significant condition;

7) An "interaction" shall mean a change in the pharmacokinetic or pharmacodynamic properties of a medicine caused by concurrent administration of another medicine, food, or any other substance;

8) An "Individual Case Safety Report" (hereinafter referred to as the "ICSR") shall mean a document which contains the largest amount of information about an individual case obtained from the primary source of reporting one or several adverse reactions during the administration of one or several medicines to a patient, and during whose preparation the Medical Dictionary for Regulatory Activities (MedDRA) is used;

9) The "CIOMS-I form" shall mean a standardized international form for the ICSR reporting, issued in 1990 by the Council for International Organizations of Medical Sciences (CIOMS) Working Group I;

10) The "Periodic Safety Update Report" (hereinafter referred to as the "PSUR") shall mean a document containing comprehensive safety information about a medicine collected within the prescribed period of time after placing the medicine on the market, for periodic assessment of medicine safety;

11) The "data lock point" (hereinafter referred to as the "DLP") shall mean the cut-off date for new data to be included in a PSUR, except for important subsequently received information;

12) An "abuse of a medicine" shall mean permanent or occasional, intentional excessive use of a medicine followed by harmful physical or psychological and physical effects;

13) An "unauthorized administration of a medicine" shall mean administration of a medicine that has a marketing authorization, but which is administered in a therapeutic indication, dosage or in the manners not listed in the summary of product characteristics and/or that is not approved;

14) "Spontaneous reporting" shall mean voluntary reporting of adverse reactions to marketed medicines which occurred during the treatment of a patient. Spontaneous reporting shall be carried out by health care institutions or health care professionals (hereinafter referred to as the "party reporting an adverse reaction"), as well as by patients;

15) "Mandatory reporting" shall mean reporting of adverse reactions to a medicine occurring during clinical trials or in the period after obtaining an authorization to place a medicine on the market. Mandatory reporting shall, for the purpose of the Rulebook, be carried out by the marketing authorization holder and sponsor of a clinical trial (hereinafter referred to as the "sponsor");

16) A "new medicine" shall, for the purpose of the Rulebook, mean a medicine which has been in use for less than five years and/or a medicine that has been in a longer use, but has a new route of administration or a new indication;

17) The "risk management system" shall mean a set of activities and intervention measures in pharmacovigilance that should ensure identification, characterization, prevention or minimization of risks during the administration of medicines, as well as assessment of efficacy of the activities and measures;

18) The "Risk Management Plan" (hereinafter referred to as the "RMP") shall mean a detailed description of the risk management system;

19) The "pharmacovigilance system" shall mean a system used by the marketing authorization holder, health care professionals and the Agency in meeting their obligations and responsibilities defined by the Rulebook for purpose of monitoring the safety of medicines with the marketing authorization, and detecting any change in the benefit-risk ratio of their administration;

20) The "Detailed Description of Pharmacovigilance System" (hereinafter referred to as the "DDPS") shall mean a description of the pharmacovigilance system which the marketing authorization holder shall use for the monitoring of one or more medicines which he or she holds the marketing authorization for;

21) The “Post-marketing Safety Study” (hereinafter referred to as the “PASS”) shall mean any clinical study at the post-marketing stage of the life cycle of a medicine, which shall be conducted in order to identify, characterize or quantify safety risk, confirm the safety profile of a medicine or assess efficacy of the measures used for risk management;

#### **Article 3**

The Agency shall organize and monitor the method of collection and assessment of adverse reactions to medicines, as well as the processing and evaluation of obtained data so that for the purpose of the health, proper information about this are made available to the health care professionals and general public, if necessary, except for the medicines registered in appropriate registries kept by the Agency.

The Agency shall collect, process, assess and provide information on adverse reactions to medicines.

## **II. PHARMACOVIGILANCE OF A MARKETED MEDICINE**

### **1. Reporting suspected adverse reactions to medicines**

#### **Article 4**

Health care professionals who are in contact with a medicine or a patient and/or a medicine consumer shall report in writing to the regional pharmacovigilance center or to the Agency on all suspected adverse reactions to the medicines marketed in the Republic of Serbia.

In addition to adverse reactions to a medicine, a health worker shall also report to the regional pharmacovigilance center or the Agency if he or she suspects of medical errors, overdose, addiction, abuse and unauthorized administration of a medicine, absence of therapeutic efficacy of a medicine and a clinically significant interaction.

#### **Article 5**

A health worker shall report adverse reactions to a medicine and/or conduct the activities referred to in Article 4, paragraphs 1 and 3 of the Rulebook by submitting a form directly, by mail, by electronic mail or by fax (hereinafter referred to as the “health worker’s report”).

As an exception, the health worker referred to in paragraph 1 of the Article, may notify a regional pharmacovigilance center and/or the Agency by phone in case of a serious or unexpected adverse reaction to a medicine, and submit the health worker’s report after the telephone notification.

The report form referred to in paragraph 1 of the Article is presented in Attachment 9 which is enclosed to the Rulebook and makes its integral part.

### **2. Contents of the report**

#### **Article 6**

The health worker’s report shall contain at least the information about the following:

- 1) The party reporting an adverse reaction;
- 2) The patient that can be identified (by initials, year of birth and gender);
- 3) The name of the medicine that is suspected to have caused an adverse reaction (trade name and/or INN);
- 4) An adverse reaction to a medicine.

### **3. Information about the reporter**

#### **Article 7**

The information about the identity of the reporter referred to in Article 6, item 1) of the Rulebook shall be confidential and not available to the third parties, in conformity with the Agency’s act on confidentiality.

When reporting an adverse reaction to a medicine through the marketing authorization holder, the marketing authorization holder shall be obliged to protect the identity of the reporter by submitting information about the reporter in the ICSR exclusively to the Agency, and he or she shall not reveal it to the third parties.

#### **Article 8**

If a health care professional participates in the capacity of the investigator in a non-interventional clinical trial of a medicine, all suspected adverse reactions to a medicine shall be reported in accordance with Art. 4 and 5 of the Rulebook.

### **4. Patients**

#### **Article 9**

Patients shall notify about suspected adverse reactions to medicines their doctor and/or other health care professional who provides them the health care (a physician, dentist, pharmacist, nurse) and whom they came into contact with.

Patients may notify in writing a regional pharmacovigilance center or the Agency or the marketing authorization holder about suspected adverse reactions to the medicines marketed in the Republic of Serbia.

An adverse reaction may be reported by a patient, and in case a patient is a person who is unable to work, a person with a mental disability or a minor, an adverse reaction shall be reported by the parent, legal representative and/or guardian of the patient.

#### **Article 10**

A patient shall inform on adverse reactions to a medicine in accordance with Article 9, paragraph 2 of the Rulebook, by sending a completed form by mail, by electronic mail or by fax (hereinafter referred to as the "patient's report").

The report form referred to in paragraph 1 of the Article is presented in Attachment 10, which is enclosed to the Rulebook and makes its integral part.

#### **Article 11**

The patient's report shall contain at least the information on the following:

- 1) The party reporting an adverse reaction;
- 2) The patient that can be identified (by initials, year of birth and gender);
- 3) The name of the medicine that is suspected to have caused an adverse reaction (trade name and/or INN);
- 4) An adverse reaction to a medicine.

### **5. Marketing authorization holder**

#### **Article 12**

The marketing authorization holder shall be obliged to organize continuous monitoring of adverse reactions to a medicine.

The marketing authorization holder shall be obliged to have an established appropriate pharmacovigilance system which shall enable monitoring and supervision of one or more medicines he or she holds the authorization for in the Republic of Serbia, and to conduct appropriate measures, if necessary.

The marketing authorization holder shall ensure continuous maintenance and upgrading of the pharmacovigilance system.

#### **Article 13**

The marketing authorization holder shall be obliged to have DDPS for one or more medicines which he or she holds the marketing authorization for in the Republic of Serbia, and which should be made available to the inspection in the field of pharmacovigilance.

#### **Article 14**

The marketing authorization holder shall be obliged to conclude an agreement for the full-time employment on the open-end basis with a person that has appropriate qualifications and who is responsible for pharmacovigilance (hereinafter referred to as the "person responsible for pharmacovigilance"), and residing in the Republic of Serbia.

The marketing authorization holder shall appoint a person responsible for pharmacovigilance for all medicines which he or she holds the marketing authorization for in the Republic of Serbia, and inform the Agency about this.

The marketing authorization holder may also appoint and/or determine another person who shall have authorizations to conduct activities of the person responsible for

pharmacovigilance and residing in the Republic of Serbia (hereinafter referred to as the "deputy"), and inform the Agency about this.

The deputy referred to in paragraph 3 of the Article shall assume all the activities of the person responsible for pharmacovigilance in his or her absence.

Activities of the person responsible for pharmacovigilance and/or the deputy may be conducted by a person graduated from the faculty of medicine, pharmacy or dentistry, and who shall have appropriate education in the field of pharmacovigilance.

The person responsible for pharmacovigilance and/or the deputy shall have completed trainings in the following areas of pharmacovigilance organized by the competent agencies:

- 1) Notions of pharmacovigilance;
- 2) Spontaneous reporting of adverse reactions to a medicine;
- 3) The method of reporting adverse reactions to a medicine and assessment of reports on adverse reactions to a medicine;
- 4) PSUR and RMP;
- 5) The knowledge of regulations in the field of pharmacovigilance (Republic of Serbia and European Union).

