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To: Prefectural Governors

Director-General of Pharmaceutical Safety and
Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Instructions for Electronic Package Inserts of Regenerative Medical Products

Efforts to ensure proper descriptions in package inserts have been made in accordance with the "Instructions for Package Inserts of Regenerative Medical Products" (PFSB Notification No. 1002-12 by the Director-General of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated October 2, 2014, hereinafter referred to as the "Former Director-General Notification").

Describing matters, such as precautions necessary for use and handling of regenerative medical products, in package inserts, etc. has been an obligation so far, and thus the matters have been defined as "Package Insert Language, etc."

Amid such circumstances, the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960) was amended by the enforcement of the Act for Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 63 of 2019, hereinafter referred to as the "Amendment Act").

By this amendment of the act, the obligation to describe precautions, etc. necessary for use and handling of regenerative medical products in package

inserts was abolished after they were defined as "Information on PRECAUTIONS, etc. (hereinafter referred to as "Information on PRECAUTIONS, etc.") "

Instead, it has been decided that the marketing authorization holder will place a code, etc. to be used to obtain necessary precautions for use and handling on the container or wrapping and then publish the Information on PRECAUTIONS, etc. by posting it on the website of the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as the "PMDA").

Based on these revisions in the regulations, we have recently established the "Instructions for Electronic Package Inserts of Regenerative Medical Products" as shown in the appendix. Taking into account the following points, please inform relevant organizations, etc. under your jurisdiction and give particular consideration to instructions on electronic package inserts of regenerative medical products as well.

1. Notification Key Points

(1) By the Amendment Act, the obligation to describe precautions, etc. necessary for use and handling of regenerative medical products in package inserts was abolished after they were defined as "Information on PRECAUTIONS, etc."

Instead, it has been decided that the marketing authorization holder will place a code, etc. necessary to obtain Information on PRECAUTIONS, etc. on the container or wrapping and then publish the Information on PRECAUTIONS, etc. by posting it on the website of the PMDA.

A document containing matters including Information on PRECAUTIONS, etc., which will be published on the website of the PMDA, will be called an "electronic package insert" by the amendment of the Act.

(2) The abbreviation of "electronic package insert" shall be "e-PI."

2. Scope of Application

The instructions shall be applied to all regenerative medical products in principle.

3. Preparation Unit of Electronic Package Insert

(1) In principle, one e-PI shall be prepared for one approved product.
(2) For regenerative medical products with sub-components in addition to the main component, if a single approval is made for products to be used in combination (combination products defined in "Points to Be Considered for Marketing Approval Application of Regenerative Medical Products" (PFSB/ELD/OMDE/C Notification No. 0812-5 by the Counsellor of Minister's Secretariat, Ministry of Health, Labour and Welfare (Evaluation and Licensing of Medical Device/Regenerative Medicine Products), dated August 12, 2014) and only sub-components will be distributed, an e-PI of the sub-components shall be prepared separately from the e-PI of the main component to prevent misunderstanding by users. However, in cases of the single approval for sub- and main components, it is acceptable to simplify some of the descriptions by specifying the main component to be used in combination.

4. Date of Implementation

This document shall come into effect from August 1, 2021.

5. Revision and Abolition of Existing Notifications

(1) Abolition

The Former Director-General Notification will be abolished and replaced with the contents of this notification.

(2) Necessary Rewording of the Director Notification

For the description in e-PIs, also refer to "Instructions for Package Inserts of Regenerative Medical Products (Detailed Rules)" (PFSB/SD Notification No. 1002-13 by the Director of Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated October 2, 2014, hereinafter referred to as the "Director Notification") in addition to this notification. When referring to the Director Notification, if the provisions and words/phrases before the revision by the Amendment Act, etc. are cited, they shall be replaced with those after the revision (e.g., the description that used to be "package insert" shall be "electronic package insert“ or “e-PI”).

