

**The procedure for communication of information concerning the safety of medicinal products and the procedure for calculation and payment of the fee for monitoring the safety and quality of medicinal products\***

**Adopted by Minister of Social Affairs Regulation No. 32 of 18 February 2005,  
took effect on 1 March 2005.**

The Regulation is enacted on Subsection 78(7) of the “Medicinal Products Act”.

**§ 1. General Provisions**

(1) This regulation establishes the procedure for communication of information concerning the safety of medicinal products, the respective duties of the State Agency of Medicines and, pursuant to subsection 78(3) of the Medicinal Products Act, the procedure for calculation and payment of the fee for monitoring the safety and quality of medicinal products.

(2) Marketing authorisation holders shall appoint an authorised person for dealing with the safety issues of medicinal products and forward his/her name and contact data to the State Agency of Medicines.

**§ 2. Adverse reaction to medicinal product**

(1) For the purpose of this regulation, an adverse reaction shall mean a dangerous and undesired effect which occurs at doses normally used in man or animal for the prophylaxis, diagnosis or therapy of a disease or for affecting a physiological function.

(2) An adverse reaction is unexpected if it has not been listed in the summary of product characteristics or if its nature, severity or outcome is not consistent with the summary of product characteristics approved upon issuing the marketing authorisation. Adverse reactions described in relation with medicinal product of the same group but not in relation with that particular product are also unexpected adverse reactions.

(3) An adverse reaction is serious if it:

- 1) results in death;
- 2) is life-threatening;
- 3) requires hospitalisation or prolongation of existing hospitalisation;
- 4) causes long-term incapacity for work, severe or profound disability;
- 5) causes congenital anomaly or birth defect.

(4) A reaction with outcome listed in subsection (3) in the case of use which is not in compliance with the summary of product characteristics, an overdose or misuse of a medicinal product also constitute severe adverse reactions.

**§ 3. Ways of communication of information concerning safety of medicinal products**

Marketing authorisation holders shall forward information about the safety of medicinal products in the form of expedited adverse reaction reporting, periodic safety update reports and urgent safety restrictions.

**§ 4. Expedited adverse reaction reporting**

(1) Physicians, dentists and veterinarians have to inform the State Agency of Medicines of all serious adverse reactions to medicinal products. The holder of the marketing authorisation has to be informed of all non-serious adverse effects.

(1<sup>1</sup>) The data on the physician, dentist or veterinarian who informed the State Agency of Medicines of the severe adverse reactions stipulated in Subsection 1 shall not be revealed.

(2) The first notice of a serious adverse reaction has to contain at least the following information:

- 1) data on the healthcare professional forwarding the notice, or data on the veterinarian in the case of a veterinary medicinal product;
- 2) data allowing for identification of the patient (initials, gender, date of birth or age), or identification data, gender and age of animal(s) or group of animals in the case of a veterinary medicinal product;
- 3) name of the medicinal product;
- 4) description of the adverse reaction.

(3) Within 15 days after receipt of the report, the marketing authorisation holder shall inform the State Agency of Medicines of:

- 1) all serious adverse reactions of the medicinal products which have occurred in Estonia and of which healthcare professionals or, in the case of veterinary medicinal product, veterinarians have informed marketing authorisation holder;
- 2) all serious adverse reactions which have occurred in the course of post-authorisation safety studies carried out in Estonia;
- 3) all unexpected serious adverse reactions which have occurred during post-authorisation outside Estonia if Estonia is the reference member state;
- 4) all unexpected serious adverse reactions which have occurred in the course of post-authorisation safety studies carried out outside Estonia if Estonia is the reference member state.

(4) All additional data on adverse reactions shall be forwarded to the State Agency of Medicines upon receipt.

## **§ 5. Urgent safety restriction**

(1) Urgent Safety Restriction is an interim change to summary of product characteristics, restricting indication or indications, changing posology, adding contra-indication or warning due to new information having a bearing on the safe use of the medicinal product.

