MINISTRY OF HEALTH

1797

Pursuant to Article 145, paragraph 4 of the Medicinal Products Act (Official Gazette 76/2013), the Minister of Health hereby issues the

ORDINANCE

ON PHARMACOVIGILANCE

Article 1

(1) This Ordinance lays down the requirements for, and procedures and activities of, healthcare professionals, applicants submitting an application for marketing authorisation for a medicinal product (hereinafter: Applicant), marketing authorisation holders for medicinal products (hereinafter: Marketing Authorization Holder), holders of the authorisation for parallel imports, importers, the wholesale, clinical trial sponsors or the representative of clinical trial sponsors and the Agency for Medicinal Products and Medicinal Devices (hereinafter: the Agency) in the field of pharmacovigilance, in order to ensure the safe use of medicinal products.

(2) This Ordinance provides for a pharmacovigilance system for the detection, assessment, understanding and prevention of, and actions to be taken in the case of, adverse reactions caused by medicinal products.

Article 2

(1) This Ordinance transposes the following Directives into the legislation of the Republic of Croatia:

1. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11. 2001),

2. Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 amending Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 33/30, 8.2.2003),

3. Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 159, 27.6.2003),

4. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (OJ L 136, 30.4.2004),

5. Directive 2009/53/EC of the European Parliament and of the Council of 18 June 2009 amending Directive 2001/83 of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 168, 30.3.2009),

6. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending Directive 2001/83 of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 276, 21.10.2011),

7. Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use as regards pharmacovigilance.

Article 3

For the purposes of this Ordinance, the following terms shall bear the following meanings:

1. CIOMS-I form is the standardised international form used to submit individual case safety reports for serious, unexpected adverse reactions/adverse events, published in 1990 by the CIOMS-I Working Party of The Council for International Organizations of Medical Sciences (CIOMS).

2. *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*, or short, *International Conference on Harmonisation (ICH)* is a project that brings together the regulatory authorities of Europe, Japan and the United States of America (USA) and the representatives of the manufacturers of pharmaceuticals in the three regions to interpret and implement technical guidelines and applications for the placing on the market of the medicinal products with the purpose to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicinal products.

3. *Medical Dictionary for Regulatory Activities (MedDRA)* is a dictionary with a systematic, medically valid terminology with an emphasis on ease of use for data entry, retrieval, analysis, and display, as well as a suitable balance between sensitivity and specificity within the regulatory environment.

4. *Development Safety Update Report* (DSUR) is an annual report and assessment of relevant safety information collected during the reporting period for the investigational medicinal product, regardless of whether the marketing authorisation has been granted, which is submitted by the clinical trial sponsor or his representative.

5. *Solicited report* is any adverse reaction report from organised data collection systems (clinical trials, post-authorisation studies, registries, surveys of patients and healthcare professionals etc.). Solicited reports shall contain an Applicant's or Marketing Authorisation Holder's assessment of causality between the use of a medicinal product and the development of adverse reactions. In Individual Case Safety Reports (ICSR) they are treated as adverse reactions from clinical trials.

6. *Individual Case Safety Report (ICSR)* is a document providing the most complete information related to an individual case provided by a primary source, which contains a description of adverse reaction(s) or suspected adverse reactions(s) related to the administration of one or more medicinal products to a patient at a particular point of time.

7. *Adverse event in a clinical trial* is an unwanted event occurring during a clinical trial, which, based on a causality assessment, can be classified as an adverse event not associated with the medicinal product or as an adverse reaction.

8. *Council for International Organizations of Medical Sciences (hereinafter: CIOMS)* is an international, non-governmental, non-profit organisation established jointly by the World Health Organisation (WHO) and UNESCO in 1949. The members of the CIOMS are international, national and associate organisations which represent biomedical disciplines and are engaged in medical science and research.

9. Transitional list is a list of active substances in the framework of the Synchronisation scheme of the periodic safety update report in the European Union for harmonisation of submission schedule for the periodic safety update reports (hereinafter: PSURs) for medicinal products containing the same active substance in the EU member states and active substances for medicinal products authorised through a national procedure with regard to the date of data lock-point (DLP).

Article 4

(1) The pharmacovigilance system referred to in Article 1, paragraph 2 of this Ordinance also covers the collection of all other data to be assessed and scientifically validated, which may be relevant to the assessment of the benefit-risk balance of medicinal products.

(2) The pharmacovigilance system of the Marketing Authorisation Holder and of the Agency must be established and maintained in accordance with the Guideline on good pharmacovigilance practices (GVP) Module I – Pharmacovigilance systems and their quality systems.

Article 5

(1) An “adverse reaction” also means noxious and unintended effects resulting from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product.

