PSB Notification No. 0607-1
June 7, 2024

To: Prefectural Governors

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

Instructions for Electronic Package Inserts of Regenerative Medical Products

The above-mentioned matter has been notified through the “Instructions for Electronic Package Inserts of Regenerative Medical Products (PSEHB Notification No. 0611-13 by the Director-General of the Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (hereinafter referred to as “MHLW”) dated June 11, 2021) (hereinafter referred to as “Former Director-General Notification”).

Since 2014, when it was decided to treat regenerative medical products as a new category, the circumstances surrounding regenerative medical products have been drastically changed, as products with various characteristics have been developed. Therefore, how to make the electronic package inserts (hereinafter referred to as “e-PIs”) easier to understand and use was reviewed in the study subject “Studies on Post-Marketing Safety Measures based on the Characteristics of Regenerative Medical Products and Validity Verification Based on Clinical Information of Regenerative Medical Products” (co-investigators: Yoshiro Saito, Deputy director general, the National Institute of Health Sciences, Japan, Rumi Sawada, Section Chief, Division of Cell-Based Therapeutic Products, the National Institute of Health Sciences, Japan) under "Studies on Post-Marketing Safety Measures for Safer and More Effective Use of New Forms of Medical Devices” (Health, Labour and Welfare Policy Research Grants (Research Projects on Regulatory Science for Pharmaceuticals and Medical Devices), principal investigator: Atsuko Miyajima, Section Chief, Division of Medical Devices, the National Institute of Health Sciences, Japan). As a result, the Instructions for Package Inserts of Regenerative Medical Products are stipulated as presented in the appendix.

Please, therefore, make the instructions thoroughly known to all relevant

industries and organizations under your jurisdiction with attention being paid to the below-mentioned points, and also make the necessary arrangements for appropriate instructions to be given regarding the e-PIs of regenerative medical products.

The Former Director-General Notification has been repealed and replaced with the contents herein.

1 Main points of the instructions

1) The sections and structure of the e-PIs were reviewed, such as establishing a new section of “PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS.”
2) Sequential numbers will be assigned to the sections: Numbers will be assigned to each section starting from “WARNINGS,” and if there is no applicable information in a section, the number of that section will be left blank.
3) Information to be described in the e-PIs was fully reorganized.

2. Timing of implementation

The present instructions shall come into effect as of October 1, 2024. For the e-PIs of products that have already been approved as of October 1, 2024, it is acceptable to revise them according to the attached instructions as soon as possible but not later than September 30, 2026.

Appendix

Instructions for Electronic Package Inserts of Regenerative Medical Products

I. Basic rules for compilation of electronic package inserts

1. Electronic package inserts (hereinafter referred to as “e-PIs”) for regenerative medical products shall be prepared by the marketing authorization holders or foreign exceptional approval holders (including designated marketing authorization holders; the same shall apply hereinafter) of the regenerative medical products in accordance with the provisions set forth in each item 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 “Pharmaceuticals and Medical Devices Act”) so that the necessary information is provided to healthcare professionals such as physicians, dentists, and pharmacists to ensure the safety of patients using the regenerative medical products and to promote their proper use.

2. The e-PI shall be compiled based on the latest knowledge obtained from research papers and other sources, and the content shall be in line with the medical practice and shall be revised as needed.

3. Information to be included in e-PIs shall be that required for use of the regenerative medical product within the scope of approval, as a rule. However, other information that is considered to be important and particularly necessary shall be evaluated and provided.

4. Information shall be presented with its section number in the order specified in II “Sections and their order.” In a section with no information to be included, the information may be omitted, but the section number shall not be moved up. For A to D shown in II, it is not necessary to indicate the section numbers and section names for A and C to D and section numbers for B.

5. The “PRECAUTIONS” shall include the sections from “1. WARNINGS” to “15. OTHER PRECAUTIONS” excluding “3. SHAPE, STRUCTURE, INGREDIENTS, QUANTITY OR NATURE,” “4. INDICATIONS OR PERFORMANCE” and “6. DOSAGE AND ADMINISTRATION OR METHODS OF USE” among those listed in Section II “Sections and their order.”