The person responsible for pharmacovigilance and/or the deputy shall attend continuous professional trainings in the field of pharmacovigilance, and records should be kept of this.

#### **Article 15**

The marketing authorization holder shall, when reporting on the person responsible for pharmacovigilance and/or the deputy, submit to the Agency the following as mandatory:

- 1) The statement of the marketing authorization holder about the appointment of the person responsible for pharmacovigilance;
- 2) CV of the person responsible for pharmacovigilance;
- 3) A photocopy of an appropriate certificate of graduation;
- 4) A photocopy of a certificate of passed training in the field of pharmacovigilance;
- 5) Evidence of the place of residence of the person responsible for pharmacovigilance;
- 6) 24/7 contact information of the person responsible for pharmacovigilance;
- 7) Evidence of establishing permanent employment of the person responsible for pharmacovigilance with the marketing authorization holder.

If the marketing authorization holder shall not appoint a deputy of the person responsible for pharmacovigilance, he or she shall be obliged to inform the Agency about this, by submitting an explanation and a statement that the person responsible for pharmacovigilance shall be the 24/7 contact in ensuring proper operation of the pharmacovigilance system.

## **6. Person responsible for pharmacovigilance**

#### **Article 16**

The person responsible for pharmacovigilance shall do the following in accordance with the Law:

- 1) be responsible for establishing, maintaining and managing the pharmacovigilance system;
- 2) monitor the safety profile and all safety issues related to all the medicines which the marketing authorization holder holds the authorization for in the Republic of Serbia;
- 3) be the 24/7 contact for the Agency;
- 4) be the contact for the inspection in the field of pharmacovigilance.

The person responsible for pharmacovigilance shall monitor the pharmacovigilance system in order to ensure operation of at least the following parts of the system:

- 1) Establishing and managing the system which shall ensure that information on all suspected adverse reactions reported to the associates of the marketing authorization holder are collected in the manner which shall ensure full access at a minimum one location in the Republic of Serbia;
- 2) Developing, acquiring and forwarding the following safety documents submitted to the Agency: ICSR, PSUR, RMP, DDPS, PASS report;

3) Continuous overall assessment of pharmacovigilance of a medicine after it has been placed on the market;

4) Monitoring of the outcome of activities of risk minimization defined within the RMP, or of the marketing authorization conditions;

5) Ensuring that any requirements of the Agency for additional information necessary for the assessment of benefits and risks of a medicine are fully presented and without delay, including information on the amount of sale and number of issued prescriptions for a medicine;

6) Submitting to the Agency all the relevant information on the assessment of benefits and risks of a medicine, including information on the assessment of medicine administration after it is being marketed.

Activities of the person responsible for pharmacovigilance of the marketing authorization holder shall also ensure proper operation of the pharmacovigilance system in all other segments including quality assurance control, standard operating procedures, data bases, contract programs, compliance with the provisions e.g. quality, comprehensiveness and timeliness in reporting serious adverse reactions to a medicine, frequency of submission of PSURs, review and assessment of individual reports of adverse reactions and training of associates in pharmacovigilance.

#### **Article 17**

The person responsible for pharmacovigilance shall carry out the following activities:

1) Establish and maintain the system for collection, processing, assessment and storing of the information on all adverse events or reactions to a medicine reported to the manufacturer of a medicine, marketing authorization holder, persons promoting a medicine, or on adverse events and/or reactions to a medicine described in the scientific literature, regardless of the geographical origin of the source of information;

2) Propose measures to the Agency which should be taken for safety reasons, and provide comprehensive and timely replies and required information needed for the assessment of medicine safety and of a health risk during its administration;

3) Report to the Agency on all adverse reactions to a medicine, regardless of the severity and expectancy, and/or suspicion of them, including any suspected transmission of an infectious agent through a medicine that has occurred on the territory of the Republic of Serbia;

4) Report to the Agency on all serious adverse reactions to a medicine, and/or suspicion of them, including any suspected transmission of an infectious agent through a medicine that has occurred on the territory of the Republic of Serbia, not later than 15 days from the date of the first receipt of the information, whereas the prescribed period shall include initial and subsequent reporting;

5) Report to the Agency on all serious, unexpected adverse reactions to a medicine, and/or suspicion of them, that have been reported outside the territory of the Republic of Serbia, including any suspected transmission of an infectious agent through a medicine that has occurred outside the territory of the Republic of Serbia, immediately or not later than 15 days from the date of the first receipt of the information, whereas the prescribed period shall include initial and subsequent reporting;

6) Report in accordance with items 3), 4) and 5) of the Article on adverse reactions to a medicine during the post-marketing non-interventional clinical trial of a medicine (pharmacoepidemiological trial) financed by the manufacturer or marketing authorization holder;

7) Report to the Agency on all suspected medical errors, overdose, addiction, abuse and unauthorized administration of a medicine, absence of therapeutic efficacy of a medicine and clinically significant interactions.

The person responsible for pharmacovigilance shall conduct the activities set out in items 3)-7) of the Article by submitting the ICSR on the CIOMS-I form.

The standardized international form for the ICSR reporting (CIOMS-I) is presented in Attachment 7, which is enclosed to the Rulebook and makes its integral part.

#### **Article 18**

The ICSR shall contain at least the information on the following:

- 1) The party reporting an adverse reaction and/or marketing authorization holder;
- 2) The patient that can be identified (by initials, year of birth and gender);
- 3) The name of the medicine that is suspected to have caused an adverse reaction (trade name and/or INN);
- 4) An adverse reaction to a medicine.

#### **Article 19**

The marketing authorization holder shall not provide the general public and professional community with the information relating to the pharmacovigilance of a medicine without previously or simultaneously informing the Agency about this.

The information on pharmacovigilance referred to in paragraph 1 of the Article, which the marketing authorization holder shall provide to the public, shall be objective and/or the information shall not have the misleading character.

## **7. Detailed description of the pharmacovigilance system**

#### **Article 20**

The marketing authorization holder shall be responsible for creating the DDPS document and submitting it to the Agency.

The marketing authorization holder, whose manufacturer is based outside the Republic of Serbia, shall submit the document referred to in paragraph 1 of the Article, which shall contain a description of the global pharmacovigilance system made by the manufacturer and a description of the local pharmacovigilance system of the marketing authorization holder in the Republic of Serbia.

As an exception, a holder of the marketing authorization for a generic medicine shall in a cover letter submitted to the Agency provide an explanation as opposed to the absence of a description of the global pharmacovigilance system created by the manufacturer in the DDPS document.

The DDPS shall refer to all the medicines which the marketing authorization holder has the authorization for in the Republic of Serbia. In case there are any particularities in the pharmacovigilance system for a particular medicine for which the marketing authorization is issued, an appendix to the description of the pharmacovigilance system shall be submitted as part of the documents required for obtaining a marketing authorization.

The DDPS and its appendices shall be developed in Serbian or in English.

The contents of the DDPS are presented in Attachment 1, which is enclosed to the Rulebook and makes its integral part.

## **8. Risk Management Plan**

#### **Article 21**

The marketing authorization holder shall submit to the Agency a description of the risk management system in the form of the RMP document.

The contents of the RMP are presented in Attachment 2, which is enclosed to the Rulebook and makes its integral part.

#### **Article 22**

The marketing authorization holder shall submit to the Agency the RMP:

1) Together with the application for issuing an authorization to market a medicine which contains a new active substance; for a biologically similar medicine; for a generic medicine when in terms of the reference medicine existence of a safety risk has been determined which shall require additional activities for its minimization;

2) With specific requests for a variation (e.g. new strength of a medicine, new route of administration, changes in the manufacturing process of a biotechnical medicine, a significant change in the indication);

3) At the request of the Agency (in the process of obtaining the marketing authorization, and in the period after obtaining the marketing authorization);

4) On the initiative of the party proposing acquisition of the marketing authorization or on the initiative of the marketing authorization holder, when they identify a specific safety signal at any stage of the life cycle of a medicine.

#### **Article 23**

After obtaining the marketing authorization, the marketing authorization holder shall in addition to every PSUR also submit to the Agency the final RMP version with additional reporting on the results of risk management activities conducted on the territory of the Republic of Serbia.

### **9. Periodic Safety Update Report**

#### **Article 24**

The marketing authorization holder shall be obliged to inform the Agency about the date of placing a medicine on the market.

The marketing authorization holder shall be obliged to submit the PSUR to the Agency, at request, every six months during the first two years from the day of placement of a medicine on the market, and afterwards once a year during the following two years.

After the period referred to in paragraph 2 of the Article, the marketing authorization holder shall submit the PSUR to the Agency in three-year intervals, or immediately after obtaining information about all adverse reactions to a medicine.

The PSUR shall also have to contain professional assessment of the risk-benefit ratio of a particular medicine.

The PSUR shall be submitted to the Agency not later than 60 days after the deadline which it refers to.

The contents of the PSUR are presented in Attachment 3, which is enclosed to the Rulebook and makes its integral part.

#### **Article 25**

On the basis of the assessment of the submitted documents during the issuance of the marketing authorization, the Agency shall determine the frequency and deadlines for the submission of PSURs.