(2) The suspicion of a possibility of there being a causal relationship between a medicinal product and an adverse event, should be sufficient reason for reporting.

Article 6

(1) The healthcare professional, the applicant for marketing authorizations, Marketing Authorization Holder, authorization holder for parallel imports, importer, and wholesale shall report the therapeutic failure of the medicinal product in accordance with the Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products.

(2) The respective pharmacovigilance systems of the Agency and Marketing Authorization Holders shall have defined algorithms for the assessment of the causal relationship between an adverse event and the medicinal product in the case of an adverse reaction to the medicinal product, in accordance with the Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products.

Article 7

(1) Adverse reactions can be serious or non-serious.

(2) An adverse reaction referred to in Article 3, item 59 of The Medicinal Products Act (hereinafter: the Act) is considered serious if it meets the following criteria:

– results in death,

– is life-threatening,

– requires inpatient hospitalisation or prolongation of existing hospitalisation,

– results in persistent or significant disability or incapacity,

– results in a development of a congenital anomaly or birth defect,

– leads to other medically important conditions.

(3) Other medically significant conditions referred to in paragraph 2, subparagraph 6 of this Article include adverse reactions specified on the List of adverse reactions published by the Agency on its internet pages.

(4) Adverse reactions that do not meet the criteria listed in paragraphs 2 and 3 of this Article are deemed to be non-serious.

Article 8

(1) An adverse reaction can be expected and unexpected.

(2) An adverse reaction is considered to be unexpected if it meets the criteria listed in Article 3, item 61 of the Act, otherwise it is deemed to be expected.

Article 9

(1) An adverse event referred to in Article 3, item 62 of the Act can be serious and non-serious.

(2) The provisions of Article 7, paragraphs 2, 3 and 4 of this Ordinance apply to adverse events referred to in paragraph 1 of this Article.

Article 10

(1) If a healthcare professional is visited by a qualified person of a Marketing Authorisation Holder for the medicinal product to which an adverse reaction was observed, he shall report such adverse reaction to the qualified person of the Marketing Authorisation Holder.

(2) If a healthcare professional has not yet reported the adverse reaction referred to in paragraph 1 of this Article to the Agency, the reporting to the Marketing Authorisation Holder shall be considered as fulfilment of the obligation prescribed by Article 145, paragraph 1 of the Act.

(3) A healthcare professional must report serious adverse reactions pursuant to Article 145 of the Act, and in particular for those medicinal products that have been subjected to additional monitoring pursuant to Article 144 of the Act and to the Guideline on good pharmacovigilance practices (GVP) Module X – Additional monitoring.

Article 11

(1) A healthcare professional coming in contact with end-users of vaccines shall notify in writing the Agency and the Croatian National Institute of Public Health (hereinafter: CNIPH) about any suspected adverse reaction to a vaccine marketed in the Republic of Croatia.

(2) If, for objective reasons, a healthcare professional is unable to report the adverse reaction both to the Agency and to the CNIPH, he shall be deemed to have fulfilled his reporting obligation if he has notified one of them in writing about the adverse reaction pursuant to Article 145, paragraph 1 of the Act.

(3) In case of adverse-reaction grouping or serious adverse reactions to vaccines resulting in death, a healthcare professional must report the case to the CNIPH and to the epidemiological department of the county institute of public health by telephone no later than 24 hours of becoming aware of it.

(4) The CNIPH shall immediately notify the Agency of the case referred to in paragraph 3 of this Article, and shall provide it with a subsequent written notification and reports, no later than 24 hours of becoming aware of it.

Article 12

(1) Submission of an adverse reaction report in writing means that a healthcare professional has submitted to the Agency a completed report form, and a CNIPH form in case of vaccines, in accordance with Article 35 of this Ordinance, or has reported an adverse reaction electronically via the Internet site of the Agency or using other electronic applications of the Agency.

(2) If a healthcare professional has not reported adverse reactions electronically, he must send the completed form referred to in paragraph 1 of this Article by post, telefax or as an electronic mail attachment to the address of the Agency and, in case of vaccines, also to the CNIPH.

(3) If a healthcare professional reports adverse reactions to a representative of the Marketing Authorisation Holder, information shall be provided on the Marketing Authorisation Holder's local adverse reaction report form.

Article 13

A valid adverse reaction report shall contain at least the following information:

– an identifiable reporter,

– an identifiable patient/user of the medicinal product (initials and/or age and/or sex),

– the name of the suspected medicinal product (invented name and/or INN),

– adverse reaction.

Article 14

(1) Information on the identity of the reporter is confidential.

(2) If an adverse reaction is reported directly to the Agency, the Agency shall not disclose the identity of the reporter to third persons, except in exceptional circumstances and only with the written consent of the reporter.

