Annex 1

RA FN No. 15 "Submission and approval of educational materials stipulated by the risk management plan"

Information for marketing authorisation holders

Submission and approval of educational materials stipulated by the risk management plan at the State Agency of Medicines

Normative documents

- Regulation (EC) No 726/2004 of the European Union and of the Council of 31st of March 2004 laying down the Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing the European Medicines Agency (hereinafter - Regulation No. 726/2004)

- Commission Implementing Regulation (EU) No. 520/2012 of 19th of June 2012 on the performance of the pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council

- Pharmaceutical Law

- 22nd of January 2013 Cabinet of Ministers Regulation No. 47 "Procedure for Pharmacovigilance" (hereinafter - Regulation No. 47)

- 8th of March 2005 Cabinet of Ministers Regulation No. 175 "Regulations for Manufacture and Storage of Prescription Forms, as well as Writing Out and Storage of Prescriptions" (hereinafter - Regulation No. 175)

- Guideline on good pharmacovigilance practices, Module V "Risk management systems"; Module XVI "Risk minimisation measures: selection of tools and effectiveness indicators"; Addendum I of Module XVI "Educational Materials"

1. Introduction

Education materials (EM) and educational programs are additional risk minimisation measures with the objective of preventing and minimising serious adverse reactions associated with the use of medicinal products, the degree of severity of such reactions and their impact on the patient health, specifically emphasising the information provided in the summary of product characteristics (SPC) and Package Leaflet (PL). These educational materials have to ensure a positive risk/benefit balance for the use of medicinal products in patients. Educational materials (EM) have a specific target audience.

When submitting the EM prepared by the marketing authorisation holder (MAH) to the State Agency of Medicines (hereinafter – SAM), SAM invites marketing authorisation holders to comply with the following requirements:

1.1. The marketing authorisation holder shall regularly update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products. The marketing authorisation holder shall submit the established risk minimisation measures to the State Agency of Medicines for approval (Regulation No. 47, Article 15.8).

1.2. The marketing authorisation holder shall ensure the availability of the developed materials for risk minimisation measures approved by the State Agency of Medicines to the doctors entitled to prescribe the appropriate medicinal product (Regulation No. 175, Article 34^4).

1.3. The marketing authorisation holder shall ensure that the provided information is objective, it shall not be misleading (Regulation No. 47, Article 19; Regulation No. 726/2004, Chapter 3, Article 24(5)).

1.4. Even if the specific medicinal product is not distributed in Latvia, the need for EM must be discussed with SAM, by e-mailing it at em_dhpc@zva.gov.lv. Please note that as soon as the medicinal product enters the market (even if prescribed to individual patients) it is the responsibility of MAH to provide updated safety information to the relevant target audience, therefore the EM approval process must begin at least a month before the medicinal product gets to the patient (in certain exceptional cases, a prompter approval process is possible, by contacting SAM).

1.5. **Patient card.** If in accordance with the EM distribution plan, the marketing authorisation holder intends to place the patient card into the secondary (outer) packaging of the medicinal product, please note that the variation IB C.I.z. must additionally be submitted, i.e. changes to the labelling. The text of the labelling with the text of Patient card enclosed must be submitted for approval.

If the Patient card is already provided in the initial marketing authorisation procedure, then the text of the card is agreed upon simultaneously with the SmPC, the patient leaflet and the labelling (it is not necessary to submit a variation).

Prior to launch of the distribution of the medicinal product (for which the text of the Patient card has already been agreed within the initial marketing authorisation procedure) in Latvia, MAH must send information about the Patient Card to the SAM and attach the mock-up or a document with the text of the card in PDF format via email address em_dhpc@zva.gov.lv, and request to add the document to the relevant medicinal product in the Medicinal Product Register of Latvia. This is not considered an EM approval procedure and does not have additional stages of agreement.

1.6. Marketing authorisation holders of parallel distributed and parallel imported medicinal products should clarify whether education materials have been prepared for the reference product by contacting MAH of the reference product, and identical education materials must be submitted to SAM for approval. MAH of reference medicinal products shall cooperate with marketing authorisation holders of parallel distributed and parallel imported medicinal products by providing information regarding EM.