In order to harmonize the frequency and deadlines for the submission of PSURs in the European Union or in the manufacturer's country, and on the basis of the assessment of the safety profile of a medicine, the Agency may change the frequency and deadlines for the submission of PSURs referred to in Article 24, paragraph 2 of the Rulebook, after obtaining the marketing authorization.

The Agency may also change the frequency and deadlines for the submission of PSURs at the request of the marketing authorization holder.

The frequency of the submission of PSURs may not be longer than three years.

#### **Article 26**

For the products whose marketing authorization was issued on the basis of the centralized procedure in the European Union, the Agency shall receive the same PSURs in the same intervals and deadlines as in the European Union.

#### **Article 27**

The marketing authorization holder shall submit the PSUR also at the request of the Agency.

### **10. Post-marketing Safety Studies**

#### **Article 28**

PASS shall be conducted in order to identify previously unknown safety risks, investigate potential and identified risks, confirm known safety profile of a medicine in its approved use, assess the frequency of adverse reactions or identify the risk factor.

Conducting of PASS shall be sponsored by the marketing authorization holder, and it may be initiated by the marketing authorization holder or the Agency.

With a view to assessing the safety of a medicine administration, the Agency may require from the marketing authorization holder to conduct an appropriate PASS at the



time of issuing the marketing authorization or at any post-marketing stage of the life cycle of a medicine.

PASS shall not be conducted in the manner that promotes the use of a medicine.

#### **Article 29**

The person responsible for pharmacovigilance shall be involved in the drafting, review and assessment of the PASS protocol.

The marketing authorization holder shall submit to the Agency the final PASS protocol.

The marketing authorization holder shall be responsible for the monitoring of available data and for the assessment of its influence on the benefit-risk ratio in the administration of an investigational medicine during the PASS implementation.

The marketing authorization holder shall inform the Agency about every new piece of information which may affect the benefit-risk ratio during administration of a medicine.

The marketing authorization holder shall in the trial protocol determine responsibilities of reporting all adverse reactions resulting from PASS.

If PASS represents an interventional clinical study, reporting of adverse reactions shall be conducted in accordance with the provisions of the Rulebook on pharmacovigilance in clinical trials.

If PASS represents a non-interventional (pharmacoepidemiological) trial, depending on how it is defined by the trial protocol, the marketing authorization holder shall report adverse reactions in accordance with Article 17 of the Rulebook, or the investigator, in accordance with Article 8 of the Rulebook.

If PASS is a non-interventional (pharmacoepidemiological) trial, the marketing authorization holder shall inform the Agency about the date of involvement of the first patient in PASS in the Republic of Serbia and about the date of completion of collection of information in the Republic of Serbia.

#### **Article 30**

The marketing authorization holder shall be obliged to start and finish PASS within the deadline defined by the protocol and/or the RMP.

The marketing authorization holder shall be obliged to submit the final PASS report to the Agency not later than 12 months after completion of collection of information.

## **11. Letter to health care professionals**

#### **Article 31**

A letter to health care professionals (hereinafter referred to as the "DHCP"), shall contain the information for safe and effective administration of a medicine, which shall be submitted to the health care professionals by the Agency or the marketing authorization holder.

The DHCP shall not contain any elements of advertising a medicine.

#### **Article 32**

The DHCP shall be sent in the following cases:

- 1) Significant amendments in the summary of product characteristics (e.g. new contraindications, reduced recommended dosage, indication restriction, restrictions in the method of issuance of a medicine, new warnings and precautions, new significant adverse reactions which may jeopardise patient's safety, etc);
- 2) Withdrawal of the marketing authorization for safety reasons;
- 3) Suspension of the marketing authorization for safety reasons;
- 4) Other cases relevant for safe administration of a medicine.

#### **Article 33**

If the marketing authorization holder on his or her own initiative, or at the request of the Agency, sends the DHCP, he or she shall obtain an approval from the Agency of the draft wording and method of distribution before the DHCP is sent to health care professionals.

The marketing authorization holder shall submit to the Agency a list of health care institutions and/or health care professionals whom he or she sent the DHCP to, and/or to

agree with the Agency, before he or she sends the DHCP, what health care institutions and/or health care professionals shall the DHCP be sent to.

The marketing authorization holder shall in addition to the DHCP also forward the summary of product characteristics, at the request of the Agency.

Simultaneously with sending the DHCP, the Agency shall publish the wording of the DHCP on its website.

## **12. Urgent safety measures**

### **Article 34**

The marketing authorization holder shall, in case he or she learns that there is a risk to the public health during administration of a medicine, initiate introduction of urgent safety measures, and he or she shall be responsible to immediately inform the Agency about this in writing.

If the Agency sends no comments within 24 hours from the moment of receiving a written notification, the urgent safety measures referred to in paragraph 1 of the Article, shall be treated as accepted.

If there is a risk to public health, the Agency may require introduction of urgent safety measures.

The Agency shall inform the ministry competent for health care affairs and health care professionals about urgent safety measures immediately or not later than 15 days from the date of introduction of the urgent safety measures.

The urgent safety measures referred to in paragraph 1 of the Article shall be taken in case of a change in the benefit-risk ratio in terms of the health which shall require significant changes in the status of a medicine, and which shall refer to the following:

- 1) Withdrawal of a medicine from the market;
- 2) Amendments to the summary of product characteristics such as introduction of contraindications, warnings or precautions, reduction of a recommended dosage, indication restriction;
- 3) Informing health care professionals and patients about newly founded risk during administration of a medicine, without delay.

## **13. Medicines and Medical Devices Agency of Serbia**

### **Article 35**

The Agency shall, in accordance with the Law, organize and monitor the method of collection and assessment of information about safe administration of medicines marketed in the Republic of Serbia and, if required, take the measures set out in Article 40 of the Rulebook.

In conducting the activities referred to in paragraph 1 of the Article, the Agency may from the marketing authorization holder require to conduct appropriate measures in the risk management system.

### **Article 36**

The Agency shall encourage health care professionals and patients to report adverse reactions to medicines and/or suspected adverse reactions to medicines.

### **Article 37**

The Agency shall participate in the programs of international monitoring of medicine safety of the World Health Organization and participate with the Uppsala Monitoring Centre.

### **Article 38**

The Agency may make a list of medicines with the issued marketing authorization, which shall be labelled with special labels for intensive monitoring of their safety profile.

The Agency shall update the list referred to in paragraph 1 of the Article and publish it on its website.

### **Article 39**

The Agency shall perform the following activities, in accordance with the Law:

1) Collect, process and assess information from the post-marketing non-interventional clinical trial of a medicine (pharmacoepidemiological trial), which shall be obtained from the marketing authorization holder;

2) Notify the marketing authorization holder of serious adverse reactions to a medicine immediately or not later than 15 days from the date of receiving the information;

3) Create a database of information collected through spontaneous reporting in pharmacovigilance that is available to the public and competent authorities in the country and abroad;

4) Exchange information collected in the pharmacovigilance system with the authorities competent for pharmacovigilance in other countries.

#### **Article 40**

On the basis of collected information about adverse reactions to medicines on the market, the Agency may:

1) Change the conditions of the marketing authorization;

2) Adopt a decision to withdraw the marketing authorization or to suspend the marketing authorization;

3) Propose to the ministry competent for health affairs to suspend or prohibit manufacturing and/or marketing of a medicine and/or withdraw a medicine from the market.

#### **Article 41**

The Agency shall monitor implementation of prescribed obligations and deadlines in the field of pharmacovigilance and, in accordance with the Law, may propose to the competent inspectors to conduct an emergency inspection in case of non-implementation of regulations in the field of pharmacovigilance.

### **14. Regional pharmacovigilance centers**

#### **Article 42**

Regional pharmacovigilance centers shall, in accordance with the Law, conduct activities of collection, processing and submission of information to the Agency about recorded adverse reactions to medicines for a particular territory of the Republic of Serbia.

The activities referred to in paragraph 1 of the Article shall refer to the following:

1) Collection and professional assessment of reported cases and entry of data in a uniform national database;

2) Regular submission of data and providing replies to the Agency;

3) Providing feedback to reporters and answers to the questions related to adverse reactions to medicines;

4) Conducting pharmacovigilance research on the initiative of and in cooperation with the Agency;

5) Encouraging health care professionals to report on adverse reactions to medicines.

A regional center shall appoint a person who shall be responsible for coordination of operation of the center and direct cooperation with the Agency.

The employees of a regional pharmacovigilance center shall undergo the provisions of Article 14, para. 5 and 7 of the Rulebook.

### **III. PHARMACOVIGILANCE IN THE CLINICAL TRIAL OF A MEDICINE**

#### **Article 43**

The sponsor shall be responsible to timely inform the Agency about a serious and unexpected adverse reaction in the clinical trial of a medicine.

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

The sponsor shall make assessment of the reports referred to in paragraph 2 of the Article.

The sponsor shall be obliged to immediately inform all the investigators, Ethics Committee and Agency about all findings that could adversely affect health of trial participants, conducting of a trial or abolition of a decision on the approval of conducting a clinical trial.

The sponsor shall be obliged to keep detailed records of all adverse events reported to him or her by the investigator, and to 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 44**

The sponsor who has an authorization to conduct an interventional clinical trial of a medicine in the Republic of Serbia shall report to the Agency the following as mandatory:

- 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 of the marketing authorization holder on the territory of the Republic of Serbia.