(3) If an adverse reaction is reported through the Marketing Authorisation Holder, the Marketing Authorisation Holder shall protect the identity of the reporter by sending the information on the reporter contained in the Individual Case Safety Report (hereinafter: ICSR) only to the Agency and never revealing it to third persons.

(4) When adverse reactions to a vaccine are reported to the CNIPH, the CNIPH shall protect the identity of the reporter by sending the information on the reporter contained in the adverse reaction report only to the Agency and never revealing it to third persons.

(5) Individual reports of adverse reactions, adverse events, medication errors, overdose, addiction or abuse of a medicinal product shall be treated as confidential and professional documents and shall not be used in assessing the liability of the healthcare professional who prescribed or dispensed the medicinal product.

(6) Electronic reporting of ICSRs for a vaccine carried out by the manufacturer of the medicinal product, the Marketing Authorisation Holder, the marketing authorisation holder for parallel import, import and wholesale, pursuant to Article 151 of the Act shall be considered as fulfilment of the obligation prescribed by Article 145, paragraph 1 of the Act and the ICSR concerned shall not have to be reported to CNIPH.

(7) The Agency shall forward the ICSRs referred to in paragraph 6 of this Article to CNIPH.

Article 15

(1) If a healthcare professional takes part in a clinical trial as an investigator, he must immediately report to the clinical trial sponsor or his representative any serious adverse events occurring in the trial, except those that, according to the trial plan and the investigator's brochure, are not required to be reported.

(2) The healthcare professional shall, in the report referred to in paragraph 1 of this Article, specify whether the causal relationship between the symptoms/events and the investigational medicinal product exists, based on which it will be determined whether it is an adverse event or an adverse reaction to the medicinal product.

(3) In the report referred to in paragraph 1 of this Article the healthcare professional shall also identify the seriousness of the symptoms/events.

Article 16

If a healthcare professional takes part in a non-interventional study as an investigator, he must report any suspected adverse reactions to a medicinal product and vaccine in accordance with the Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products.

Article 17

(1) A patient/user of a medicinal product shall notify his physician or pharmacist, or another healthcare professional with whom he has come in contact, of any suspected adverse reactions to the medicinal product or vaccine.

(2) Pursuant to Article 146 of the Act a patient/user of a medicinal product may directly notify in writing the Agency or the Marketing Authorisation Holder of any suspected adverse reactions to medicinal products and vaccines marketed in the Republic of Croatia.

Article 18

(1) Submission of an adverse reaction report in writing means that a patient/user of a medicinal product has submitted a completed report form to the Agency in accordance with Article 34 of this Ordinance, or to the Marketing Authorisation Holder, or has reported an adverse reaction electronically via the Internet application form of the Agency.

(2) In case the report is not submitted in the manner specified in paragraph 1 of this Article, it shall be sent by post, telefax or as an electronic mail attachment to the address of the Agency or the Marketing Authorisation Holder.

(3) A valid adverse reaction report shall contain at least the following information:

– an identifiable reporter,

– an identifiable patient/user of the medicinal product (initials and/or age and/or sex),

– the name of the suspected medicinal product (invented name and/or INN),

– adverse reaction.

Article 19

(1) The Marketing Authorisation Holder's person responsible for pharmacovigilance in the Republic of Croatia (hereinafter: the person responsible for pharmacovigilance) must meet the requirements of Article 3, item 58 of the Act and Articles 20 and 21 of this Ordinance.

(2) The person responsible for pharmacovigilance must reside in the Republic of Croatia.

(3) If the person responsible for pharmacovigilance is not an employee of the Marketing Authorisation Holder, the Marketing Authorisation Holder may designate a contracted person responsible for pharmacovigilance, who must be registered for performing adverse reactions monitoring activities, or pharmacovigilance activities, or must be employed by a legal person registered in the Republic of Croatia for performing adverse reactions monitoring activities or pharmacovigilance activities.

(4) If the person responsible for pharmacovigilance is not a medical doctor, access to a medical doctor must be available, which must be appropriately documented.

(5) The Marketing Authorisation Holder shall designate one person responsible for pharmacovigilance for each pharmacovigilance system for the medicinal products authorised in the Republic of Croatia and shall:

– submit to the Agency a copy of the authorisation of the person responsible for pharmacovigilance at the time of the marketing of the medicinal product authorised in the Republic of Croatia through a decentralised procedure at the latest,

– submit to the Agency a copy of the authorisation of the person responsible for pharmacovigilance, that is, proof of submitting an application for the authorisation of the person responsible for pharmacovigilance before the submission of an application for marketing authorisation for a medicinal product in the Republic of Croatia through a national procedure, the mutual recognition, or decentralised procedure.