1.7. MAH may not use healthcare professional or patient contact information obtained as part of an educational program for the purposes of medicinal product advertisement.

2. When preparing EM, please note the following:

2.1. Content

2.1.1. The wording of the EM should be directed towards specific safety issues included in the risk management plan (key elements). The text should not be unjustly supplemented with information not directly related to the relevant safety issue or with information that is adequately reflected in the SPC and PL of the relevant medicinal product. The content of the EM should be completely compliant with the approved product information (SPC and PL) in effect in Latvia. Furthermore, EM should include directions to seek further information in the SPC and PL.

2.1.2. The implementation of educational programs should not be associated with measures promoting prescription, use or marketing of medicinal products.

2.1.3. EM of centrally authorised medicinal products or EM required as a result of European Union (EU) assessment procedures should include the key elements of the relevant materials approved by the Committee for Medicinal Products for Human Use (CHMP), Coordination Group for Mutual Recognition and Decentralised Procedures-Human (CMDh) or Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) or by the European Commission.

2.1.4. EM should be made as brief as possible. If the EM is more extensive, it should include an introduction summarising the key messages and a list of contents, if necessary.

2.1.5. In case of submission of an updated version of a previously approved EM, text of the previous version with tracked changes and an updated version number should be submitted. Updates of EM must be submitted only in case of significant changes that affect the key elements of the EM. Proofreading, minor, and insignificant changes may be submitted as part of the next approval procedure for significant changes, or sooner in case no redistribution of the EM to the target audience is planned (in such a case, the approval takes place via e-mail only).

2.1.6. The target audience of EM may be healthcare professionals or patients. It must be indicated in the EM – an additional heading at the top of the first page of each EM:

2.1.6.1. In materials intended for doctors, pharmacists and other healthcare professionals (in Latvian) – "Svarīga informācija veselības aprūpes speciālistiem par zāļu riska mazināšanu" *("Important information for healthcare professionals regarding medicinal product risk minimisation")*.At the top right corner, next to the heading, there must be an orange image of the palm of a hand sized 1.8 by 1.5 cm (see Figure and the "Mock-up of the palm"). This is an international warning sign that indicates that the material has been approved by SAM;

The mock-up of the palm image is available in a separate document, see here.

2.1.6.2. In materials intended for patients (provided to patients by the relevant healthcare professional) (in Latvian) – "Svarīga informācija pacientam par zāļu riska mazināšanu" *("Important information for patients regarding medicinal product risk minimisation")* At the top right corner, next to the heading, there must be an orange image of the palm of a hand sized 1.8 by 1.5 cm (see Figure and the "Mock-up of the palm"). This is an international warning sign that indicates that the material has been approved by SAM;

The mock-up of the palm image is available in a separate document, see here.

2.1.6.3. Credit-card-sized materials intended for patients and to be inserted in the outer packaging or attached to it, and are to be shown to all healthcare professionals (hereinafter - HCP) treating the patient, the heading is "Pacienta kartīte" ("*Patient card*").

2.1.6.3.1 In the patient card intended to be placed in secondary packaging, the orange hand image need not be placed.

2.1.6.3.2 In the patient card that is not intended to be placed in secondary packaging, the orange hand image must be placed at the top right corner of Page 1.

The mock-up of the palm image is available in a separate document, see here.

2.1.7. If the medicinal product is under additional monitoring, the symbol ▼ should be added in the EM right after the heading together with the standard explanatory text (in Latvian):

2.1.7.1. In materials intended for doctors, pharmacists and other healthcare professionals – "Šīm zālēm tiek piemērota papildu uzraudzība, lai iespējami ātri identificētu jaunāko informāciju par šo zāļu drošumu. Veselības aprūpes speciālisti tiek aicināti ziņot par jebkādām nevēlamām blakusparādībām" *("This medicinal product is subject to additional monitoring. This will allow to quickly identify new information regarding the safety of this medicinal product. Healthcare professionals are asked to report any possible adverse reactions");*

2.1.7.2. In materials intended for patients – "Šīm zālēm tiek piemērota papildu uzraudzība, lai iespējami ātri identificētu jaunāko informāciju par šo zāļu drošumu. Jūs varat palīdzēt, ziņojot par jebkādām novērotajām blakusparādībām" *("This medicinal product is subject to additional monitoring. This will allow to quickly identify new information regarding the safety of this medicinal product. You can help by reporting any observed*

adverse reactions").