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Appendix

Instructions for Electronic Package Inserts of Regenerative Medical Products

1. Principles of Description of Electronic Package Insert

(1) Electronic package inserts (hereafter referred to as e-PIs) of Regenerative medical products shall be prepared by marketing authorization holders or persons with special approval regarding foreign manufacturing (including designated marketing authorization holders, the same shall apply hereafter) for the purpose of providing necessary information to healthcare professionals, such as physicians, dentists, and pharmacists, in order to ensure the safety of patients who receive regenerative medical products and promote their proper use pursuant to the provisions of Article 68-2, Paragraph 2, Item 3 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960. hereinafter referred to as the "Act").

(2) The e-PI shall be prepared based on findings obtained from the latest papers, etc., the contents shall be consistent with the clinical practice, and revisions, etc. shall be made as needed.

(3) Contents to be described in e-PIs shall, in principle, be matters that are necessary when the regenerative medical product is used within the scope of the marketing approval (hereinafter referred to as "approval"). However, even in other cases, information considered important and particularly necessary shall be evaluated and described.

(4) The order of descriptions shall be in accordance with those in "2. Description Items and Order of Descriptions" in principle.

(5) Deletion or change of matters already described shall be made based on sufficient backgrounds.

(6) Description items from "(1) Year and month of preparation or revision" to "(4) Brand name" shown in "2. Description Items and Order of Descriptions" shall be described in the upper part of page 1 of the electronic package insert, and the contents in and after "(5) Warnings" shall be described in the text.

(7) Precautions, etc. including the following matters shall be described as characteristics of regenerative medical products.

1) The letters of "designated regenerative medical product" for designated regenerative medical products, and the letters "regenerative medical product" for other regenerative medical products

2) For designated regenerative medical products, a statement to the effect that the risk of transmission of infections derived from raw materials

cannot be completely eliminated and a summary of safety measures taken to prevent transmission of infections

3) Descriptions that healthcare professionals such as physicians, who handle regenerative medical products, need to explain to persons eligible for the use of the product about the efficacy and safety of the product as well as other matters necessary for the proper use and to obtain their consent

4) Other matters necessary for the proper use of the regenerative medical product

2. Description Items and Order of Descriptions

(1) Date of Preparation or Revision
(2) Approval Number, etc.
(3) Category and Nonproprietary Name, etc.
(4) Brand Name
(5) Warnings
(6) Contraindications
(7) Shape, Structure, Ingredients, Quantity or Nature
(8) Indications or Performance
(9) Dosage and Administration or Methods of Use
(10) Precautions
(11) Clinical Studies
(12) Principle/Mechanism
(13) Pharmacokinetics
(14) Storage Method and Shelf Life, etc.
(15) Precautions for Handling
(16) Conditions for Approval and Time-Limits
(17) References and Reference Request
(18) Name, Address, etc. of Marketing Authorization Holder

3. Instructions

(1) Date of Preparation or Revision

Describe the year and month of preparation or revision and the version number of the e-PI. When a revision is made, guarantee its continuity by making its history clear.

(2) Approval Number, etc.

Describe "Do not reuse" in principle, in addition to the approval number.

(3) Category and Nonproprietary Name, etc.

Describe the category and nonproprietary name of the regenerative medical product assigned at the time of approval. If the marketing approval for the product falls into conditional and time-limited approval, emergency approval, or special approval, it should be described.

If a single approval was made for a combination product comprising multiple nonproprietary names, describe in parentheses the nonproprietary name of the main component stated in the column of nonproprietary name in the approval letter as well as the nonproprietary names, etc. of the sub-components stated in the column of remarks in the approval letter, etc.

(4) Brand Name

Describe the approved brand name.

(5) Warnings

Describe precautions related to occurrence of serious health damage within the scope of the use of the regenerative medical product. Prepare subsections and describe items including "Applications (patients)," "Concomitant Therapy," "Method of Use," etc. in the subsections, if applicable.

(6) Contraindications

Describe contraindications related to serious health damage within the scope of the use of the regenerative medical product. Prepare subsections and describe items including "Applications (patients)," "Concomitant Therapy," "Method of Use," etc. in the subsections, if applicable.

(7) Shape, Structure, Ingredients, Quantity or Nature

In principle, use illustrations, photos, etc. for each component so that the overall structure of the regenerative medical product can be easily understood. (For a product with a single component just being filled in a container, it is acceptable to omit illustrations.) For each component, describe the contents of the main ingredient and the accompanying ingredients that cannot normally exist in the body.