If a multicenter clinical trial is also conducted in the Republic of Serbia, the sponsor shall report serious, unexpected adverse reactions to a medicine which occurred in any of the countries outside the Republic of Serbia in which a clinical trial is conducted.

The sponsor who has an authorization to conduct a clinical trial in the Republic of Serbia shall submit to the Agency all relevant safety information about a medicine whose investigation is conducting in Serbia, and which originates from other clinical trials.

#### **Article 45**

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 referred to in paragraph 1 of the Article.

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.

The sponsor shall submit to the Agency an annual periodic report on all adverse reactions which occurred in a clinical trial of a medicine, and after completion of a trial, he or she shall submit the final report on the safety of an investigational medicine.

The contents of the annual safety report are presented in Attachment 6, which is enclosed to the Rulebook and makes its integral part.

#### **Article 46**

The initial report referred to in Article 45 of the Rulebook shall contain at least the following information:

- 1) The identification code of a patient (trial participant);
- 2) The information about an investigational medicine and about a medicine suspected to have caused an adverse reaction;

- 3) Exhibited adverse event which is assessed to be serious and unexpected, and which is suspected to be related to the administration of a medicine;
- 4) The identification number of a clinical trial;
- 5) The name and address of the sponsor.

#### **Article 47**

In case of incomplete information about a case, the sponsor shall be obliged to actively gather from the investigator all the relevant information required for the assessment of the causal link and submit them in the report referred to in Article 45 of the Rulebook. The follow-up report shall contain all the relevant information on the following:

- 1) The 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) The patient and/or trial participant: initials, identification code, age, gender, weight, height, country;
- 3) The 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 administration of a medicine;
- 4) Adverse reactions;
- 5) Concurrent medicines, including non-prescription medicines (traditional and homeopathic medicines), diet products etc, with the same information as for the medicine suspected to have caused a reaction;
- 6) The party reporting an adverse reaction: name and surname, phone number, occupation, signature and date of the report;
- 7) The sponsor: name and address of the sponsor, date when serious, unexpected adverse reactions were reported to the sponsor.

#### **Article 48**

The information on adverse reactions referred to in Article 47, item 4) of the Rulebook, shall contain the following:

- 1) A 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) The date and time of the commencement and cessation of reactions;
- 3) The corrective therapy and other measures taken in relation to the occurred adverse reactions;
- 4) The information on the presence or absence of adverse reactions after stopping with the administration of a medicine and after re-introduction of a medicine;
- 5) The information about the outcome of exhibited 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) The 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 49**

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

The CIOMS-I form is presented in Attachment 7, which is enclosed to the Rulebook and makes its constituent part.

#### **Article 50**

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 an exhibited 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 51**

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

#### **Article 52**

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

- 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 ministry competent for health affairs to suspend or prohibit a clinical trial of a medicine.

### **IV. REPORTING DEVIATIONS FROM THE STANDARDS OF QUALITY OF A MEDICINE BY A HEALTH CARE PROFESSIONAL**

#### **Article 53**

Deviation from a prescribed medicine quality standard (hereinafter referred to as the "deviation from the quality standard") shall mean any difference in the appearance, physical and chemical, microbiological and pharmaceutical and technological properties between a medicine and information from the marketing authorization.

Deviation from the quality standard shall also mean any discrepancy between the outer and immediate packaging of a medicine and package leaflet and information in the marketing authorization.

Deviation from the quality standard of a medicine class I shall include such a deviation from the quality standard of a medicine which may be life-threatening or pose a serious threat to the human and animal health, and it shall refer to the following:

- 1) Wrong product (the labelling and composition of a product do not refer to the same product);
- 2) Wrong strength which may cause serious medical consequences;
- 3) Microbiological contamination of sterile parenteral or ophthalmic products;
- 4) Chemical contamination which may cause serious medical consequences;
- 5) Wrong active substance in a medicine having several active substances, which may cause serious medical consequences.

Deviation from the quality standard of a medicine class II shall include such a deviation from the quality standard of a medicine which may cause a disease or inadequate treatment, and which may refer to the following:

- 1) Wrong labelling (incorrect or omitted wording or data);
- 2) Absence of package leaflet or wrong instructions;
- 3) Microbiological contamination of sterile medicines which do not fall into the group of parenteral and ophthalmic products, and which may have medical consequences;
- 4) Chemical or physical contamination (larger amount of impurities, cross-contamination, mechanical impurities);
- 5) Deviation of medicine quality from the specification requirements (amount of the active substance, stability, filling);

6) Loose seal on the packaging which may cause serious medical consequence (medicines with strong effect, cytotoxic medicines, medicines with safety caps).

Deviation from the quality standard of a medicine class III shall include a deviation from the quality standard of a medicine which does not pose a particular risk to the human and animal health, however, a medicine may be withdrawn from the market for other reasons related to the following:

- 1) Lack or incorrect data on the package (absence or incorrect batch number or expiry date);
- 2) Poor package sealing;
- 3) Microbiological or mechanical impurities.

#### **Article 54**

Health care institutions shall have an established system for handling cases of detected deviation from the quality standard of medicines.

Health care professionals who are in contact with a medicine shall be obliged to report in a written form to the ministry competent for health affairs any detected and/or determined deviation from the quality standard of a medicine.

The report form referred to in paragraph 2 of the Article is presented in Attachment 8, which is enclosed to the Rulebook and makes its integral part.

If a deviation from the quality standard of a medicine according to the assessment of a health care professional represents a serious risk to the public health, the health care professional shall as soon as possible inform the ministry competent for health affairs about this by phone.

#### **Article 55**

If a health care professional detects a deviation from the quality standard of a medicine before he or she has issued the medicine, the health care professional shall not issue the medicine to the customer and he or she shall inform medicine inspection about this.

If a health care professional detects a deviation from the quality standard of a medicine during its administration to the patient in a health care institution, the health care professional shall inform medicine inspection about this and terminate administration of the medicine.

The health care professional referred to in para. 1 and 2 of the Article shall ensure that a medicine, or in case of suspected validity of the whole batch, medicines with the same batch number are not used and/or kept for the sampling requirements of the medicines and medical devices inspector.

#### **Article 56**

The completed report form referred to in Article 54, paragraph 3 of the Rulebook shall be submitted by a health care professional by mail, by electronic mail or by fax to the ministry competent for health affairs within 12 hours after a detected deviation from the quality standard, if the sample of a medicine with suspected quality has been administered to a patient, and/or within 24 hours, if the sample of a medicine with suspected quality has not been administered to a patient.

#### **Article 57**

In case a determined deviation from the quality standard belongs to class I and represents a serious risk to the public health, the competent ministry shall inform the population about the withdrawal of a medicine from the market.

## **V. FINAL PROVISIONS**

#### **Article 58**

The Rulebook on the method of reporting, collecting and monitoring of adverse reactions to medicines ("Official Gazette of RS", No. 99/06) shall cease to be affective on the date of entry into force of the Rulebook.

#### **Article 59**

The Rulebook shall enter into force eight days after the date of its publication in the "Official Gazette of the Republic of Serbia".

## **ATTACHMENT 1**

### **Contents of the document - Detailed Description of Pharmacovigilance System (DDPS)**

The Detailed Description of Pharmacovigilance System shall include information from the global and local system which may create a part of the Detailed Description of Pharmacovigilance System created by the manufacturer and/or Detailed Description of Pharmacovigilance System of the applicant and/or marketing authorization holder in the Republic of Serbia.

Parts of the Detailed Description of Pharmacovigilance System shall be as follows:

1. Information on the person responsible for pharmacovigilance of the marketing authorization holder in the Republic of Serbia:

- A brief description of activities of the person responsible for pharmacovigilance;
- A description of the support system in case of absence of the person responsible for pharmacovigilance;
- Attachment 1 which shall contain CV of the person responsible for pharmacovigilance, CV of the deputy of the person responsible for pharmacovigilance and contact information about the person responsible for pharmacovigilance and support system (address, phone number, cell number, e-mail, etc) which may be identical with the contact information submitted during the registration of the person responsible for pharmacovigilance and his or her deputy in the Agency;

2. Organization of the pharmacovigilance system:

- The name and seat of the global pharmacovigilance division;
- Places of availability of all the information about pharmacovigilance (individual cases of adverse reactions to a medicine, PSURs and global information on pharmacovigilance);
- Charts of organizational units of the pharmacovigilance system with a short description of activities conducted by a particular unit, including contract organizations;
- Charts of the flow of processing and reporting on individual cases of adverse reactions to a medicine, PSURs and other information about pharmacovigilance (show the connection between the person reporting an adverse reaction-global unit-marketing authorization holder-Agency);

Note: The parts of the Detailed Description of Pharmacovigilance System referred to in items 1 and 2 of the Rulebook shall be described by the marketing authorization holder in the Republic of Serbia.