2.1.7.3. The Patient card may contain the shortened text: "Šīm zālēm tiek piemērota papildu uzraudzība, Aicinām palīdzēt, ziņojot par jebkādām novērotajām blakusparādībām." *("This medicinal product is subject to additional monitoring. Please help us by reporting any observed adverse reactions").*

2.1.8. EM must include the requirement to report any adverse reactions with the following standard text and have the QR codes specified below to facilitate the reporting:

2.1.8.1. In materials for doctors, pharmacists and other healthcare professionals:

Atgādinām, ka saskaņā ar zāļu blakusparādību ziņošanas noteikumiem Latvijā ārstniecības personām un farmaceitiem jāziņo par novērotām iespējamām zāļu blaknēm Zāļu valsts aģentūrai (ZVA) elektroniski ZVA mājaslapā www.zva.gov.lv, klikšķinot uz izvēlnes "Ziņot par zāļu blaknēm, negadījumiem ar ierīcēm, biovigilanci" un zem "Veselības aprūpes speciālistiem un iestādēm" izvēloties "Ziņot par zāļu blaknēm" vai skenējot zemāk attēloto QR kodu. Papildinformācijas nepieciešamības gadījumā jāsazinās ar ZVA pa tālr.: 67078438.

("We remind you that in accordance with the regulation regarding reporting of adverse drug reactions in Latvia healthcare providers and pharmacists must report observed suspected adverse reactions to the State Agency of Medicines (SAM) electronically on SAM website www.zva.gov.lv, selecting "Report adverse drug reactions, incidents with medical devices, and biovigilance" and under "For healthcare professionals", selecting "Report adverse drug reactions", or by scanning the QR code shown below. For additional information please contact SAM via phone: 67078438.")

* The minimum size of the QR code is 2 by 2 cm.

2.1.8.2. In materials for patients:

Jūs varat ziņot par blakusparādībām tieši Zāļu valsts aģentūrai (ZVA) elektroniski interneta vietnē www.zva.gov.lv, klikšķinot uz izvēlnes "Ziņot par zāļu blaknēm, negadījumiem ar ierīcēm, biovigilanci" un zem "Iedzīvotājiem" izvēloties "Ziņot par zāļu blaknēm" vai skenējot zemāk attēloto QR kodu.

("You can report adverse reactions directly to the State Agency of Medicines (SAM) electronically on SAM website www.zva.gov.lv by selecting "Report adverse drug reactions, incidents with medical devices, and biovigilance" and under "Society" "Report adverse drug effects", or by scanning the QR code below.

* The minimum size of the QR code is 2 by 2 cm*;*

2.1.8.3. The Patient card that is not intended to be inserted in secondary packaging must include the text and the QR code below that leads to the reporting form intended for society (with the approval of SAM, exceptions are possible whereby an abbreviated text is included without the QR code):

Jūs varat ziņot par blakusparādībām Zāļu valsts aģentūrai interneta vietnē www.zva.gov.lv vai skenējot zemāk attēloto QR kodu.

("*You can report adverse effects to the State Agency of Medicines on website www.zva.gov.lv, or by scanning the QR code below*").

* The minimum size of the QR code is 2 by 2 cm;

A QR code leading to a reporting form does not need to be included in the 'Patient Card' which is intended to be inserted into the secondary packaging.

2.1.8.4. If the relevant medicinal product is a biological medicinal product (vaccines, biomedicines, or biosimilars), the text should be supplemented with

the following text in Latvian:

Šīs zāles ir bioloģiskas izcelsmes, tāpēc, ziņojot par blaknēm, jānorāda zāļu oriģinālnosaukums un sērijas numurs.

("This medicinal product is a biological medicinal product, therefore, the original name and serial number of the product should be indicated upon reporting adverse reactions.").