6. Deletion or change of information currently included shall only be done on the basis of sufficient rationale.

7. Information shall not be repeated in two or more different sections.

8. Related sections should be mutually referred to.

9. The sections from "A. Date of Preparation or Revision " to "D. Brand Name" listed in the II. Sections and their order should be described at the top of the first page of the e-PI, and the contents starting from "1. WARNINGS" should be placed in the main text.

10. The following precautions shall be included as characteristics of regenerative medical products.
    1) For designated regenerative medical products, a description 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.
    2) Other matters necessary for the proper use of the relevant regenerative medical product.

11. The e-PIs should be compiled for the purpose of 1. above. Therefore, matters about which healthcare professionals are considered to have already been cautioned for providing medical care irrespective of the individual regenerative medical product shall not be included.

II. Sections and their order

A. Date of Preparation or Revision
B. Approval Number, etc.
C. Category and Nonproprietary Name, etc.
D. Brand Name

1. WARNINGS
2. CONTRAINDICATIONS
3. SHAPE, STRUCTURE, INGREDIENTS, QUANTITY OR NATURE
4. INDICATIONS OR PERFORMANCE
5. PRECAUTIONS CONCERNING INDICATIONS OR PERFORMANCE
6. DOSAGE AND ADMINISTRATION OR METHODS OF USE
7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHODS OF USE

8. IMPORTANT PRECAUTIONS
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS
   - 9.1 Patients with Complication or History of Diseases, etc.
   - 9.2 Patients with Renal Impairment
   - 9.3 Patients with Hepatic Impairment
   - 9.4 Patients with Reproductive Potential
   - 9.5 Pregnant Women
   - 9.6 Breastfeeding Women
   - 9.7 Pediatric Use
   - 9.8 Geriatric Use
10. INTERACTIONS
   - 10.1 Contraindications for Concomitant Use (Concomitant use is prohibited.)
   - 10.2 Precautions for Concomitant Use (Concomitant use should be with caution.)
11. DEFECTS/ADVERSE REACTIONS
   - 11.1 Clinically Significant Adverse Reactions
   - 11.2 Other Adverse Reactions
   - 11.3 Clinically Significant Defects
   - 11.4 Other Defects
12. INFLUENCE ON LABORATORY TESTS
13. OVERDOSE
14. PRECAUTIONS CONCERNING USE
15. OTHER PRECAUTIONS
   - 15.1 Information Based on Clinical Use
   - 15.2 Information Based on Nonclinical Studies
16. PHARMACOKINETICS
17. CLINICAL STUDIES
   - 17.1 Clinical Studies for Efficacy and Safety
   - 17.2 Post-marketing Surveillance, etc.
   - 17.3 Others
18. PRINCIPLE/MECHANISM
19. STORAGE METHOD AND SHELF LIFE, etc.
20. PRECAUTIONS FOR HANDLING
21. APPROVAL CONDITIONS AND TIME-LIMITS
22. REFERENCES
23. REFERENCE REQUEST AND CONTACT INFORMATION
24. MARKETING AUTHORIZATION HOLDER, etc.

III. Instructions

A. Date of Preparation or Revision

1) The date of preparation or revision and the version number shall be indicated. When a revision is made, guarantee its continuity by making its history clear.
2) When a revision is made because of the release of reexamination or reevaluation results, the review results of application for approval after a conditional and time-limited approval of regenerative medical products, or a change in the “indications or performance” or in the “dosage and administration or method of use”, such a fact shall be stated.

B. Approval Number, etc.

1) The approval number shall be included.
2) The date of initial marketing in Japan shall be included.

C. Category and Nonproprietary Name, etc.

1) 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.
2) If a single approval was made for a combination product comprising multiple nonproprietary names, describe the nonproprietary name of the main component as stated in the column of the 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.in parentheses.
3) In the case of a designated regenerative medical product, “designated regenerative medical product” shall be indicated, and in the case of other regenerative medical products, “regenerative medical product” shall be indicated.

D. Brand Name

Describe the approved brand name. In addition, the brand name in English should be described if available.

1. 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 sections including "Applications (patients)," "Concomitant Therapy," "Method of Use," etc. in the subsections, if applicable.