3. Documented procedures:

It is necessary to specify for which of the following activities require written procedures:

- Activities of the person responsible for pharmacovigilance in the Republic of Serbia and support system in case of absence of the responsible person;
- Collecting, processing, control, coding, classification, medical assessment and reporting on individual cases of adverse reactions to a medicine (separately stated for local reports and reports on adverse reactions to a medicine from other countries);
- Request for additional information on reported adverse reactions to a medicine;
- Detecting duplicate reports of adverse reactions to a medicine;
- Procedure for emergency reporting on adverse reactions to a medicine;
- Preparation, processing, quality control, assessment and submission of PSURs;
- Continuous monitoring of safety profiles of medicines (detecting signals, assessment of the benefit-risk ratio in the administration of a medicine, notifying regulatory bodies and health care professionals about amendments to the safety profile of a medicine, etc),



- Relation between the safety and administration of a medicine and defects in the medicine quality;
- Reply to the requests of the regulatory bodies;
- Actions in case of emergency safety measures and amendments to the marketing authorization on the basis of the information about safe administration of a medicine;
- Execution of requests of regulatory bodies;
- Use of the database and other data recording systems;
- Internal supervision of the pharmacovigilance system;
- Training of employees;
- Archiving;

#### 4. Databases

Inventory of the main databases, their locations and a brief description (a commercial base or a locally developed database), validation method;

#### 5. Contractual relations

List main contractual relations related to pharmacovigilance. A description of the system shall contain the following: roles of contract partners, joint marketing, person responsible for pharmacovigilance, emergency reporting of adverse reactions to a medicine, keeping a database of adverse reactions to a medicine, assessment of the benefit-risk ratio and drafting PSURs.

Considering that the information about contract partners may be different for every finished medicine, the marketing authorization holder in the Republic of Serbia shall present the information about contract partners in the form of an appendix to the Detailed Description of Pharmacovigilance System for each individual request, which in the process of issuing a marketing authorization and/or amendment and/or renewal of a marketing authorization, shall be attached to the Module 1, item 1.8.1.

#### 6. Training of employees

It is necessary to describe the contents of the training and state where the training records, CVs and job descriptions shall be archived. The training on pharmacovigilance should be attended not only by the employees who are directly involved in pharmacovigilance, but also by all the employees involved in the sale and/or promotion of the medicines of the marketing authorization holder.

#### 7. Documents

It is necessary to give a description of locations of original documents (reports on adverse reactions from the Agency, from health care professionals, records of meetings, etc), including archiving.

#### 8. Quality assurance system

Briefly describe the quality assurance system which shall supervise the pharmacovigilance system, including supervision of contract organizations.

#### 9. Supporting documents

The Detailed Description of Pharmacovigilance System shall demonstrate that such a system exists and that it has been accordingly documented. The supporting documents shall not be enclosed (SOP, etc), however, it must be available and submitted at the request of the Agency.

For particular medicines, the Detailed Description of Pharmacovigilance System should be supported by an appendix if some procedures refer only to a particular medicine. The appendix shall be submitted together with the application for issuing a marketing authorization and/or amendment and/or renewal of the marketing authorization with the Module 1, item 1.8.1.

When drafting a local description of the pharmacovigilance system, the applicant may in specific items of the local plan refer to the global plan to avoid repetition of the parts contained in the global plan.

## Contents of the document – Risk Management Plan (RMP)

### Part I:

1. Safety specification
2. Pharmacovigilance plan

### Part II:

3. Assessment of the need for conducting risk minimization activities
4. Risk minimization plan

#### 1. Safety specification

The safety specification shall define identified risks, potential risks and risks resulting from the lack of significant information and it shall contain at least the following parts:

##### 1.1 Pre-clinical data

1.1.1 Toxicity (including toxicity in repeated dosage, reproductive and/or developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity, etc).

1.1.2. General pharmacovigilance (cardiovascular system, including prolongation of the QT interval, nervous system, etc).

##### 1.1.3 Medicine interactions

##### 1.1.4 Other data related to medicine toxicity.

##### 1.2 Clinical data

##### 1.2.1 Limited data on the safety of administration of a medicine to human subjects

1.2.2. Exposure (exposure in clinical studies, exposure in epidemiological studies and in the post-marketing period)

1.3. Populations not investigated at the pre-registration stage (children, elderly, pregnant or lactating women, patients with relevant comorbid conditions such as hepatic or renal disorders, patients with varying severity of a disease compared to the one investigated in clinical studies, carriers of known and relevant genetic polymorphisms, patients of different race and/or ethnicity)

##### 1.4 Post-marketing experience

1.4.1. Information on the intended administration of a medicine after receiving it and/or significant amendments to the marketing authorization (initial RMP or significant change of an indication)

1.4.2. Actual data on the administration of a medicine after receiving the marketing authorization (subsequent RMP versions)

##### 1.4.3. Conducted regulatory measures

##### 1.5 Adverse events and/or adverse reactions

##### 1.5.1. New identified safety issues (since the last submitted version of the RMP)

1.5.2. Detailed information about identified and potential risks, including new identified risks

1.6. Identified and potential interactions with other medicines, food and other substances

##### 1.7. Epidemiological data on an indication and relevant adverse events

1.7.1. Incidence, prevalence, mortality and demographic profile of the target population for every indication

##### 1.7.2. Significant comorbidities in the target population for each indication

1.7.3. Epidemiological data on identified or potential risks (e.g. liver failure) in the target population not exposed to a medicine

##### 1.8. Pharmacological class effects

##### 1.9. Additional requirements

##### 1.9.1. Overdose potential

##### 1.9.2. Potential of transmission of an infectious agent

##### 1.9.3. Potential of abuse

##### 1.9.4. Potential of off-label use

##### 1.9.5. Potential of off-label use in pediatric population

1.10 A summary of existing safety issues (identified risks, potential risks and risk resulting from the lack of relevant information)

2. Pharmacovigilance plan

2.1. Routine pharmacovigilance

2.2. Summary of existing safety issues and planned pharmacovigilance activities (routine and/or additional)

2.3. Detailed action plan for specific safety issues

2.4. Overview of protocols of studies within the pharmacovigilance plan

2.5. Overview of available results and impacts on the safety specification (for the subsequent RMP versions)

2.6. Summary of activities with envisaged objectives and deadlines

3. Assessment of the need to conduct risk minimization activities

3.1. Table overview of planned activities for every risk according to the safety specification

3.2. Potential for medical errors

4. Risk minimization plan (in case of additional minimization activity)

5. Summary of the Risk Management Plan

6. Contact details

RMP appendices (summary of product characteristics, package leaflet, summary of ongoing and completed clinical and pharmacoepidemiological studies, protocols for planned and ongoing studies within the pharmacovigilance plan, available study reports, details of planned educational program, etc).

Educational program shall not contain any form of advertising a medicine.

## ATTACHMENT 3

### Contents of the document – Periodic Safety Update Report (PSUR)

PSUR shall contain a cover page with the following information:

1) The trade name of a medicine;

2) The name and address of the legal entity which created the PSUR on the basis of manufacturer's data;

3) The international birth date (IBD);

4) The period covered by the periodical report;

5) The date of development of the document.

PSUR shall contain:

An abstract with the following information:

- An updated registration status of a medicine worldwide;

- The degree of exposure of patients to a medicine;

- The information about the number of reports of adverse reactions to a medicine;

- The summary of the most important findings;

- Conclusions.

1) An introduction with basic data on a medicine (in addition to other data, the summary should contain the date and number of the existing marketing authorization and/or its renewal, of every pharmaceutical form, strength and packaging of a medicine);

2) A list of the countries in which a medicine has the marketing authorization and/or in which the application for obtaining a marketing authorization has been refused: the date shall be stated for the first marketing authorization issued in all the countries where an application for obtaining a marketing authorization was reviewed, as well as the date of the last renewal, date of placing a medicine on the market (launch dates), conditions from the marketing authorization (e.g. restriction of the scope of indications), refusal of an application for obtaining or renewing a marketing authorization or withdrawal of an application, as well as the trade name of a medicine and approved indications for the administration of a medicine;

3) An overview of measures taken for safety reasons (the dates and reasons for taken measures shall be stated such as: prohibition of the post-marketing interventional clinical

trial of a medicine, refusal of an application for issuing a marketing authorization or revocation of the marketing authorization, distribution restriction, and/or withdrawal of a medicine from the market, change in the dosage, scope of indications, target population, or formulation, DHCPs forwarding, emergency safety measures and other safety measures);

4) Changes in the reference document on a medicine and/or in the basic manufacturer's document on a medicine from the period to which the previous PSUR refers to (all changes are stated in the basic manufacturer's document on a medicine or in the summary of product characteristics relating to the information about the safety of medicine, new contraindications, precaution measures and warnings, adverse reactions or interactions already entered in the basic document in the period for which the periodical report was drafted, wherein the revised documents are used as references for the next periodical reporting);

5) A degree of exposure of a patient to a medicine (state the estimated number of the patients on a therapy with a medicine in the reporting period in the country or abroad, or other measures of exposure of a patient to a medicine with a description of the method used such as e.g. the number of patients who received a medicine in a single day, the number of dosage units - pills, capsules, etc, number of defined doses, number of prescriptions and/or order and number of packaging sold);

6) An overview of individual cases (when describing cases, terminology for adverse reactions should conform to the standard terminology of the World Health Organization - WHO-ART, and /or the Medical Dictionary for Regulatory Activities - MedDRA, with mandatory use of the terminology which the primary investigator used in a report, provided that the complex of symptoms listed in a report may be proposed, and thus use the appropriate diagnosis against the medical classification of diseases - MKB-10).