(6) By way of derogation from paragraph 5 of this Article, one person may be appointed the person responsible for more farmacovigilance systems of one Marketing Authorisation Holder, on condition that he/she is able to fulfil all obligations.

(7) One person responsible for pharmacovigilance may be responsible for separate farmacovigilance systems of multiple Marketing Authorisation Holders, or for farmacovigilance systems with shared parts, on condition that he/she is able to fulfil all obligations.

Article 20

(1) The person responsible for pharmacovigilance referred to in Article 19 of this Ordinance shall:

– be responsible for establishing and implementing the Marketing Authorisation Holder's pharmacovigilance system in the Republic of Croatia,

– have an overview of the safety profiles and any safety concerns in relation to the medicinal products for which the Marketing Authorisation Holder holds authorisations,

– act as a contact point for the Agency, available 24 hours,

– act as a contact point for pharmacovigilance inspections in the Republic of Croatia.

(2) The person responsible for pharmacovigilance may delegate certain tasks to appropriately qualified and trained individuals, but must maintain full overview of the safety profiles and any safety concerns in relation to the medicinal products of the Marketing Authorisation Holder. Any such delegation shall be appropriately documented.

(3) The person responsible for pharmacovigilance must have oversight of the pharmacovigilance system to ensure in particular the following system components:

1. the establishment and maintenance of a system which ensures that information about all suspected adverse reactions occurring in the Republic of Croatia are collected and collated in order to be accessible at least at one point in the Republic of Croatia,

2. the preparation, collection and/or forwarding of the following safety documents that are to be submitted to the Agency:

– Individual Case Safety Report (ICSR),

– Periodic Safety Update Report (PSURs),

– Risk Management Plan (RMP) and all associated additional risk minimisation measures,

– Development Safety Update Report (DSUR),

– Direct Healthcare Professionals Communication (DHPC)

3. the reporting to the Agency the latest knowledge based on the evaluation of safety of a medicinal product after authorising the marketing of the medicinal product in the Republic of Croatia,

4. the ensuring that any request from the Agency for the provision of additional information necessary for the evaluation of the benefits and the risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned,

5. the provision to the Agency of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including information on post-authorisation studies.

(4) The activities of the Marketing Authorisation Holder's local person responsible for pharmacovigilance shall ensure the functioning of the pharmacovigilance system in all aspects, including quality control and assurance, standard operating procedures (SOPs), databases, contractual arrangements, compliance with provisions of the Act and of this Ordinance.

Article 21

(1) If the local person responsible for pharmacovigilance is not a medical doctor specialised in clinical pharmacology but is a medical doctor, a dental medicine doctor, a master of pharmacy, a master of medical biochemistry, or a doctor of veterinary medicine without documented two-year experience in pharmacovigilance, he/she must have at least two years of experience in pharmacovigilance and documented training in the following areas:

– pharmacovigilance terminology,

– spontaneous and solicited reporting of adverse reactions,

– methods of adverse reaction reporting, evaluation of adverse reaction reports, preparation of Individual Case Safety Reports (ICSRs), PSURs, RMPs and DSURs.

(2) The person responsible for pharmacovigilance must continuously improve his/her professional competencies in pharmacovigilance and keep records thereof.

(3) Pharmacovigilance inspection may check whether the local person responsible for pharmacovigilance meets the requirements of Article 19 of this Ordinance.

Article 22

(1) An application for an authorisation of the person responsible for pharmacovigilance shall be submitted to the Agency in accordance with the Ordinance on granting marketing authorisations for medicinal products and in accordance with Articles 19, 20 and 21 of this Ordinance.

(2) The Marketing Authorisation Holder may, pursuant to Article 19, paragraph 5 of this Article, submit an application for an authorisation of an additional person responsible for pharmacovigilance, alongside the person responsible for pharmacovigilance previously approved by the Agency, but only if the application is related to a Marketing Authorisation Holder's new pharmacovigilance system.

(3) The Agency shall notify the Applicant in writing about the authorisation of the responsible person and the deputy.

(4) The Agency shall maintain a register of persons responsible for pharmacovigilance and their deputies, with all contact details.

Article 23

(1) The Marketing Authorisation Holder may nominate a deputy person responsible for pharmacovigilance (hereinafter: the deputy), who will act as a contact point for the Agency in the absence of the person responsible for pharmacovigilance and undertake other delegated activities in accordance with Article 20 of this Ordinance.

(2) The deputy referred to in paragraph 1 of this Article must be adequately qualified as required by paragraphs 3 and 4 of this Article and reside in the Republic of Croatia.

(3) The deputy must be a medical doctor, a dental medicine doctor, a master of pharmacy, a master of medical biochemistry, or a doctor of veterinary medicine and must perform pharmacovigilance activities for the Marketing Authorisation Holder.

