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To: Commissioners of Prefectural/Cities with Established Health Centers/Special District Health Department (Bureau)

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

Director, Pharmaceutical Safety Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
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Considerations for Use of the Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) (Comirnaty intramuscular injection)

The coronavirus modified uridine RNA vaccine (SARS-CoV-2) (marketed under the brand name of Comirnaty intramuscular injection; hereinafter referred to as “Comirnaty”) was today granted special approval for emergency for the indication of “prevention of disease caused by SARS-CoV-2 infection (COVID-19).”
Special approval for emergency is the process to exceptionally approve a drug requiring emergency use to prevent the spread of a disease that may significantly affect people’s lives and health and the spread of other health hazards, pursuant to the provisions of Article 14-3, Paragraph 1 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”). Comirnaty was approved in expectation of its efficacy for the prevention of new coronavirus infections. Because of limited information on its safety, etc. in Japan, however, medical institutions and physicians using Comirnaty are requested to make special considerations especially until post-vaccination data are accumulated.

Please inform the medical institutions under your jurisdiction of this notification so that they will pay attention to the following points as specific precautions for the use of Comirnaty. Also, please inform the wholesalers and distributors under your jurisdiction of this notification so that they will respond appropriately

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1. Positioning of Comirnaty

Comirnaty is a specially approved product pursuant to the provisions of Article 14-3, Paragraph 1 of the Pharmaceutical and Medical Device Act, as described below. Given that Comirnaty was approved with different procedures from those for ordinary approval pursuant to the provisions of Article 14, Paragraph 1 of the Pharmaceutical and Medical Device Act, it is requested that Comirnaty should be handled with special attention and consideration.

Related provisions:

Article 14-3 If a product that an applicant for approval prescribed in Article 14 intends to market is a pharmaceutical falling under both of the following items, as specified by the Cabinet Order, the Minister of Health, Labour and Welfare may, notwithstanding of the provisions of Paragraphs 2, 6, 7, and 9 of the same Article, grant approval for such a product prescribed in the same Article after obtaining opinions from the Pharmaceutical Affairs and Food Sanitation Council:

(i) Pharmaceuticals for any urgent needs in the prevention of the spread of disease or other health hazards that may have serious effects on lives and the health of the general public, and for which no proper method is available other than the use of such pharmaceuticals;

(ii) With respect to use, pharmaceuticals that are authorized to be sold, provided, or stored or displayed for the purpose of sale or provision thereof in a foreign country (limited to countries specified by the Cabinet Order as those having a marketing approval system or other systems recognized as being of an equivalent level to that of Japan in terms of quality, efficacy, and safety to be secured for the pharmaceuticals).

2. Approval Conditions

(1) The Marketing Authorization Holder (hereinafter referred to as MAH) is obliged to fulfil the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 2 of the Pharmaceuticals and Medical Devices Act.

1) Matters related to Item 1

There is limited information on the long-term stability, etc., at the time of the approval. Therefore, after the market launch, the MAH is required to collect and report the information.

2) Matters related to Item 2

When learning about diseases, disorders, or death suspected to be caused by Comirnaty, the MAH is required to report them promptly.

3) Matters related to Item 3

The MAH is required to take necessary actions to ensure that healthcare professionals who use Comirnaty can understand, and appropriately explain to vaccine recipients or their legally acceptable representatives, that Comirnaty has been granted Special Approval for Emergency and the objectives of said approval.

4) Matters related to Item 4

The MAH is required to report the quantity sold or provided, as necessary.

(2) Comirnaty has been approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:

1) The MAH is required to develop and appropriately implement a risk management plan.

2) Since there is limited information on Comirnaty currently, the MAH is required to promptly collect safety data such as information of side effects according to a predetermined plan and submit the data to the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as the “PMDA”) and take necessary actions to ensure the proper use of Comirnaty. Information obtained from the national health survey, etc., should be reflected appropriately.

3) Results of the ongoing or planned Japanese and foreign clinical studies should be submitted to PMDA promptly whenever they become available. The most recently updated information on the efficacy and safety of Comirnaty should be made easily accessible to healthcare professionals and vaccine recipients. The MAH is required to appropriately assist the government in disseminating information on the efficacy and safety of Comirnaty.

4) The efficacy and safety data of Comirnaty will be accumulated as the vaccination program progresses. The MAH is required to give physicians appropriate instructions to ensure that they administer Comirnaty to vaccine recipients who, or whose legally acceptable representatives, have been provided with the latest efficacy and safety information of Comirnaty in written form, and who have provided written informed consent through the vaccine screening questionnaire, etc. before the vaccination.

5) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 6 months after the approval. If new data etc., submitted in accordance with approval conditions (1) -1), (2) -2), or (2) -3), necessitate a change in the approved product information, the change

may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

(3) The product is approved based on Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The approval may be withdrawn in accordance with the provision in Article 75-3 of the Act in a case where (1) the product does not conform to any Item of Article 14-3, Paragraph 1 of the Act or (2) the withdrawal is necessary to prevent the emergence or expansion of public health risks.

3. Indication of Comirnaty

The indication of Comirnaty is “prevention of disease caused by SARS-CoV-2 infection (COVID-19).”