2.1.9. EM should be limited to the approved key messages. Additional information such as efficacy data, comparative data with other medicines or statements regarding "good tolerance" or "lack of adverse reaction reports" should not be included. On some occasions, efficacy data may be included in the EM, if the MAH can justify the need for this.

2.1.10. MAHs should come to a mutual agreement to prepare common/identical EM for their medicinal products containing the same active substance. The EM of generic medicinal products should comply with the EM of the reference medicinal product, if not regulated/required otherwise. In certain cases, SAM can take part in the distribution of these common materials if the distribution plan includes the sending of electronic EM to professional associations with requests to forward those materials to association members, as well as helping with the involvement in the approval process of representatives of the case specific active substance containing medicinal products distributed in Latvia. See clause 1.6 for EM preparation for parallel imported and parallel distributed medicinal products.

2.1.11. The EM should include the company's contact information, as well as the contact information of the MAH's national level contact regarding pharmacovigilance issues in Latvia (NLCP) (phone number and address), so that healthcare professionals could communicate in the official state language. The contact information must be submitted without personal data and must not contain private phone numbers or e-mail addresses.

2.1.12. When preparing materials for risk minimisation the MAH should comply with grammatical, stylistic and terminology requirements (see zva.gov.lv sections List of pharmaceutical terms ("Farmācijas termini"), Medical Dictionary for Regulatory Activities www.meddra.org, and Pharmacovigilance terminology ("Farmakovigilances termini")) in order to ensure effective communication. If the aforementioned quality requirements are not met, the materials are returned to the submitter for editing.

2.2. Format

2.2.1. The name of the active substance and/or therapeutic group of medicinal product should be indicated throughout the EM. In some cases, the original name of the medicinal product (e.g. biological medicinal product) may also be indicated after reaching an agreement with a SAM expert during the approval process.

2.2.2. The number of the version of the materials should be indicated (a simplified

identifier is preferable, e.g. “Version 1.0/1.3/3.0”). The date of the last revision of the text should be indicated on the first and last page, using the format mm.yyyy.

2.2.3. In order for the information to be clearly presented, bullet points should be used whenever necessary.

2.2.4. EM regarding medicinal product safety issues **should not** contain advertisement elements, product brand logo, colours, images, slogans or statements that promote prescription, supply, marketing or use of the medicinal product.

2.2.5. The materials should not include references to literature or documents, but they may include a reference or a QR code to the websites of SAM and the European Medicines Agency or to website specifically designed by the MAH (see 2.3), if it contains a publicly available updated summary of product characteristics and package leaflet.

2.2.6. References to other websites “for additional information” are not acceptable, except cases when it is agreed by SAM, for example, reference to a specific antibody test, a link, or a QR code to video or audio instructions for the patient/physician in the use of the drug/medical device specifically created on the MAH website or SAM social media accounts.

2.2.7. EM must include QR codes (shown in this documents, see 2.1.8) with a link to the adverse drug effect reporting forms on the SAM website, with the note “Ziņošana par zāļu blakusparādībām” (“*Reporting on adverse drug effects*”).

2.2.8. References to other medicinal products are not permitted.

2.2.9. The full set of the educational materials for healthcare professionals (healthcare providers or pharmacists) and patients should be submitted to SAM in Latvian and the original document in English should be attached.

2.2.10. After the end of the EM approval process, the company may send a mock-up of the EM (if any) to the SAM e-mail address (em_dhpc@zva.gov.lv), with a request to replace the final version of the EM published in the Medicinal Product Register of Latvia.

2.3. Publication of educational materials on a dedicated MAH website

2.3.1. ***The MAH may publish its educational materials in PDF format or on a website specifically designed for this purpose, if the MAH complies with the following requirements:***

2.3.1.1. SAM has approved this mode of distribution.

2.3.1.2. SAM has been notified of the address of the website.

2.3.1.3. A statement, that the information reflected on the website is compliant with the EM approved by SAM, is submitted to SAM.

2.3.1.4. The dedicated website may not contain references to other documents or websites that are not approved by SAM.

2.3.1.5. All of the elements and information on the website should be in Latvian (in separate cases SAM may approve some EM elements in English).

