Pharmaceuticals and Medical Devices Safety Information

No. 386 October 2021

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Available information is listed here

Access to the latest safety information is available via the PMDA Medi-navi.

The PMDA Medi-navi is an e-mail mailing list service that serves to provide essential safety information released by MHLW and PMDA. Subscribing to the Medi-navi will allow you to receive this information on the day of its release.

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Pharmaceutical Safety and Environmental Health Bureau, Labour and Welfare,
Ministry of Health, Labour and Welfare
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-8916 Japan

Translated by
Pharmaceuticals and Medical Devices Agency

Pharmaceuticals and Medical Devices Agency
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo
100-0013 Japan E-mail: safety.info@pmda.go.jp

This English version of PMDSI is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Pharmaceuticals and Medical Devices Safety Information

No. 386 October 2021

Ministry of Health, Labour and Welfare
Pharmaceutical Safety and Environmental Health Bureau, Japan

[Outline of Information]

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E: Distribution of Dear Healthcare Professional Letters of Emergency Communications, *R:* Distribution of Dear Healthcare Professional Letters of Rapid Communications, *P*: Revision of Precautions, *C*: Case Reports

Reporting of safety information such as adverse reactions to the Minister of Health, Labour and Welfare is a duty of medical and pharmaceutical providers.

If medical and pharmaceutical providers such as physicians, dentists, and pharmacists detect adverse reactions, infections associated with drugs or medical devices, or medical device adverse events, it is mandatory for such providers to report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As medical and pharmaceutical providers, drugstore and pharmacy personnel are also required to report safety issues related to drugs and medical devices.

Abbreviations

ADR	Adverse drug reaction
EPPV	Early Post-marketing Phase Vigilance
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency

1

Precautions for Shock, Anaphylaxis in Patients Who Received Joyclu 30 mg intra-articular injection to Improve Joint Function

1. Introduction

Joyclu 30 mg intra-articular injection (non-proprietary name: diclofenac etalhyaluronate sodium, hereinafter referred to as “this drug”) is used to improve joint function. Since its marketing approval on March 23, 2021, a total of 10 cases of serious shock, anaphylaxis have been reported in patients treated with this drug as of May 28 (estimated number of patients who have received this drug: approximately 5 500). One of the cases was reported to have led to death, although the causal relationship with the drug is unknown.

In response, the MHLW on June 1, 2021 instructed the marketing authorization holder (MAH) of this drug to newly add a WARNING section and to revise the IMPORTANT PRECAUTIONS and the Clinically Significant Adverse Reactions sections in the package insert while issuing a Dear Healthcare Professionals Letter of Rapid Safety Communication (BLUE LETTER) to alert healthcare professionals and other concerned parties to this safety concern without delay. This section introduces the details of the revision.

2. Background

This drug is an intra-articular injection that contains diclofenac etalhyaluronate sodium as the active ingredient in which diclofenac is covalently bonded to hyaluronate sodium. This drug was approved on March 23, 2021 with osteoarthritis (in the knee and hip joints) as its indication and was launched on May 19, 2021. Osteoarthritis is a joint disease that occurs when joints deteriorate. Symptoms include pain, swelling, deformity, and limited range of motion in joints in the extremities such as the knee and hip as well as in the finger joints. When joints in the lower extremities are affected, gait disturbance accompanies these symptoms and thereby affects the daily life activities and QOL of patients. This drug reduces pain and inflammation in the knee and hip joints and improves joint movement by stimulating the production of high molecular weight hyaluronic acid in synovial cells as well as by suppressing the synthesis of enzymes that break down proteins in the cartilage, and prostaglandins that cause inflammation.

As adverse reactions to this drug, anaphylactic reactions and anaphylactic shock were observed in the clinical studies submitted at the time of application for marketing approval and a causal relationship with this drug to the events was considered reasonably possible. It was decided that it was necessary to place a precaution for the risk of such events following administration of this drug in the package insert and to continue close monitoring of their occurrence.

To reflect the decision, a precaution for shock, anaphylaxis as clinically significant adverse reactions was included and patients with a history of hypersensitivity to any components of this drug were contraindicated in the package insert at the time of marketing approval of this drug.

However, the situations listed below and others prompted us to conclude that an alert for, and proper responses to, anaphylaxis associated with this drug should be further ensured through a BLUE LETTER.