4. Precautions for Drug Preparation and Administration

(1) Thawing method

1) When thawed in a refrigerator (2°C to 8°C), thaw and dilute the vaccine within 5 days.
2) When thawed at room temperature, thaw and dilute the vaccine within 2 hours.
3) During thawing, minimize exposure to room light and avoid exposure to direct sunlight and ultraviolet light.
4) Do not refreeze the thawed vaccine.

(2) Diluting method

1) Allow the vaccine to reach room temperature before dilution.
2) During the operation, exercise caution to prevent bacterial contamination because the vaccine does not contain preservatives.
3) Add 1.8 mL of isotonic sodium chloride solution (Japanese Pharmacopoeia) to the vaccine vial and mix by gentle inversion until a white homogeneous solution is obtained. Do not shake the mixture.
4) White particulates may be contained in the solution before dilution but will dissolve by dilution. Do not use if the vaccine contains particulates after dilution.
5) The diluted solution contains 6 doses of the vaccine (0.3 mL/dose). If a low dead-volume injection needle or syringe is used, 6 doses can be extracted. If a standard injection needle and syringe are used, a 6th dose may not be extracted. If a full dose of 0.3 mL cannot be extracted from the remaining solution, discard the content.
6) Store the diluted solution at 2°C to 30°C and use within 6 hours after dilution. Discard any unused solution if it was not used within 6 hours after dilution.
7) During storage after dilution, minimize exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.

(3) Precautions for administration of the vaccine

1) Extract a dose of 0.3 mL from the diluted vial at room temperature and visually confirm that the solution has no particulates or discoloration. Do not use if any abnormalities are observed.

2) Usually administer the vaccine intramuscularly into the deltoid muscle. Do not administer the vaccine intravenously, intradermally, or subcutaneously.

5. Proper Use of Comirnaty

(1) Comirnaty should be used with reference to the “Vaccination Practice Regulations.”

(2) Vaccination is not appropriate for individuals with a history of severe hypersensitivity to any component of Comirnaty.

Components of Comirnaty:
- Tozinameran (active ingredient)
- [(4-hydroxybutyl) azandiyl]bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
- 2-[(polyethylene glycol)-2000]-N, N-ditetradecylacetamide
- 1, 2-distearoyl-sn-glycero-3-phosphocholine
- Cholesterol
- Sucrose
- Sodium chloride
- Potassium chloride
- Sodium hydrogenphosphate dihydrate
- Potassium dihydrogen phosphate

(3) Shock or anaphylaxis may occur. It is therefore desirable to adequately ask vaccine recipients about their history of hypersensitivity and to observe their condition for a certain period of time after the vaccination.

(4) Syncope may occur as a vasovagal reflex, including a psychogenic reaction to injection, immediately after or after the vaccination. To avoid a fall due to syncope, it is desirable to have the recipient sit in a chair, etc. and observe the recipient’s condition for a certain period of time after the vaccination.

(5) Comirnaty should be administered to women who are or may be pregnant only if the expected benefits of the vaccination outweigh its possible risks.

(6) Continuation or discontinuation of breastfeeding should be considered in view of the benefits of the vaccination and those of breastfeeding. It is not known whether Comirnaty is excreted in human milk or not.

(7) The efficacy and safety of Comirnaty in individuals younger than 16 years of age have not been established.

(8) Unlike influenza vaccines, etc. for subcutaneous injection currently distributed in Japan, Comirnaty is intended to be injected intramuscularly.

Therefore, these differences should be carefully recognized before vaccination.

(9) In addition, careful attention should be paid to other precautions for vaccination, etc. included in the package insert.

6. Request for Cooperation in Post-marketing Surveillance, etc. of Comirnaty

As a condition for approval for Comirnaty, it is required to promptly collect post-marketing data on the safety of Comirnaty according to a predetermined plan. Given that the current knowledge of Comirnaty is limited, it is necessary to collect its safety data preferentially. Therefore, medical institutions using Comirnaty are requested to cooperate in providing data promptly.

7. Prompt Reporting of Suspected Adverse Reaction to Comirnaty

Pursuant to the provisions of Article 12, Paragraph 1 of the Immunization Act (Act No. 68 of 1948), if it is found that a person receiving a temporary vaccination experiences symptoms stipulated by the Minister of Health, Labour and Welfare, the establisher of a hospital or a clinic, or a physician (hereinafter referred to as “physicians, etc.”) is required to report it to the Minister of Health, Labour and Welfare. Therefore, when having made a diagnosis of any symptom meeting the reporting criteria in Attached Form 1 of “Handling of Reports, etc. of Suspected Adverse Reactions to Routine Vaccination, etc.” (HSB Notification No. 0330-3 and PFSB Notification No. 0330-1; Notifications issued jointly by the Directors of the Health Service Bureau and the Pharmaceutical and Food Safety Bureau, MHLW, dated March 30, 2013) after administration of Comirnaty, physicians, etc. are required to promptly report it to the PMDA using Attached Form 1 or Form 2 (in case of using the Application for Entering Post-vaccination Suspected Adverse Reaction Report) of the notifications. The PMDA website should be referred to for the instructions for reporting.

In addition, it should be noted that a dedicated fax number (0120-011-126), which is different from the fax number for other vaccines, is used for reporting of suspected adverse reactions to the novel coronavirus infection (Covid-19) vaccine.

The MAH or the PMDA may conduct a detailed investigation on reported information. Therefore, reporting medical institutions are requested to cooperate in such a detailed investigation by the MAH, etc.