(4) If the deputy does not possess the qualifications required by paragraph 3 of this Article but is carrying out pharmacovigilance activities for the Marketing Authorisation Holder, he/she must have documented training referred to in Article 21, paragraph 1 of this Ordinance.

(5) The Marketing Authorisation Holder shall provide the Agency with the information on the nomination of the deputy and relevant contact details, and obtain the approval from the Agency.

Article 24

(1) When notifying the Agency of the person responsible for pharmacovigilance referred to in Article 19 of this Ordinance, the Marketing Authorisation Holder shall submit:

– the original statement of the Marketing Authorisation Holder's responsible person about the nomination of the person responsible for pharmacovigilance,

– a signed curriculum vitae of the person responsible for pharmacovigilance,

– a copy of the certificate attesting to the completion of the required degree,

– a copy of the certificate attesting to the completion of specialised studies (clinical pharmacology) or, if the person responsible for pharmacovigilance is not specialised in clinical pharmacology, proof of two-year experience in pharmacovigilance, or proof that the person concerned has received training referred to in Article 21, paragraph 1 of this Ordinance,

– proof of residence of the person responsible for pharmacovigilance,

– 24-hour contact details of the person responsible for pharmacovigilance,

– proof that the person responsible for pharmacovigilance is employed with the Marketing Authorisation Holder or with a legal person registered in the Republic of Croatia for performing adverse reactions monitoring activities or pharmacovigilance activities, with which the Marketing Authorisation Holder has entered into a contract for pharmacovigilance activities.

– a copy of the contract with the contracted person responsible for pharmacovigilance.

(2) When submitting to the Agency the application for the authorisation of the deputy person responsible for pharmacovigilance referred to in Article 23 of this Ordinance, the Marketing Authorisation Holder shall also submit:

– a statement of the Marketing Authorisation Holder's person responsible about the nomination of the deputy of the person responsible for pharmacovigilance,

– a copy of the certificate attesting to the completion of the degree, or proof of completion of other education in accordance with Article 21, paragraph 1 of this Ordinance,

– contact details of the deputy person responsible for pharmacovigilance,

– proof of employment with the Marketing Authorisation Holder or with a legal person registered in the Republic of Croatia for performing adverse reactions monitoring activities or pharmacovigilance activities, with which the Marketing Authorisation Holder has entered into a contract for pharmacovigilance activities,

– a copy of the contract with the contracted deputy responsible person for pharmacovigilance.

Article 25

The Marketing Authorisation Holder for parallel import of the medicinal products is responsible for pharmacovigilance activities in the following cases:

– if the Marketing Authorisation Holder in the Republic of Croatia has no authorised responsible person for pharmacovigilance in accordance with Articles 19, 20 and 21 of this Ordinance,

– if an authorisation for the parallel import of medicinal products has been granted in accordance with the Act and the ordinance adopted pursuant to this Act.

Article 26

(1) The Marketing Authorisation Holder is responsible to report all suspected adverse reactions to marketed medicinal products in accordance with Article 151 of the Act.

(2) The Marketing Authorisation Holder is responsible for the collection, assessment and reporting suspected serious and non-serious adverse reactions to medicinal products and vaccines, as well as ICSRs, in accordance with the Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products.

(3) If it is assessed that there is no causal relationship between an event/symptom and the medicinal product, the event/symptom shall be considered as an adverse event and shall not be reported to the Agency.

(4) The Marketing Authorisation Holder is responsible to perform activities related to determining new risks or changes of known risks connected to the medicinal products (detection of signals) pursuant to the Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management.

Article 27

(1) The Marketing Authorisation Holder, the marketing authorisation holder for the parallel import, the importer and the wholesale, shall notify the Agency of any events/observations that could affect the risk-benefit balance of the use of the medical product and/or public health and that do not meet the requirements of ICSR reporting, in accordance with the Guideline on

good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products).

(2) The healthcare professional, the Applicant, the Marketing Authorisation Holder, the marketing authorisation holder for parallel import, importer and wholesale shall report adverse reactions and other data of relevance to the safety profile of the medicinal product in accordance with the Guideline on good pharmacovigilance practices (GVP), Module VI – Management and reporting of adverse reactions to medicinal products.

(3) Except from those referred to in paragraph 2 of this Ordinance, the healthcare professional, the Applicant for submitting an application for authorisation, the Marketing Authorisation Holder, the marketing authorisation holder for parallel import, importer and wholesale shall report adverse reactions and other data of relevance to the safety profile of the medicinal products in the following cases:

– use of medicinal product(s) during pregnancy or breastfeeding,

– use of medicinal product(s) in children or elderly,

– overdose, abuse and misuse of medicinal products (off-label use),

– incorrect use, medication errors or professional exposure,

– inefficacy of the medicinal product.