- Adverse reactions involving serious shock, anaphylaxis including death have been reported.
- Although a precaution regarding shock, anaphylaxis had been in place since its marketing approval in March 2021 under the Clinically Significant Adverse Reactions section in the package insert of this drug, cases of an onset after the patient returned home following administration of this drug were identified in addition to cases in which the adverse reactions occurred immediately following administration. Besides healthcare professionals, a precaution was also considered necessary for patients or their caregivers.

3. Summary of precautions

Considering that cases of serious shock or anaphylaxis have been reported, an enhanced precaution for healthcare professionals was decided based on the following three points.

1. Arrangements for proper responses to an emergency should be ensured prior to administration of this drug.
2. Conditions of patients should be carefully monitored under the supervision of a physician for at least 30 minutes after administration of this drug. It should be noted that cases have been reported where the symptoms occurred not only immediately after administration but also after patients returned home from medical institutions.
3. Patients and their caregivers should be fully informed of the risk of shock, anaphylaxis, as well as the signs and symptoms, and should be instructed to seek medical attention immediately if any abnormalities are noted.

In addition, the leaflet for patients and their caregivers alerts them to the following.

- Anaphylaxis may occur in the first few hours following administration of this drug.
- Conditions of patients should be carefully monitored for any changes immediately following administration until and after they reach home.
- If any abnormalities are noted, medical attention should be sought immediately. Medical institutions should be informed at their visit that patients have been administered Joyclu intra-articular injection.
- Pale look, loss of consciousness, and difficulty in breathing are a medical emergency. Immediate responses are required such as calling an ambulance.

[References]

- Precautions for Shock, Anaphylaxis in Patients Who Received Joyclu 30 mg intra-articular injection to Improve Joint Function
  https://www.mhlw.go.jp/stf/houdou/0000073061_00004.html (only in Japanese)
  English translation of Appendix 2 and Appendix 3 (in part) by PMDA
  Appendix 2
  https://www.pmda.go.jp/english/safety/info-services/drugs/esc-rsc/0001.html (June 1, 2021)
  Appendix 3
  https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0009.html (June 2, 2021)

2
Revision of Precautions (No.326)

This section presents details of revisions to the Precautions of package inserts and brand names of drugs that have been revised in accordance with the Notifications dated July 27, September 7, 2021.

1 Vaccines
COVID-19 (SARS-CoV-2) vaccine (recombinant chimpanzee adenovirus vector)

Branded name **[Under New instructions]**	Vaxzevria Intramuscular Injection (AstraZeneca K.K.)
2. PERSONS UNSUITABLE FOR VACCINATION (newly added)	Persons with a history of capillary leak syndrome
8. IMPORTANT PRECAUTIONS	Cases of serious thrombosis with thrombocytopenia (sometimes accompanied by bleeding) have been reported following inoculation with this vaccine including very rare forms of venous thrombosis and arterial thrombosis such as cerebral venous sinus thrombosis and splanchnic vein thrombosis. In many of the reported cases, serious thrombosis developed within 28 days following inoculation with this vaccine, and a fatal outcome resulted in some cases. When vaccinating individuals with risk factors for thromboembolism or thrombocytopenia, benefits and potential risks of immunization should be considered. In addition, from 4th to 28th day post-inoculation with this vaccine particularly, vaccinees should be instructed to be alert for, and seek medical attention immediately if they experience, symptoms such as severe or persistent headache, blurred vision, confusion, seizure, shortness of breath, chest pain, swelling of legs, pain of lower extremities, persistent abdominal pain, as well as non-vaccination site skin haemorrhage or petechiae. Vaccinees in whom thrombocytopenia was observed following inoculation with this vaccine should be thoroughly scrutinized for signs of thrombosis. In addition, platelet counts should be evaluated in vaccinees who developed thrombosis following inoculation with this vaccine. For diagnosis and treatment of thrombosis with thrombocytopenia, appropriate guidelines should be referred to.
(newly added)	Although a causal relationship has not been established, very rare cases of capillary leak syndrome have been reported following inoculation with this vaccine. Vaccinees should be instructed in advance to seek medical attention immediately if they experience any symptoms that could suggest capillary leak syndrome (such as oedema extremities, hypotension). Although a causal relationship has not been established, very rare cases of Guillain-Barré syndrome have been reported following inoculation with this vaccine. Vaccinees should be instructed in advance to seek medical attention immediately if they experience any symptoms that could suggest Guillain-Barré syndrome (such as flaccid paralysis starting from distal limb, decreased or absent tendon reflex).
11. ADVERSE REACTIONS **11.2 Other Adverse Reactions**	Haematologic: Lymphadenopathy, thrombocytopenia