2. CONTRAINDICATIONS

Describe contraindications related to serious health damage within the scope of the use of the regenerative medical product. Prepare subsections and describe sections including "Applications (patients)," "Concomitant Therapy," "Method of Use," etc. in the subsections, if applicable. In the case of regenerative medical products including devices, etc., which are allowed to be used only once as sub-components, describe that reuse is prohibited.

3. SHAPE, STRUCTURE, INGREDIENTS, QUALITY OR NATURE

1) In consideration of the nature of the regenerative medical product, the shape, structure, component cells, transgene, etc. shall be stated.
2) 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).
    i. 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
    ii. 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 (Evaluation and Licensing of Medical Device and Regenerative Medicine Product), Ministry of Health, Labour and Welfare dated October 2, 2014).)
    iii. In cases where human blood or substances obtained from the human blood are accessory ingredients, or in cases where the products are manufactured using other 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)
    iv. 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

4. INDICATIONS OR PERFORMANCE
   1) Describe the approved indications or performance.
   2) For regenerative medical products that have already completed reexamination or reevaluation, the indications or performance shall be described on the basis of the results of the reexamination or reevaluation.

5. PRECAUTIONS CONCERNING INDICATIONS OR PERFORMANCE

   Precautions for the selection of patients and treatment within the scope of approved indications shall be included. In principle, information falling under the section “2. CONTRAINDICATIONS” shall not be necessary in this section.

6. DOSAGE AND ADMINISTRATION OR METHODS OF USE
   1) Describe the approved dosage and administration or methods of use.
   2) When cells/tissues are collected from patients each time the product is manufactured, prepare a subsection for the collection method and describe the method.
   3) For regenerative medical products that have already completed reexamination or reevaluation, the dosage and administration or methods of use shall be described on the basis of the results of the reexamination or reevaluation.

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION OR METHODS OF USE

   The dosage and administration or methods of use under specific conditions and precautions that are particularly necessary for adjustment of dosage and administration or methods of use within the scope of the approved dosage and administration shall be described.

8. IMPORTANT PRECAUTIONS
   1) Important precautions for performing tests necessary upon treatment with the regenerative medical products, duration of use, and other relevant matters shall be concisely described in order to prevent clinically significant defects/adverse reactions.

2) Based on the provisions of Article 68-4 of the Act, describe that healthcare professionals such as physicians, who handle regenerative medical products, are required 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.
3) If the regenerative medical products must be used in compliance with the manuals, etc. provided by the marketing authorization holders, such a fact should be stated.

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

1) Precautions concerning patients with specific backgrounds shall be provided in the following cases: Clinical use in such patients is anticipated on the basis of indications or performance and other relevant matters, and more special attention is required for them compared with other patients when using the regenerative medical products; there is information on appropriate use.
2) When the regenerative medical products shall not be used in the said patients, such a fact shall be stated in the “2. CONTRAINDICATIONS” section as well.
3) In addition to the precautions concerning patients with specific backgrounds, objective data obtained from clinical studies, nonclinical studies, post-marketing surveillance, epidemiological studies, and other relevant matters shall be provided so that users can judge risks.

9.1 Patients with Complication or History of Diseases, etc.

This section shall be filled out for patients requiring more special attention than other patients based on their complications, past history, family history, genetic predispositions, and other relevant factors if they do not fall under the sections from “9.2 Patients with Renal Impairment” to “9.8 Geriatric Use.”

9.2 Patients with Renal Impairment

1) For cases in which it is necessary to adjust dosage and administration or methods of use on the basis of pharmacokinetics and the occurrence of adverse reactions and cases in which special attention is required, such facts shall be stated while considering the severity of renal impairment.
2) The information on dialysis patients and removal by dialysis, if any,

shall be briefly described.

9.3 Patients with Hepatic Impairment

For cases in which it is necessary to adjust dosage and administration or methods of use on the basis of pharmacokinetics and the occurrence of adverse reactions and cases in which special attention is required, such facts shall be stated while considering the severity of hepatic impairment.

9.4 Patients with Reproductive Potential

1) When patients and their partners are required to practice contraception, such a fact shall be stated with the required period of contraception.
2) If pregnancy tests are necessary before and periodically during the use of the regenerative medical products, such a fact shall be mentioned.
3) If it is necessary to pay attention to the effects on gonads, fertility, etc., such a fact shall be stated.