2.3.1.6. The dedicated website should not contain references to other medicinal products that are not authorised in Latvia.

2.3.1.7. The website may contain references to documents such as SPC, PL or risk management plan.

3. Procedure for submission and approval of documents

3.1. Submission of EM to SAM

3.1.1. The set of documents and cover letter is **submitted by the MAH representative electronically** to the following e-mail address: **em_dhpc@zva.gov.lv**. If the submitter is not an NLCP in pharmacovigilance, then the NLCP must be added as a carbon-copy ("cc") recipient of the e-mail message, to indicate that the NLCP has been informed of the process and is available in case of questions. The cover letter must be signed with a secure electronic signature. If joint EM are submitted for multiple MAHs with one active substance, then the cover letter is signed by all the MAHs involved. The checklist (see Addendum) recommended by SAM must be used when preparing the EM submission document package (hereinafter – "checklist").

3.1.2. The following documents must be submitted:

3.1.2.1. Cover letter indicating:

3.1.2.1.1 justification for preparation and submission of EM (indicating specific justifying documentation);

3.1.2.1.2 List of documents included in the EM package with version numbers;

3.1.2.1.3 if an update of a previously approved EM is submitted, only partially amending the previously approved EM, indicate a list of documents with version numbers amended as a result of the regulatory procedure, and, to expedite the approval process, a list of the remaining unamended EMs with version numbers;

3.1.2.1.4 EM target audience and distribution plan in Latvia;

3.1.2.1.5 Indicate, if the format and content, as well as the target audience and distribution plan of the EM was discussed with scientific associations, professional associations or healthcare professionals, etc.;

3.1.2.1.6 Specific distribution requirements and how the MAH shall meet them in Latvia, if such requirements are set (for example, a requirement to provide cooling bags, etc.);

3.1.2.1.7 Contact information (at least the e-mail address, phone number) of the EM submitter (MAH's NLCP for pharmacovigilance issues);

3.1.2.2. EM in Latvian in MS WORD format:

3.1.2.2.1 All of the updated EMs intended for healthcare professionals;

3.1.2.2.2 All of the updated EMs intended for patients;

3.1.2.2.3 If an update of a previously approved EM is submitted, only partially amending the previously approved EM, each EM section being updated as result of the regulatory procedure must be submitted separately (with tracked changes);

3.1.2.3. Copies of documents justifying the necessity for EM (for example, a European Commission decision, marketing authorisation conditions or risk minimisation measures laid down in the MAH risk management plan);

3.1.2.4. EM in English.

3.1.3. SAM will start the EM approval only after it has received a package containing all of the documents according to the requirements laid out in this section and the checklist.

3.2. EM approval

3.2.1. The EMs should be prepared according to the requirements for grammar, language, terminology, EM contents and format, as well as distribution plan and target audience in Latvia. If the aforementioned quality requirements are not met, the approval process is not started, and the materials are forwarded to the submitter for editing.

3.2.2. SAM expert may contact the submitter via telephone or e-mail, if necessary, in order to:

3.2.2.1. Invite the MAH to consult with terminologists, linguists, medical and pharmaceutical professional associations, as well as separate specialists in order to clarify or verify:

3.2.2.1.1 Compliance of terminology;

3.2.2.1.2 Comprehensibility and perceptibility of the information;

3.2.2.1.3 Whether the information is compliant with the medical and laboratorial possibilities available in Latvia.

3.2.2.2. Request that HAM submit additional information or materials

3.2.3. If the SAM expert has no further objections to the content, format, distribution plan and target audience in Latvia of the materials submitted in the package of documents, the expert will send an e-mail invitation to submit the final EM version to SAM.

3.3. Submission of the final EM version to SAM

3.3.1. The set of documents must be submitted electronically to the following e-mail address: **em_dhpc@zva.gov.lv**, indicating "Final version_name of medicinal product/ active substance_mm.yyyy" in the subject field (date of the updated EM version in Latvian, see 2.2.2).