Article 28

(1) The Marketing Authorisation Holder is required to develop and maintain the PSMF for all authorised medicinal products in accordance with the Guideline on good pharmacovigilance practices (GVP) Module II – Pharmacovigilance system master file.

(2) The Agency may, in accordance with Article 148 of the Act, require to inspect and assess the complete PSMF during and after the authorisation of the medicinal product.

Article 29

The Marketing Authorisation Holder is required to develop and maintain the risk management system in accordance with Articles 49 and 149 of the Act and with the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems.

Article 30

(1) The Agency shall approve the introduction of additional risk minimisation measures, regardless of the type of the procedure based on which the marketing authorisation for the medicinal product was granted.

(2) In the case referred to in paragraph 1 of this Article the Marketing Authorisation Holder is required to act in accordance with the Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: Selection of tools and effectiveness indicators.

(3) The Marketing Authorisation Holder shall obtain approval from the Agency prior to distributing educational materials and performing other activities that are part of additional risk minimisation measures in order to harmonize the content of communication, the list of recipients, modalities, time schedule and distribution of these materials.

(4) The Agency shall approve educational materials that are part of additional risk minimisation measures in the procedure of the approval of the modification.

(5) The Agency may conduct the assessment of the effectiveness of additional risk minimisation measures or request that the Marketing Authorisation Holder conduct the assessment of the effectiveness of additional risk minimisation measures.

Article 31

(1) The Marketing Authorisation Holder is required to develop PSURs in accordance with the Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report.

(2) If an active substance has not been listed in EURD but has been listed on a transitional list, the provisions of this Act and this Ordinance related to EURD list apply to the transitional list.

Article 32

(1) Post-authorisation safety studies (PASS) encompass all interventional and non-interventional studies carried out to evaluate the safety of authorised medicinal products and for which the Marketing Authorisation Holder takes responsibility for their initiation, management and/or financing.

(2) The person responsible for pharmacovigilance in the European Union shall be involved in the development, review and evaluation of the protocols of non-interventional safety studies of the use of medicinal products in accordance with the Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies.

(3) The Marketing Authorisation Holder shall notify the person responsible for pharmacovigilance on each non-interventional safety study for medicinal products and shall have access to the study plan performed by the Marketing Authorisation Holder.

(4) All procedures related to the post-authorisation safety studies for the medicinal product shall be performed in accordance with the provisions of the Act, this Ordinance and the Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies.

Article 33

(1) The Agency shall establish its own pharmacovigilance system in accordance with the Article 153 of the Act.

(2) The Agency shall continuously monitor the safety profile of marketed medicinal products and those in clinical studies on the territory of the Republic of Croatia and shall take necessary measures, monitor the fulfilment of obligations by the Marketing Authorisation

Holder and the clinical trial sponsor or his representative in respect of pharmacovigilance obligations prescribed by the Act and this Ordinance.

Article 34

(1) As a National centre for adverse reactions, the Agency is actively involved in the activities of the International system for monitoring adverse reactions of the World Health Organization and as a representative of the Republic of Croatia, it actively participates with its collaborating centre, The Uppsala Monitoring Centre.

(2) Pursuant to Article 154, paragraph 1 of the Act, the Agency shall report to the Eudravigilance database all adverse reactions recorded in the Republic of Croatia.

(3) Until all functions of Eudravigilance have been established, the Agency shall also report adverse reactions to the World Health Organisation's adverse reaction database, by secure electronic transmission and protecting the confidentiality of personal data, in E2B format. For the coding of adverse reactions and submission of ICSRs, the Agency shall use the Medical Dictionary for Regulatory Activities.

Article 35

(1) Pursuant to Articles 145, 146 and 154 of the Act, the Agency receives directly from healthcare professionals and patients/users reports of adverse reactions to medicinal products that are authorised for marketing in the Republic of Croatia, for parallel import, or imported/introduced in accordance with Article 129 of the Act.

(2) The Agency shall encourage reporting of adverse reactions by providing an easy access to paper-based or electronic adverse reaction report forms suitable to be used by healthcare professionals and patients and published on its internet pages or otherwise.

(3) Adverse reaction report form/application shall include at least the following information:

– details of the reporter (name, address, telephone number, e-mail address),

– information about the patient (initials, age, sex),

– information about the adverse reaction (date of onset and end date of the adverse reaction, duration of the adverse reaction, description and diagnosis of the adverse reaction, de-challenge and re-challenge information),

– outcome of the adverse reaction,

– seriousness of the adverse reaction,

– suspected medicinal product(s) that caused the adverse reaction,

– other medicinal products used,

– information from patient's medical history.