A list of cases (the list should include all the cases of serious adverse reactions to a medicine reported spontaneously by the authority competent for monitoring pharmacovigilance occurring in post-marketing trials or described in the literature, as well as unexpected reactions which are not serious in their character, and are reported spontaneously or described in the literature) with the following information:

- Report reference number;
- The country in which the case was registered;
- A source of data;
- Patient's age and gender;
- The daily dose, dosage regime and route of administration of a suspect medicine;
- The date of commencement and date of cessation of a reaction or the best estimate of the time of its exhibition from the commencement of the therapy with a medicine, or delay of a reaction after stopping with the administration of a medicine;
- The duration of a therapy;
- A description of adverse reactions;
- The outcome of adverse reactions (e.g. unknown, recovery, hospitalization, permanent consequences, congenital anomalies, threat to life, death);
- Important comments: assessment of the causal link between a medicine and reaction, concurrent medicines, indications for the administration of a suspect and other medicines and, if available, results of stopping of administration and reintroduction of a medicine).

A summary table overview of adverse reactions (the table overview should be enclosed to every list of cases, provided that serious adverse reactions should be presented in a separate table). The summary table overview shall contain the number of exhibited adverse reactions with the report identification number, and adverse reactions shall be presented according to the system of organs where they occurred and according to the source of information – databases of the World Health Organization, spontaneously reported to the Agency, spontaneously reported to the marketing authorization holder, clinical trial, pharmacoepidemiological study, a case described in the literature.

An analysis of individual cases (brief comments of the marketing authorization holder related to the information specified for every individual case, as well as an analysis of all serious and unexpected adverse reactions in terms of their nature, mechanisms of occurrence of a reaction, clinical importance and frequency of reporting).

7) An overview of studies (concisely presented results and/or new analysis of results of all completed pre-clinical, clinical and epidemiological studies significant for the safety of a medicine, as well as all the studies which are in progress or are planned for safety reasons, in addition to the basic information about all the listed trials and their objectives, as well as results of the studies published in the literature);

8) Information about a medically significant report on the absence of efficacy of the medicine intended for prevention or therapy of a severe disease that is life-threatening, new and significant information collected subsequently, information relating to the RMP, assessment of the benefit-risk ratio;

9) An assessment of the total safety of a medicine (implies a short analysis of all submitted information with particular emphasis on all new information related to the change of the character of an expected adverse reaction or its seriousness, or outcome of a reaction, as well as patients with expressed reaction, increased frequency of expected reactions, unexpected adverse reactions, interactions, overdose, misuse, abuse, administration during pregnancy and lactation, administration to children, elderly and persons with damaged organs, as well as effects of long-term administration);

10) A conclusion (it should emphasize information about the safety of a medicine which shall change the previous cumulative experience of the medicine, as well as specific measures to be taken, providing a statement of reasons).

The enclosed PSUR contains manufacturer's reference document on a medicine which contains reference safety information about a medicine which were used for the development of the PSUR.

Additionally, the cover letter, which shall be enclosed to the PSUR, shall contain all relevant differences between the last approved summary of product characteristics and applicable reference safety information.

## **ATTACHMENT 4**

### **Contents of the document – Summary Bridging Report (SBR)**

The Summary Bridging Report shall provide a short incorporated overview of two or more PSURs or PSURs and Addendum Report, and it shall not contain any new information.

The format of the Summary Bridging Report shall be identical to the PSUR format, however, the contents shall consist of the summary of the main conclusions and overviews of the information taken from PSURs.

The Summary Bridging Report shall contain the following information:

1) An introduction (a brief description of the purpose of the document specifying the period and PSURs which the document refers to and which are enclosed in the attachment);

2) The registration status of a medicine in the world (the number of countries where a medicine is authorized and/or registered);

3) An overview of measures taken for security reasons by the regulatory authorities or marketing authorization holders (the summary of measures, if undertaken);

4) Significant changes in safety information in a reference document on a medicine during the entire reporting period;

5) The extent of exposure of a patient to a medicine (an assessment of the total number of exposed patients during the reporting period);

6) An overview of individual cases (a brief statement on the total number of cases presented in a set of PSURs classified according to organ systems, seriousness and expectancy). When there is an important safety issue that has not been properly addressed in one or more PSURs, a cumulative list of individual cases should be made

or a table overview of the cases of special interest with registered adverse reactions classified according to the System Organ Class (SOC), seriousness and expectancy, in the period including the Summary Bridging Report; it is necessary to emphasize if there are differences in comparison to the previous lists of individual cases and table overviews, and explain those differences;

7) Studies (the summary of main targeted clinical safety trials);

8) Other information (only highly significant safety information recorded after the data lock point);

9) An overview of safety issues;

10) A conclusion.

In addition, the cover letter, which shall be enclosed to the Summary Bridging Report, shall also contain all relevant differences between the approved summary of product characteristics and applicable reference safety information.

## **ATTACHMENT 5**

### **Contents of the document – Addendum Report**

The Addendum Report shall represent a complement to the last PSUR and shall be developed in case the Agency needs to be submitted with an appendix on safety information in addition to the usual cycle of submissions of PSURs. The Addenda Report shall be submitted three months or more after the DLP of the last biannual or annual PSUR and/or six months or more after the DLP of the last PSUR that covers a period over one year. It is also possible to issue the Addenda Report which shall complement the SBR.

The Addenda Report shall contain safety information about a medicine collected in the period between the DLP of the last PSUR and the date required by the Agency, and shall not present a detailed analysis of cases, as they will be included in the next PSUR. Depending on the circumstances and scope amount of collected information, the Addenda Report may have the PSUR or a simplified format.

The Addenda Report with a simplified format shall contain the following sections:

1) An introduction (purpose; stating the PSUR with complemented Addenda Report);

2) Changes of reference safety information about a medicine;

3) An overview of significant measures to be taken due to safety reasons by the regulatory authorities or marketing authorization holders;

4) A list of individual cases or a table overview of adverse reactions;

5) A conclusion.

## **ATTACHMENT 6**

### **Contents of the document –Annual Safety Report**

The Annual Safety Report for a clinical trial shall consist of the following three parts:

- Part I: Analysis of the safety of trial participants in the relevant clinical trial;

- Part II: Line listing of all serious adverse reactions (including all serious unexpected adverse reactions) which have occurred in the relevant clinical trial, including those occurring in the world;

- Part III: A summary table overview of all serious adverse reactions occurring in the relevant trial.

Part I: Analysis of the safety of trial participants in the relevant clinical trial

This section shall give a short overview and analysis from the safety aspect of all relevant information that could have a significant impact on trial participants, and assessment of the benefit-risk ratio in the relevant clinical trial. This section shall in a concise manner describe all new and relevant information obtained by the sponsor, and which are related to the safety of trial participants in the relevant clinical trial. This shall include new information about the safe administration of an investigational medicine or

other therapy used in a clinical trial, as well as all other information relating to trial procedures. New information about an investigational medicine shall refer to the information that is not listed in the applicable reference document (investigator's brochure or summary of product characteristics) at the beginning of the period that the report refers to. Conclusions and/or recommendations of the independent Data Monitoring Committee shall be reviewed and attached to the report.

This section shall contain an analysis of the safety profile of an investigational medicine taking into account all available safety data, including also exclusion of a trial participant from a trial due to safety reasons. This section shall review the following issues:

- The dosage, duration of administration and progress of treatment;
- Reversibility;
- Evidence of previously unknown toxic effect on a trial participant;
- An increased frequency of toxic effect;
- Overdose and overdose treatment;
- Interactions or other associated risk factors;
- Specific safety issues related to the administration of a medicine to a specific population such as the elderly, children or other risk group;
- Positive and negative experience during pregnancy and/or lactation;
- Abuse;
- Risks that could be associated with a laboratory trial or diagnostic procedure used in a clinical trial;
- Risks that could be associated with inadequate quality of an investigational medicine.

The report should also review results of pre-clinical tests and other experience with an investigational medicine that are likely to influence the safety of trial participants.

The report should also contain an analysis of a possible effect of new safety data on the trial population such as:

- Previously and currently proposed measures for minimizing the identified risk;
- A detailed explanation of the need to introduce amendments to the plan for a trial, informed consent and investigator's brochure.

The end of the first part of the summary Annual Safety Report should contain re-assessment of the benefit-risk ratio.

#### Part II: Line listing of all serious adverse reactions

This part should contain an overview of all suspected serious adverse reactions which were reported from all trial sites in the period which the report refers to.

The line listing shall provide key information, but not necessarily all collected information about individual cases.

The line listing shall include every trial participant only once, regardless of the number of reported adverse reactions. In case more than one adverse reaction is reported, all adverse reactions shall be listed, however, the case shall be recorded according to a reaction which shall be considered as the most serious according to the assessment of the sponsor.

It is possible to record several adverse reactions for the same trial participant in different intervals. In this case, individual reporting shall be considered an individual case. Therefore, it may happen that the same trial participant occurs several times in one line listing in which case cross-reference is recommended

Cases shall be presented according to the MedDRA SOC.

Most often only one line listing shall be created for every trial, however, separate line listings may also be created for the control medicine or placebo, if this is required or relevant, such is the case with the trials of different medicine formulations, indications, or route of administration of an investigational medicine, etc. Expectancy of adverse reaction at the moment of their occurrence shall be assessed in comparison to the reference document that was valid at the beginning of the period which the Annual Safety Report refers to.