3.3.2. The e-mail must indicate:

3.3.2.1. Justification for preparation and submission of EM (indicating specific justifying documents);

3.3.2.2. List of documents included in the EM package with version numbers (indicating precise title and number of pages);

3.3.2.3. If an update of a previously approved EM is submitted, only partially amending the previously approved EM, indicate a list of EM final versions with version numbers approved as a result of the regulatory procedure, as well as a list of the remaining unamended EMs with version numbers;

3.3.2.4. SAM approved list of EM target audiences and distribution plan in Latvia;

3.3.2.5. A statement, that the information reflected on the website is compliant with the EM approved by SAM, if applicable;

3.3.2.6. Organisations and persons with whom the materials were discussed, if any;

3.3.2.7. Special conditions for distributions and how the MAH will ensure them in Latvia (e.g., a requirement to provide cooling bags, etc.), if any,

3.3.2.8. Additional standard text: "Izglītojošo materiālu gala versiju <RAĪ> iesniedz pēc izglītojošo materiālu saskaņošanas ar ZVA ekspertu" (*"<MAH> submits the final version of educational materials after receiving approval of educational materials from a SAM expert").*

The following documents must be submitted:

3.3.3. Final versions of the following EM documents approved by SAM:

3.3.3.1. Complete and updated EMs intended for healthcare professionals (all of the materials intended for healthcare professionals and their amended and unamended sections, if any, together) in a **single** pdf format file for publication in the Medicinal Product Register of Latvia on SAM website,

3.3.3.2. Complete and updated EMs intended for patients (all of the materials intended for patients and their amended and unamended sections, if any, together) in a **single** pdf format file for publication in the Medicinal Product Register of Latvia on SAM website,

3.3.3.3. If an update of a previously approved EM is submitted, only partially amending the previously approved EM, the EM sections amended as a result of the regulatory procedure must be submitted separately (MS WORD or pdf format).

3.4. Confirmation of SAM approval of EM

SAM will inform the submitter of EM approval by sending an electronically signed letter via e-mail indicating "On risk minimisation educational materials." in the subject field.

3.5. Publication of information on SAM website regarding approval of EM

In accordance with Article 34^4 of the 8 March 2005 Cabinet of Ministers Regulation No. 175 "Regulations for Manufacture and Storage of Prescription Forms, as well as Writing and Storage of Prescriptions" the information regarding list of medicinal products, for which the MAH has established risk minimisation measures that have been approved by the State Agency of Medicines, shall be published on SAM website www.zva.gov.lv in the section "Zāļu riska

mazināšanas izglītojošo materiālu saraksts" *("List of risk minimisation educational materials for medicines.").*

3.6. EM inclusion in the public Medicinal Product Register of Latvia on SAM website

The approved EM version shall be added to the appropriate medicinal product in the Medicinal Product Register of Latvia published on SAM website within two working days.

In case of any questions, please contact the experts of the SAM Medicinal Product Safety Division. Phone: +371 67078442, e-mail: em_dhpc@zva.gov.lv.

Checklist for EM submission recommended by the State Agency of Medicines (SAM)

Documents required for submission to the State Agency of Medicines (SAM)

1. **Copies of documents justifying EM preparation and distribution:**
   - EC decision and relevant appendices of the decision ☐
   - CHMP documents ☐
   - RMP version, reflecting the relevant risk minimisation measures ☐

2. **EM in Latvian, in MS WORD format:**
   - All of the EMs intended for healthcare professionals ☐
   - All of the EMs intended for patients ☐
   - If an updated of a previously approved EM is submitted, only partially amending the previously approved EM, the EM sections amended as a result of the regulatory procedure must be submitted separately ☐

3. **EM in English** ☐

4. **Cover letter** ☐

The cover letter must include the following information:

- **Justification for EM preparation and distribution (naming the justifying documents)** ☐
- **List of documents included in the EM package, indicating version numbers** ☐
  - If an update of a previously approved EM is submitted, indicate a list of documents with version numbers amended as a result of the regulatory procedure, as well as a list of the remaining unamended EMs with version numbers, ☐
- **Target audience and distribution plan for EM in Latvia** ☐
- **E-mail address, phone number of EM submitter (MAH's national level contact person for pharmacovigilance issues)** ☐