(4) The Agency shall perform activities with regard to the determination of new risks or the change to known risks from the use of medicinal products (signal detection) in accordance with the Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management.

Article 36

After it has received reports of adverse reactions recorded in the Republic of Croatia in accordance with Article 145 of the Act, the Agency shall act in accordance with the Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products.

Article 37

All medicinal products subject to additional monitoring shall be identified as such on the product information by an inverted equilateral black triangle, and the Guideline on good pharmacovigilance practices (GVP) Module X – Additional monitoring, shall be applied to additional monitoring of such medicinal products.

Article 38

The Agency shall not receive reports on adverse reactions occurring in clinical trials directly from an investigator, but only ICSRs from the sponsor of a clinical trial or from his representative.

Article 39

(1) The safe use of vaccines shall be monitored by the Agency and the CNIPH in accordance with Article 145 of the Act.

(2) For the purposes of harmonised evaluation of adverse reactions to vaccines and synchronised action in the area of safe use of vaccine the Expert Group on Adverse Reactions and Safe Use of Vaccines has been set up by the director of the Agency.

(3) The members of the Expert Group referred to in paragraph 2 of this Article can be employees of the Agency and employees of the CNIPH's Service for the Epidemiology of Infectious Diseases.

Article 40

(1) A Letter to Healthcare Professionals (hereinafter: the letter) is information aimed at ensuring safe and effective use of medicinal products which is delivered to healthcare professionals by the Agency or the Marketing Authorisation Holder.

(2) The Letter from paragraph 1 of this Article shall not contain any form of advertising of the medicinal product.

(3) Before the delivery of the Letter, the Marketing Authorisation Holder shall reach an agreement with the Agency with regard to the contents, communication plan, recipient's signature and schedule of delivery of the Letter.

(4) When composing the letter and as regards the method of communication with healthcare professionals and the public, the Marketing Authorisation Holder and the Agency shall act in accordance with the Guideline on good pharmacovigilance practices (GVP) Module XV – Safety communication.

(5) The Agency shall publish the text of the Letter to healthcare professionals on its website.

Article 41

In order to achieve a harmonised reporting of adverse reactions, the Agency shall publish on its website a list of adverse reactions that are also considered serious reactions, although not unambiguously determined according to the seriousness criteria in accordance with the Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products.

Article 42

(1) No later than 30 June each year the Agency shall publish on its website a Report of Adverse Reactions reported in the preceding calendar year.

(2) The Report referred to in paragraph 1 of this Article shall contain at least the following elements:

– Total number of reports,

– Reports of adverse reactions to medicinal products and vaccines,

– Sources of reports,

– Characteristics of reports of adverse reactions to medicinal products and vaccines,

– Medicinal product classification,

– Age and sex of the patient,

– Type of adverse reaction,

– The number of concomitant medicinal products,

– Seriousness of adverse reactions,

– Outcome of the adverse reaction,

– Degree of causality between the adverse reaction and the medicinal product,

– Adverse reactions by system organ classes.

(3) Adverse reactions shall be presented in the Report by INN, ATC and system organ classes, and particular attention shall be given to medicinal products that were subjected to special

monitoring in the calendar year covered by the Report referred to in paragraph 1 of this Article.

Article 43

(1) On the basis of the significance of changes in safety information in the Patient Information Leaflet and/or the Summary Product Characteristics, the Agency may, when approving change(s) in safety information, set a deadline by which the Marketing Authorisation Holder must distribute the amended version of the Patient Information Leaflet and/or the Summary Product Characteristics.

(2) If not otherwise determined by the Agency, the Marketing Authorisation Holder must include the amended Patient Information Leaflet containing new safety information in the packaging of medicinal products constituting the first batch placed on the market after the change in safety information is approved, and not later than 6 months after being notified by the Agency that the change(s) in safety information is/are approved.

(3) If not otherwise determined by the Agency, the Marketing Authorisation Holder must ensure that the amended Summary Product Characteristics are made available to healthcare professionals after the Agency's approval of the change(s) to safety information and not later than 7 days after receiving a notification of such approval.

Article 44

The clinical trial sponsor or his representative, the investigator and the Agency shall fulfil their obligations with regard to pharmacovigilance in clinical trials in accordance with the Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’) 2011/C 172/01), the Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products, and the provisions of the Act and this Ordinance.

Article 45

(1) The investigator in the clinical trial shall act in accordance with the Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’) 2011/C 172/01).

(2) For reported adverse events, in particular for reported death of a subject, the investigator shall, if requested by the clinical trial sponsor, the representative of the clinical trial sponsor, the Central Ethics Committee (hereinafter: CEC) and/or the Agency and/or the ministry responsible for health, submit any additional medical information and documents regarding the subject concerned (e.g. autopsy findings, doctor's report on the cause of death).