#### Part III: A summary table overview of all suspected serious adverse reactions

The summary table overview of all serious adverse reactions recorded in a clinical trial shall provide an overview of trials. The table overview shall contain signs, symptoms and/or diagnosis or serious adverse reactions of all trial participants. For this reason, the table overview shall in most cases contain a larger number of signs, symptoms and/or diagnosis than trial participants. When the number of recorded adverse reactions is small, it is more appropriate to give a short descriptive overview.

The table overview shall list the total number of reports classified according to the following criteria:

- The organ system;
- An adverse reaction;
- For every therapy group, if applicable (an investigational medicine, comparator or placebo, blinded therapy).

Unexpected adverse reactions may be clearly indicated in the table overview.

In case the sponsor conducts several trials with the same medicine in the Republic of Serbia and/or European Union, he or she shall be responsible to prepare one joint Annual Safety Report which shall include all trials. In this case, the report shall contain:

- A short global analysis of the safety profile of an investigational medicine, taking into account all new and relevant information related to the administration of an investigational medicine and analysis of a possible effect of the information on the trial population;
- Annual safety reports for every individual clinical trial.



# ATTACHMENT 7

<b>SUSPECT ADVERSE REACTION REPORT</b>																					
	<table border="1" style="width: 100%; height: 20px; border-collapse: collapse;"> <tr> <td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td><td style="width: 5%;"> </td> </tr> </table>																				

### I. REACTION INFORMATION

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

### II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG 1of 1 (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 DRUGS 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	Spontaneous report	
24c. DATE RECEIVED BY MANUFACTURER		24b. MFR CONTROL NO.
		24d. BY MANUFACTURER STUDY LITERATURE HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE INITIAL <input type="checkbox"/> FOLLOWUP <input type="checkbox"/>	

## REPORTING DEVIATIONS FROM THE STANDARD OF QUALITY OF A MEDICINE

**URGENT**

<b>Report No:</b>	
<b>Ministry of Health</b> Nemanjina Street No. 22-26 11000 Belgrade <span style="float: right;">Phone:</span>	
Level of urgency: I    II    III    (circle)	Type of product (circle): medicine medical device
Name of product:	Pharmaceutical form:
Strength:	Type and size of packaging:
Batch number:	Expiry date:
Marketing authorization older and/or holder of a medical device entry into the Registry:	
Manufacturer:	
Description of a detected deviation from the quality standard	
Date and time of a detected deviation from the quality standards:	
Name, surname and phone number of the person detecting a deviation from the quality standards:	
Name and address of the institution of the person who detected a deviation from the quality standards:	
Patient's initials:	Institution where the medicine is administered:
Taken measures in terms of the patient:	
Name, surname and phone number of the person reporting a deviation from the quality standard:	
Signature:	Date: Time:

Агенција за лекове и медицинска средства Србије	Војводе Степе 458, 11152 Београд Тел: 011 39 51 145 Факс: 011 39 51 130 И-мејл: <a href="mailto:mf@alims.gov.rs">mf@alims.gov.rs</a> <a href="http://www.alims.gov.rs">www.alims.gov.rs</a>	Број: Датум:
	НЦФ бр:	СЗО бр:
Регионални центар за фармаковигиланцу		

### Образац за пријављивање НЕЖЕЉЕНИХ РЕАКЦИЈА НА ЛЕК (НРЛ) за здравственог радника

Уколико сумњате да је нежељена реакција у вези са применом једног или више лекова/вакцина, молимо Вас да попуните овај образац и пошаљете га поштом, факсом или и-мејлом. Немојте одустати ако Вам неки подаци недостају. Довољна је само сумња на нежељену реакцију. Нека Вам не буде тешко да попуните образац, јер подаци могу бити значајни за безбедну примену лекова

1. ПОДАЦИ О ПАЦИЈЕНТУ И НЕЖЕЉЕНИМ РЕАКЦИЈАМА НА ЛЕК (НРЛ)											
Иницијали*	Датум рођења	Старост*	Тежина г	Пол*	ПОЧЕТАК НРЛ*			ЗАВРШЕТАК НРЛ			Да ли сматрате испољене реакције озбиљним? <input type="checkbox"/> ДА <input type="checkbox"/> НЕ
				<input type="checkbox"/> М <input type="checkbox"/> Ж	дан	месец	година	дан	месец	година	
ОПИС РЕАКЦИЈА* (знаци или симптоми, укључујући релевантне податке лабораторијских тестова):										Означити поља уколико је НРЛ узроковала: <input type="checkbox"/> смрт <input type="checkbox"/> животну угроженост <input type="checkbox"/> укључење или продужење болничког лечења <input type="checkbox"/> трајно или тешко оштећење/инвалидност <input type="checkbox"/> конгениталне аномалије <input type="checkbox"/> медицински значајно стање (навести):	
ДИЈАГНОЗА / СИНДРОМ ИСПОЉЕНИХ РЕАКЦИЈА:											
ПРИМЕЊЕНА ТЕРАПИЈА ЗА ЛЕЧЕЊЕ РЕАКЦИЈА:  Уколико немате довољно простора, молимо Вас да приложите додатне стране овом образцу.											
ИСХОД НРЛ: <input type="checkbox"/> опоравак без последица <input type="checkbox"/> опоравак са последицама <input type="checkbox"/> опоравак у току <input type="checkbox"/> нема опоравка <input type="checkbox"/> смрт <input type="checkbox"/> непознато											
2. ПОДАЦИ О ЛЕКОВИМА ЗА КОЈЕ СУМЊАТЕ ДА СУ ДОВЕЛИ ДО НРЛ											
ЛЕКОВИ ПОД СУМЊОМ* (заштитено име, INN, облик, јачина, произвођач, бр. серије)				Начин примене	Режим дозирања	ИНДИКАЦИЈА		ПОЧЕТАК ПРИМЕНЕ	КРАЈ ПРИМЕНЕ		
НЕЖЕЉЕНА РЕАКЦИЈА ЈЕ ПРЕСТАЛА НАКОН ОБУСТАВЕ ПРИМЕНЕ ЛЕКА: <input type="checkbox"/> ДА <input type="checkbox"/> НЕ <input type="checkbox"/> НЕПОЗНАТО						НЕЖЕЉЕНА РЕАКЦИЈА СЕ ПОНОВО ЈАВИЛА ПОСЛЕ ПОНОВНЕ ПРИМЕНЕ ЛЕКА: <input type="checkbox"/> ДА <input type="checkbox"/> НЕ <input type="checkbox"/> НЕПОЗНАТО					
3. ПОДАЦИ О ИСТОВРЕМЕНО ПРИМЕЊИВАНИМ ЛЕКОВИМА											
ОСТАЛИ ПРИМЕЊИВАНИ ЛЕКОВИ (заштитено име, INN, облик, јачина, произвођач, бр. серије)				Начин примене	Режим дозирања	ИНДИКАЦИЈА		ПОЧЕТАК ПРИМЕНЕ	КРАЈ ПРИМЕНЕ		
4. ВАЖНИ АНАМНЕСТИЧКИ ПОДАЦИ (алергије, друге болести, трауме са датумом последње менструације, алкохол, пушење и сл.)											

5. ПОДАЦИ О ИЗВЕШТАЧУ ОВОГ СЛУЧАЈА НРЛ		
Име и презиме*, специјалност:	Извештач је:	Врста пријаве:
Установа*:	<input type="checkbox"/> Лекар	<input type="checkbox"/> прво пријављивање случаја
Адреса:	<input type="checkbox"/> Фармацевт	<input type="checkbox"/> додатне информације о већ пријављеном случају
Телефон:	<input type="checkbox"/> Стomatолог	Пријава се односи на неинтервенцијско клиничко испитивање:
Потпис:	<input type="checkbox"/> Остали (навести):	<input type="checkbox"/> Не <input type="checkbox"/> Да, навести које:
И-мејл:		
Датум:		

**\*Обавезно навести податке *Hvala što ste prijavili neželjenu reakciju na lek.***

Medicines and Medical Devices Agency of Serbia	Vojvode Stepe 458, 11152 Belgrade Phone: 011 39 51 145 Fax: 011 39 51130 E-mail: <a href="mailto:ncf@alims.gov.rs">ncf@alims.gov.rs</a> www.alims.gov.rs	No: Date:
Regional pharmacovigilance center	NPC No:	WHO No:

Form for reporting ADVERSE REACTIONS TO A MEDICINE (ARM)  
for the health care professional

*In case of suspected adverse reaction to one or more administered medicine(s)/vaccines, please fill in this form and send it by mail, fax or e-mail. Do not give up if some information is missing. A suspected adverse reaction is sufficient. Please find time to fill in the form as the data may be significant for the safe administration of medicines.*

1. INFORMATION ON THE PATIENT AND ADVERSE REACTIONS TO A MEDICINE (ARM)											
Initials*	Date of birth	Age*	Weight	Gender*	COMMENCEMENT OF THE ARM*			COMPLETION OF THE ARM			Do you consider that the exhibited reactions are serious? YES NO
					Day	Month	Year	Day	Month	Year	
				Male Female							
DESCRIPTION OF REACTIONS* (signs or symptoms, including relevant laboratory test findings):											Check all appropriate to adverse reaction:  Patient died  Life-threatening  Involved or prolonged inpatient hospitalization  Involved persistence or significant disability or incapacity  Congenital anomalies  Medically significant condition (report):
DIAGNOSIS/SYNDROM OF REACTIONS EXHIBITED:											
THERAPY APPLIED TO TREAT REACTIONS:											
In case you do not have enough space here, please enclose additional pages to the form.											