(2) The marketing authorisation holder shall forthwith inform the State Agency of Medicines authority and if any objections are not raised within within 24 hours following receipt of that information, the urgent safety restrictions shall be deemed as accepted. Corresponding application for a Type II variation shall be submitted in no case later than 15 days after initiation of the urgent safety.

## **§ 6. Periodic safety update report**

(1) Periodic safety update report (hereafter PSUR) is a report prepared by marketing authorisation holder on safety of a medicinal product. The data presented in PSUR should be in the following order:

- 1) Executive Summary of PSUR with a description of the most important information (a summary of the marketing authorisation status worldwide, exposure data, number of case reports covered by the PSUR, overall findings of the PSUR, conclusions);
- 2) Introduction;
- 3) Worldwide Marketing Authorisation Status;
- 4) Update of Regulatory Authority or Marketing Authorisation Holder Actions taken for Safety Reasons;
- 5) Changes to Reference Safety Information;
- 6) Patient Exposure;
- 7) Presentation of Individual Case Histories;
- 8) Studies;
- 9) Other information (incl. information concerning lack of efficacy (vaccines, contraceptives), late-breaking information, received after the database was frozen for review and report preparation, Risk Management Plan, Benefit-Risk Analysis Report)
- 10) Overall Safety Evaluation;

11) Conclusion (indicate which safety data do not remain in accord with the previous cumulative experience and with the reference safety information, specify and justify any action recommended or initiated).

(2) Marketing authorisation holder should prepare the PSUR as follows:

For medicinal products authorised after 20 November 2005:

1. upon request of State Agency of Medicines
2. at least every 6 months for two years after authorisation
3. once a year for the following two years
4. thereafter at 3-yearly intervals

(3) For marketing authorisations renewed at least once before 20 November 2005:

1. upon request of State Agency of Medicines,
2. with the renewal application,
3. thereafter at 3-yearly intervals;

(4) For marketing authorisations not yet renewed before 20 November 2005:

1. upon request of State Agency of Medicines,
2. at least every 6 months for two years after authorisation,
3. once a year for the following three years, incl. with the renewal application,
4. thereafter at 3-yearly intervals

(5) PSUR should be prepared and submitted more frequently than laid down in section 2, 3 and 4 when such requirements have been laid down at the time of granting the authorisation.

(6) To determine the data lock points (see sections 2, 3 and 4) the Marketing Authorisation Holder may use the first marketing authorisation date of a Member State of the European Economic Area or with written consent of State Agency of Medicines the first marketing authorisation date in third country.

(7) Each PSUR should cover the period of time since the last PSUR and should be submitted within 60 days after the data lock point (see sections 2, 3 and 4).

(8) PSUR should be submitted electronically, one copy. Upon request of State Agency of Medicines on paper form.

(9) For marketing authorisation renewal the PSUR should be submitted at least 180 days before expiry date of the marketing authorisation. Safety data should cover period of 4 years and 4 months. For that purpose in addition to PSUR the PSUR Addendum Report should be submitted if necessary and always PSUR Summary Bridging Report.

(10) PSUR Summary Bridging Report provides a brief summary bridging two or more PSURs and is meant to assist State Agency of Medicines with a helpful overview of the appended PSUR.

(11) PSUR Addendum Report is a safety update to the most recently completed PSUR and it is presented when a State Agency of Medicines requests a safety update outside the usual PSUR submission schedule. An Addendum Report should be used when more than 3 months (for a 6-monthly or yearly PSUR) and more than 6 months (for a PSUR covering 3 or 5 years) have elapsed since the data lock point of the most recent PSUR. The Addendum Report should summarise the safety data received between the data lock point of the most recent PSUR and the State Agency of Medicines requested cut-off date.