Article 46

The clinical trial sponsor or the representative of the clinical trial sponsor shall act in accordance with the Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’) 2011/C 172/01.

Article 47

The clinical trial sponsor or the representative of the clinical trial sponsor shall report adverse reactions from clinical trials on an expedited basis in accordance with Article 152 of the Act, whereas the reporting of safety issues not considered suspected unexpected serious adverse reactions (hereinafter: SUSAR) shall be carried out in accordance with the Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') 2011/C 172/01).

Article 48

(1) The clinical trial sponsor or the representative of the clinical trial sponsor shall submit to the Agency and the CEC at least once in six months a linear list of all SUSARs for the monitored period from all EU member states, and from third countries, where applicable, accompanied by a report by the clinical trial sponsor or the representative of the clinical trial sponsor highlighting the main safety concerns in accordance with the Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on investigational medicinal products for human use ('CT-3') 2011/C 172/01).

(2) The clinical trial sponsor or the representative of the clinical trial sponsor shall submit the linear list referred to in paragraph 1 of this Article in an electronic form on a CD, accompanied by a summary in which he shall list the names and identification of clinical trial plan(s) with the investigational medicinal product in the Republic of Croatia.

Article 49

The clinical trial sponsor or the representative of the clinical trial sponsor shall conduct the procedures of unblinding in accordance with the Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') 2011/C 172/01).

Article 50

(1) The clinical trial sponsor or the representative of the clinical trial sponsor shall fulfil their obligations with regard to the Development Safety Update Report in accordance with the Guideline ICH E2F.

(2) The clinical trial sponsor or the representative of the clinical trial sponsor shall submit the Development Safety Update Reports (DSURs) in electronic form on a CD, accompanied by a summary in which they shall state the name and identification of clinical trial plan(s) for the medicinal product in the Republic of Croatia by the time the electronic reporting system has been set up.

Article 51

The clinical trial sponsor or the representative of the clinical trial sponsor shall regularly inform all investigators of serious unexpected adverse reactions observed in the concerned trial in the Republic of Croatia, the European Union and in third countries, and of other safety information that could affect the safety of subjects in the trial in accordance with the Detailed

guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') 2011/C 172/01).

Article 52

The Agency shall conduct inspection in the field of pharmacovigilance pursuant to Article 193, paragraph 2 of the Act and in accordance with the Guideline on good pharmacovigilance practices (GVP) Module III – Pharmacovigilance inspections.

Article 53

The Agency and the Marketing Authorisation Holder are required to conduct an internal audit of the pharmacovigilance system in accordance with the Guideline on good pharmacovigilance practices (GVP) Module IV – Pharmacovigilance audits.

Article 54

The supervision of the implementation of provisions of the Act and this Ordinance shall be carried out by the inspection of the Agency.

Article 55

(1) The Marketing Authorisation Holder shall submit to the Agency a written statement for the medicinal products marketed in the Republic of Croatia and authorised through a centralised procedure, confirming that he has at his disposal a person responsible for pharmacovigilance approved by the Agency.

(2) In addition to the statement referred to in paragraph 1 of this Article the Marketing Authorisation Holder shall submit a copy of the statement on the Agency's approval of the person responsible for pharmacovigilance.

(3) For medicinal products authorised through a centralised procedure and marketed in the Republic of Croatia, and for which there is no person responsible for pharmacovigilance approved by the Agency, the Marketing Authorisation Holder shall submit an application for the approval of the person responsible for pharmacovigilance in accordance with the provisions of this Ordinance.

(4) In case of change of the Marketing Authorisation Holder, or the person responsible for pharmacovigilance, for medicinal products authorised through the national procedure, the procedure of mutual recognition, or decentralised procedure before 1 July 2013, and whose marketing authorisations were valid on 1 July 2013, the Marketing Authorisation Holder shall submit to the Agency an application for the approval of the person responsible for pharmacovigilance in accordance with Article 19 of this Ordinance.

Article 56

For all medicinal products with a valid marketing authorisation in accordance with Article 15, items (a) and (b), Article 19 and Article 108 of the Medicinal Products Act (Official Gazette 71/07, 45/09 and 124/11) the obligation to submit PSURs ceases to exist after 1 July 2013, except in cases provided for in Article 169 of the Act.

Article 57

On the date of entry into force of this Ordinance, the Ordinance on Pharmacovigilance (Official Gazette 125/09) shall cease to have effect:

Article 58

This Ordinance shall be published in the Official Gazette and shall enter into force on 2 July 2013.

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Zagreb, 26 July 2013

Minister

Prof. Rajko Ostojić, MD, PhD,

m.p.