In addition, describe the following matters for human- or animal-derived raw materials (raw materials or materials, or constituent raw materials of them (those from which raw materials or materials used for manufacturing are derived, the same shall apply hereafter), the same shall apply hereafter).

1) Of raw materials or materials (including those used in the manufacturing process, the same shall apply hereafter) for the regenerative medical product, the names of human- or animal-derived ingredients

2) The names of humans or animals and the name of parts, etc. for raw materials of the regenerative medical product (for the range of raw materials, refer to the "Operations of Standards of Biological Raw Materials, " (Joint Notification of PFSB/ELD Notification No. 1002-1 and PFSB/ELD/OMDE/C Notification No. 1002-5 by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, and Counsellor of Minister's Secretariat, Ministry of Health, Labour and Welfare (Evaluation and Licensing of Medical Device and Regenerative Medicine Product) dated October 2, 2014).)

3) In cases where human blood or substances obtained from the human blood are accessory ingredients or the products are manufactured using human blood as raw materials, etc., the name of the country where the blood as a raw material, etc. was collected and the method of blood collection (blood donation or non-donation)

4) In cases where the products are manufactured using allogeneic human cell/tissue raw materials as raw materials (limited to the designated regenerative medical products), the name of the country where the cells or tissues as the allogeneic raw material, etc. were collected

(8) Indications or Performance

Describe the approved indications or performance.

(9) Dosage and Administration or Methods of Use

Describe the approved dosage and administration or methods of use.

When cells/tissues are collected from patients each time the product is manufactured, prepare a subsection for the collection method and describe the method.

(10) Precautions

Describe the following general precautions for the use of the regenerative medical product (if applicable). Also, prepare subsections for precautions for "Applications (patients)," "Concomitant Therapy," and "Method of Use" and describe them.

In addition, based on the provisions of Article 68-4 of the Act, describe that healthcare professionals such as physicians, who handle regenerative medical products, need to explain to persons eligible for the use of the product about the efficacy and safety of the product as well as other matters necessary for the proper use and to obtain their consent before using the products.

1) Precautions (Caution is necessary for the following patients.)
2) Important Precautions
3) Interactions (concomitant use with other drugs, medical devices, etc.)
    [1] Contraindications for Concomitant Use (Concomitant use is prohibited.)
    [2] Precautions for Concomitant Use (Concomitant use should be with caution.)
4) Defects/Adverse Reactions
    [1] Clinically significant defects/adverse reactions
    [2] Other defects/adverse reactions
5) Geriatric use
6) Use in pregnant, parturient and nursing women, or pediatric use
7) Influence on laboratory tests
8) Overuse
9) Other Precautions

(11) Clinical Studies

Describe the results of clinical studies used for the approval application or post-marketing clinical studies.

(12) Principle/Mechanism

The principle and mechanism by which the regenerative medical product is considered to exert its efficacy or performance shall be briefly described.

(13) Pharmacokinetics

Describe findings on distribution in body, duration of engraftment, duration of effect, etc. of the regenerative medical product, when accumulated.

(14) Storage Method and Shelf Life, etc.

Prepare subsections for the storage method and shelf life and describe them.

(15) Precautions for Handling

For products to which precautions for handling are specified in standards or approval letters, describe the precautions.

For designated regenerative medical products, based on the provisions of Article 68-7 Paragraphs 3 and 4 of the Act, describe that healthcare professionals such as physicians, who handle designated regenerative medical products, need to record the names, addresses, etc. of the

persons to whom the product is given and retain the record at the medical institution, etc.

(16) Approval Conditions and Time-Limits

Pursuant to the provisions of Article 23-26, Paragraph 1 of the Act or Article 79 of the Act, if there are any conditions for approval, describe the conditions and time-limits. If the approval is a "conditional and time-limited approval" under the provisions of Article 23-26, Paragraph 1 of the Act, describe that.

(17) References and Reference Request

Describe the name, address, and telephone number for reference requests.

(18) Name, Address, etc. of Marketing Authorization Holder

Describe the name, address, and telephone number of the marketing authorization holder (including designated marketing authorization holder).