9.5 Pregnant Women

1) Necessary information shall be included while considering not only placental transfer and teratogenicity but also the amount of fetal exposure, the duration of exposure during pregnancy, clinical use experience, the availability of alternative treatments, and other relevant matters.
2) Precautions shall be described basically using “This regenerative medical product should not be used.” “It is advisable not to use this regenerative medical product.” or “This regenerative medical product should be administered only if the expected therapeutic benefits outweigh the possible risks associated with treatment.”

9.6 Breastfeeding Women

1) Necessary information shall be provided while considering not only transfer to breast milk but also effects on breastfed babies anticipated from pharmacokinetics and principle/mechanism, as well as clinical use experience, and other relevant matters.
2) Matters concerning the effects on breast milk secretion shall be included separately from the effects on breastfed babies.
3) Precautions shall be described basically using “Women should be instructed to avoid breastfeeding.” “It is advisable not to breastfeed.” or “The continuation or discontinuation of

breastfeeding should be considered while taking account of the expected therapeutic benefits and the benefits of maternal feeding."

9.7 Pediatric Use

For regenerative medical products that may be used in low-birth-weight babies, neonates, babies, infants, or children (hereinafter referred to as "children"), if they are considered to have special adverse effects on children or special precautions are considered to be necessary on the basis of their pharmacokinetics and principle/mechanism, such facts shall be described while considering age categories.

9.8 Geriatric Use

For cases in which it is necessary to adjust dosage and administration or methods of use on the basis of pharmacokinetics and the occurrence of adverse reactions and cases in which special attention is required, such facts shall be concisely described.

10. INTERACTIONS

1) When concomitant use with other drugs, etc. causes the enhancement or reduction of the pharmacological actions of the regenerative medical product of concern or the concomitant drugs, etc. or it causes the augmentation of adverse reactions, occurrence of new adverse reactions, or aggravation of underlying diseases, etc., the combinations requiring a precaution in clinical practice shall be listed. This shall include important interactions with physical therapy, food, beverages, etc.
2) In case an interaction is associated with changes in pharmacokinetics, if information is available on metabolic enzymes, etc. responsible for the mechanism of onset, this information shall be included in a preceding paragraph.
3) Information provided in the "10.1 Contraindications for Co-administration" section shall also be included in the "2 CONTRAINDICATIONS" section. Descriptions for contraindications for co-administration should maintain consistency so that drugs, etc., causing interactions are mutually contraindicated.
4) For the information in "10.1 Contraindications for Co-administration" and "10.2 Precautions for Co-administration," the names of drugs, etc., the clinical symptoms and measures, mechanisms of action, risk factors, etc. that cause interaction shall be given briefly. Interactions

with different types or mechanisms of action etc. shall be described in different paragraphs.

5) In the “10.1 Contraindications for Co-administration” section, non-proprietary names and representative brand names shall be provided as the names of the drugs, etc.
6) In the “10.2 Precautions for Co-administration” section, non-proprietary names or the names of therapeutic categories shall be indicated as the names of the drugs, etc. If the names of therapeutic categories are listed, in principle, representative non-proprietary names shall also be listed.

11. DEFECTS/ADVERSE REACTIONS

1) Adverse reactions occurring in association with the use of the regenerative medical product and defects of the relevant regenerative medical product shall be listed separately.
2) The frequency of adverse reactions shall be included on the basis of the results of clinical studies, etc. that were accurately and objectively conducted.
3) The “11.1 Clinically Significant Adverse Reactions” section and the “11.3 Clinically Significant Defects” section shall be described with attention being paid to the following points:
   i. Information requiring a special precaution shall be described while considering the outcome and seriousness of defects/adverse reactions.
   ii. If necessary, clinically significant defects/adverse reactions shall be described by the target disease and a subsection with the name of the disease shall be provided. Defects/adverse reactions before (e.g., when cell/tissue collection is performed) and after use of the relevant regenerative medical product shall be described separately as necessary.
   iii. Event names of defects/adverse reactions shall be used as section names. If initial symptoms (including abnormal laboratory values), the mechanism of onset, time to onset, risk factors, preventive measures, special measures, and other relevant matters are known, such data shall be described under relevant sections as necessary.
   iv. Clinically significant defects/adverse reactions that have occurred overseas only shall also be provided as necessary.
   v. Clinically significant defects/adverse reactions known to occur with the use of similar products shall be included only when the same precautions are considered to be necessary.