OUTCOME OF ARM	Recovery without consequences	Recovery with consequences	Patient under recovery	No recovery	Death	NA	
<b>2. INFORMATION ON MEDICINES WITH SUSPECTED ADVERSE REACTIONS</b>							
SUSPECT MEDICINES* (trade name, INN, form, strength manufacturer, batch number)		Route of administration	Dosage regime	INDICATION		START DATE OF ADMINISTRATION	STOP DATE OF ADMINISTRATION
ADVERSE REACTION <b>ABATED</b> AFTER STOPPING MEDICINE YES NO NA				ADVERSE REACTION <b>REOCCURRED</b> AFTER REINTRIDUCTION YES NO NA			
<b>3. INFORMATION ON CONCOMITANT MEDICINES</b>							
OTHER CONCOMITANT MEDICINES (trade name, INN, form, strength manufacturer, batch number)		Route of administration	Dosage regime	INDICATION		START DATE OF ADMINISTRATION	STOP DATE OF ADMINISTRATION
<b>4. IMPORTANT ANAMNESTIC DATA</b>							
(allergies, other diseases, pregnancy with date of the last menstruation, alcohol, smoking, etc.)							
<b>5. INFORMATION ON THE PERSON REPORTING AN ADVERSE REACTION TO A MEDICINE</b>							
Name and surname*, specialty:				Person reporting an adverse reaction is:		Type of report:	
Institution:				Doctor Pharmacist Dentist Other (please state):		First reporting of the case Additional information on the already reported case	
Address:						Report refers to a non-interventional clinical trial:	
Phone:		E-mail:				No Yes, please state what:	
Signature:		Date:					

\*Mandatory information

Thank you for reporting an adverse reaction to a medicine.

## ATTACHMENT 10

Агенција за лекове и медицинска средства Србије	Војводе Степе 458, 11152 Београд Тел: 011 39 51 145 Факс: 011 39 51 130 И-мејл: <a href="mailto:ncfa@alims.gov.rs">ncfa@alims.gov.rs</a> <a href="http://www.alims.gov.rs">www.alims.gov.rs</a>	Број: Датум:
	НЦФ бр:	СЗО бр:
Регионални центар за фармаковигиланцу		

### Образац за пријављивање НЕЖЕЉЕНИХ РЕАКЦИЈА НА ЛЕК (НРЛ) за пацијента

Уколико сумњате да је примена лека довела до нежељене реакције, попуните овај образац и пошаљите га поштом, факсом или и-мејлом.

1. ПОДАЦИ О ПАЦИЈЕНТУ И НЕЖЕЉЕНИМ РЕАКЦИЈАМА НА ЛЕК (НРЛ)											
Иницијали*	Датум рођења	Старост*	Тежина г	Пол*	ПОЧЕТАК НРЛ*			ЗАВРШЕТАК НРЛ			НРЛ је била: <input type="checkbox"/> умерена <input type="checkbox"/> непријатна, али није утицала на свакодневне активности <input type="checkbox"/> таква да је утицала на свакодневне активности <input type="checkbox"/> таква да је узроковала посету лекару <input type="checkbox"/> таква да је узроковала болничко лечење <input type="checkbox"/> таква да је узроковала тешко обољење <input type="checkbox"/> таква да је узроковала смрт <input type="checkbox"/> друго (навести):
				<input type="checkbox"/> М <input type="checkbox"/> Ж	дан	месец	година	дан	месец	година	
ОПИС РЕАКЦИЈА* (значи или симптоми, укључујући податке лабораторијских тестова):											
Уколико немате довољно простора, молимо Вас да приложите додатне стране овом образцу.											
ИСХОД НРЛ: <input type="checkbox"/> опоравак, нема више симптома <input type="checkbox"/> опоравак у току <input type="checkbox"/> још увек су присутни симптоми НРЛ <input type="checkbox"/> погоршање стања <input type="checkbox"/> смрт <input type="checkbox"/> непознато											
2. ПОДАЦИ О ЛЕКОВИМА ЗА КОЈЕ СУМЊАТЕ ДА СУ ДОВЕЛИ ДО НРЛ											
ЛЕКОВИ ПОД СУМЊОМ* (назив лека, произвођач)				Начин примене	Режим дозирања	РАЗЛОГ ПРИМЕНЕ ЛЕКА			ПОЧЕТАК ПРИМЕНЕ	КРАЈ ПРИМЕНЕ	
НЕЖЕЉЕНА РЕАКЦИЈА ЈЕ ПРЕСТАЛА НАКОН ОБУСТАВЕ ПРИМЕНЕ ЛЕКА:						НЕЖЕЉЕНА РЕАКЦИЈА СЕ ПОНОВО ЈАВИЛА ПОСЛЕ ПОНОВНЕ ПРИМЕНЕ ЛЕКА:					
<input type="checkbox"/> ДА <input type="checkbox"/> НЕ <input type="checkbox"/> НЕПОЗНАТО						<input type="checkbox"/> ДА <input type="checkbox"/> НЕ <input type="checkbox"/> НЕПОЗНАТО					
3. ПОДАЦИ О ИСТОВРЕМЕНО ПРИМЕЊИВАНИМ ЛЕКОВИМА											
ОСТАЛИ ПРИМЕЊИВАНИ ЛЕКОВИ (назив лека, произвођач)				Начин примене	Режим дозирања	РАЗЛОГ ПРИМЕНЕ ЛЕКА			ПОЧЕТАК ПРИМЕНЕ	КРАЈ ПРИМЕНЕ	
4. ВАЖНИ ДОДАТНИ ПОДАЦИ О ПАЦИЈЕНТУ											
(алергије, друге болести, трудноћа са текућом гослалом неструктуриране, лактоза, глутен и сл)											

5. ПОДАЦИ О ОСОБИ КОЈА ПРИЈАВЉУЈЕ СЛУЧАЈ НРЛ		
Име и презиме:	НРЛ се исподила:	Уколико желите, упишите контакт податке Вашег изабраног лекара:
Адреса:	<input type="checkbox"/> Вама	Име и презиме:
Телефон:	<input type="checkbox"/> Вашем детету	Установа:
И-мејл:	<input type="checkbox"/> Неком другом (навести):	Адреса:
Потпис:	Датум:	Телефон:

**\*Обавезно навести податке *Hvala što ste prijavili neželjenu reakciju na lek.***

Medicines and Medical Devices Agency of Serbia	Vojvode Stepe 458, 11152 Belgrade Phone: 011 39 51 145 Fax: 011 39 51130 E-mail: <a href="mailto:ncf@alims.gov.rs">ncf@alims.gov.rs</a> <a href="http://www.alims.gov.rs">www.alims.gov.rs</a>	No: Date:
Regional pharmacovigilance center	NCP No:	WHO No:

Form for reporting ADVERSE REACTIONS TO A MEDICINE (ARM)  
for the patient

*In case of **suspected** adverse reaction to an administered medicine, please fill in this form and send it by mail, fax or e-mail.*

1. INFORMATION ON THE PATIENT AND ADVERSE REACTIONS TO A MEDICINE (ARM)													
Initials*	Date of birth	Age*	Weight	Gender*			COMMENCEMENT OF THE ARM*			COMPLETION OF THE ARM			ARM was:
				Male	Female		Day	Month	Year	Day	Month	Year	
DESCRIPTION OF REACTIONS* (signs or symptoms, including relevant laboratory test findings):												Moderate Unpleasant, but did not affect daily activities Affected daily activities Caused a visit to the doctor Caused hospitalization Caused severe disease Caused death Other (please report):	
In case you do not have enough space here, please enclose additional pages to the form.													
OUTCOME OF ARM	Recovered, no symptoms	Patient under recovery	ARM symptoms still present	Deterioration	Death		NA						
2. INFORMATION ON MEDICINES WITH SUSPECTED ADVERSE REACTIONS													
SUSPECT MEDICINES* (name, manufacturer)			Route of administration	Dosage regime	REASON FOR ADMINISTRATION			START DATE OF ADMINISTRATION			STOP DATE OF ADMINISTRATION		
ADVERSE REACTION <b>ABATED</b> AFTER STOPPING MEDICINE						ADVERSE REACTION <b>REOCCURRED</b> AFTER REINTRIDUCTION							
YES NO NA						YES NO NA							
3. INFORMATION ON CONCOMITANT MEDICINES													
OTHER CONCOMITANT MEDICINES (name, manufacturer)			Route of administration	Dosage regime	REASON FOR ADMINISTRATION			START DATE OF ADMINISTRATION			STOP DATE OF ADMINISTRATION		

**4. IMPORTANT ANAMNESTIC DATA**

(allergies, other diseases, pregnancy with date of the last menstruation, alcohol, smoking, etc.)

**5. INFORMATION ON THE PERSON REPORTING AN ADVERSE REACTION TO A MEDICINE**

Name and surname*, specialty:  Institution:  Address:  Phone:  Signature:	E-mail:  Date:	ARM exhibited on:	Feel free to write contact details of your selected doctor:
		You	Name and surname:
		Your child	Institution:
		Somebody else (please report):	Address:
			Phone:

\*Mandatory information

Thank you for reporting an adverse reaction to a medicine.