## **§ 7. Obligations of State Agency of Medicines in communication of information concerning safety of medicinal products**

(1) The State Agency of medicines shall have the following duties concerning the safety of the pharmaceuticals for which marketing authorisations have been issued:

- 1) It shall inform the marketing authorisation holder and the European Medicines Agency of all the serious adverse reactions which have occurred in Estonia and are known to it within 15 days of the receipt of the data;
- 2) In the case of mutual recognition procedure and if Estonia is the reference member state, the State Agency of Medicines shall be responsible for gathering safety data on medicinal products, for coordination of the forwarding of such data and the respective communication; however, this shall not free the marketing authorisation holder from the obligation to inform each respective authority;
- 3) Where, as a result of the evaluation of pharmacovigilance data, the State Agency of Medicines considers that marketing authorisation should be suspended, revoked or varied, it shall forthwith inform the European Medicines Agency, the other member states and the marketing authorisation holder;
- 4) Upon urgent suspension of marketing authorisation, it shall inform the European Medicines Agency, the European Commission and the other member states not later than the following working day;
- 5) It shall forward to the World Health Organization four times per year the data on all serious adverse reactions which have occurred in Estonia and of which healthcare professionals or marketing authorisation holders have informed the State Agency of Medicines.
- 6) It shall inform the agencies of medicines of other member states in all cases referred to in subsection 2.
- 7) It shall ensure the availability of the notice on the suspected serious adverse reactions to the marketing authorisation holder within 15 calendar days of the receipt at the latest.

(2) In the case Estonia participates in the mutual recognition procedure as a reference member state, the State Agency of Medicines shall inform the respective competent authorities of the other member states about the safety of pharmaceuticals with marketing authorisation if:

- 1) the marketing authorisation terms and conditions are changed or the authorisation is suspended;
- 2) significant changes in the safety data are made to the summary of product characteristics (a new contraindication or warning added, the recommended dose reduced, the indications or the availability of the medicinal product limited);
- 3) it is considered necessary to immediately inform healthcare professionals, patients or, in the case of veterinary products, veterinarians and animal owners of the risks involved with a medicinal products;
- 4) it is revealed that the risk-benefit balance of a pharmaceutical has deteriorated, which may be the result of reports of unexpected adverse reactions, an increase in the incidence of expected adverse reactions, the deterioration of the severity of adverse reactions or consequences thereof, study data indicating that the medicinal product is less efficient than earlier known and the risks involved with the use of the medicinal product are greater than those of other products of similar efficiency.

## **§ 8. The payment of the fee for monitoring the safety and quality of medicinal products**

(1) State Agency of Medicines will submit invoice for the payment of the fee for monitoring the safety and quality of medicinal products for the previous year latest on 1 February.

(2) Based on a reasoned request of a marketing authorisation holder, the State Agency of Medicines has the right to release the authorisation holder from payment of the fee for monitoring the safety and quality of a medicinal product if:

- 1) the medicinal product has not been marketed during that period
- 2) The sales of the medicinal product according to turn-over of wholesalers is less than 75000 Estonian crowns per year and less than 2000 packages were sold per marketing authorisation.

(3) The reasoned request to release the marketing authorisation holder from payment of the fee for monitoring the safety and quality of a medicinal product indicating the fulfilment of conditions laid down in section 2, should be sent to State Agency of Medicines latest by 25. February.

#### **§ 9. Entry into force of Regulation**

The regulation enters into force on 1 March 2005.

\* Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to pharmaceuticals for human use (OJ L 311, 28.11.2001, p. 67-128); Directive 2004/27/EC of the European Parliament and of the Council amending Directive 2001/83/EC on the Community code relating to pharmaceuticals for human use (OJ L 136, 30.04.2004, p. 34-57); Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to veterinary pharmaceuticals (OJ L 311, 28.11.2001); Directive 2004/28/EC of the European Parliament and of the Council amending Directive 2001/82/EC on the Community code relating to veterinary pharmaceuticals (OJ L 136, 30.04.2004).