4) Information in the “11.2 Other Adverse Reactions” section and “11.4 Other Defects” section shall be described with attention being paid to the following points:
   i. If necessary, other defects/adverse reactions shall be described by the target disease and a subsection with the name of the disease shall be provided. Defects/adverse reactions before (e.g., when cell/tissue collection is performed) and after use of the relevant regenerative medical product shall be described separately as necessary.
   ii. Other defects/adverse reactions shall be classified by the site of occurrence or mechanism of onset and described along with each frequency category.
   iii. Other defects/adverse reactions that have occurred overseas only shall also be included as necessary.

12. INFLUENCE ON LABORATORY TESTS

This section shall be included when the use of the regenerative medical product causes apparent changes in laboratory data that are clearly not associated with disorder in organs or functional impairment of patients.

13. OVERDOSE

Symptoms of intoxication that occur on overdose (including misuse and accidental exposure) shall be described. Items to be monitored and measures shall also be indicated, if known.

14. PRECAUTIONS CONCERNING USE

1) Precautions necessary for use such as the administration route, administration rate, administration site, method of preparation, and instructions to patients shall be included.
2) Information shall be concretely described by adding appropriate sections such as “Precautions Concerning the Preparation of the Regenerative Medical Product” and “Precautions Concerning Administration of the Regenerative Medical product,” or others.

15. OTHER PRECAUTIONS

15.1 Information Based on Clinical Use

1) If there is any particularly important information such as a safety concern or lack of efficacy, it shall be accurately summarized and described even if the evaluation has not been established.
2) If the product is approved as Type I Use Regulations under the Cartagena Act, it should be stated that the Regulations must be

observed for the use of the relevant regenerative medical product.

15.2 Information Based on Nonclinical Studies

Particularly important findings of toxicity that are observed in animals shall be briefly described even if it is unclear whether or not they can be extrapolated to humans.

16. PHARMACOKINETICS

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

17. CLINICAL STUDIES

17.1 Clinical Studies for Efficacy and Safety

1) The results of pivotal clinical studies, which were accurately and objectively conducted, of which reliability was ensured, which were intended to investigate efficacy and safety, and which can be used as rationales for approved indications or performance and for approved dosage and administration or methods of use, shall be included. In addition, for autologous cell-processed products, the number of cases in which regenerative medical products meeting their specifications were not able to be provided in clinical trials shall be stated.
2) Study designs (including the amount of use, the duration of use, and the number of subjects/patients) and main efficacy and safety results shall be briefly provided in accordance with the approved dosage and administration or methods of use.
3) The results of secondary endpoints may be briefly included only when they are particularly important.

17.2 Post-marketing Surveillance, etc.

1) List the results of clinical studies that are particularly important in complementing "17.1 Clinical Studies for Efficacy and Safety" (e.g., at the end of reexamination, results of reevaluation, etc.) due to very limited clinical study data at the time of approval. If a product that has received an approval with conditions and time limits is approved, the results should be described. In this case, for autologous cell-processed products, the number of cases in which the product meeting its specifications could not be provided should be stated.
2) In principle, the results should be described in accordance with

the Ministerial Ordinance on “Standards for Conducting Post-Marketing Surveillance and Studies of Regenerative Medical Products” (Ministerial Ordinance No. 90 of the Ministry of Health, Labour and Welfare, 2014).

3) Describe the results of studies in patients with specific backgrounds using medical information databases that are beneficial to clinical practice.

18. PRINCIPLE/MECHANISM

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

19. STORAGE METHOD AND SHELF LIFE, etc.

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

20. PRECAUTIONS FOR HANDLING

1) For products to which precautions for handling are specified in standards or approval letters, describe the precautions.
2) For designated regenerative medical products, under 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.

21. 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.

22. REFERENCES

The main data supporting the description of each section should be described in this section as the main literature (References).

23. REFERENCE REQUEST AND CONTACT INFORMATION

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

24. MARKETING AUTHORIZATION HOLDER, etc.

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