15. OTHER PRECAUTIONS
15.1 Information Based on Clinical Use (newly added)

Although a causal relationship has not been established, very rare cases of capillary leak syndrome have been reported overseas following inoculation with this vaccine with oedema extremities, hypotension, haemoconcentration, or hypoalbuminaemia as typical symptoms. In addition, these reports included cases of vaccinees with a history of capillary leak syndrome and of fatal outcomes.

2 Antiparkinsonism agents
Istradefylline

Branded name [Under Old instructions]

Nouriast Tablets 20 mg (Kyowa Kirin Co., Ltd.)

Precautions concerning Dosage and Administration

The blood concentration of this drug may increase in the following patients. The dosage should not exceed 20 mg once daily.
· Patients with moderate liver disorder
· Patients receiving drugs that strongly inhibit CYP3A

Drug Interactions

This drug is mainly metabolized by CYP1A1 and CYP3A (CYP3A4 and CYP3A5). In addition, this drug inhibits CYP3A and P-glycoprotein.

Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs that strongly inhibit CYP3A (itraconazole, clarithromycin, etc.)	When co-administered at 40 mg with ketoconazole, the $AUC_{0-\infty}$ of this drug increased 2.47 fold and $t_{1/2}$ extended 1.87 fold. Effects of this drug may be enhanced. When co-administered with drugs that strongly inhibit CYP3A, the dosage of this drug should not exceed 20 mg once daily.	Co-administration with CYP3A inhibitors may inhibit metabolism and increase the blood concentration of this drug.
Drugs that inhibit CYP3A (erythromycin, fluconazole, etc.)	Effects of this drug may be enhanced.	
Drugs that induce CYP3A (rifampicin, carbamazepine, etc.) Food containing St. John's Wort	Effects of this drug may be attenuated.	Co-administration with CYP3A inducers may promote metabolism and decrease the blood concentration of this drug.
Drugs that act as CYP3A substrates (midazolam, atorvastatin, lomitapide mesilate, etc.)	Effects of the drugs listed on the left may be enhanced.	Co-administration with this drug may inhibit metabolism and increase the blood concentration of the drugs that act as CYP3A substrates.

[Under New instructions]

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

7.2 The blood concentration of this drug may increase in the following patients. The dosage should not exceed 20 mg once daily.

· Patients with moderate liver disorder
· Patients receiving drugs that strongly inhibit CYP3A

10. INTERACTIONS

10.2 Precautions for Co-Administration

This drug is mainly metabolized by CYP1A1 and CYP3A (CYP3A4 and CYP3A5). In addition, this drug inhibits CYP3A and P-glycoprotein.

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs that strongly inhibit CYP3A (itraconazole, clarithromycin, etc.)	Effects of this drug may be enhanced.	Co-administration with CYP3A inhibitors may inhibit metabolism and increase the blood concentration of this drug. The $AUC_{0-\infty}$ of this drug increased and $t_{1/2}$ extended when co-administered with ketoconazole.
Drugs that inhibit CYP3A (erythromycin, fluconazole, etc.)	Effects of this drug may be enhanced.	Co-administration with CYP3A inhibitors may inhibit metabolism and increase the blood concentration of this drug.
Drugs that induce CYP3A (rifampicin, carbamazepine, etc.) Food containing St. John's Wort	Effects of this drug may be attenuated.	Co-administration with CYP3A inducers may promote metabolism and decrease the blood concentration of this drug.
Drugs that act as CYP3A substrates (midazolam, atorvastatin, lomitapide mesilate, etc.)	Effects of the drugs listed on the left may be enhanced.	Co-administration with this drug may inhibit metabolism and increase the blood concentration of the drugs that act as CYP3A substrates.

3 Agents for hyperlipidemias

Lomitapide mesilate

Branded name
[Under Old instructions]
Juxtapid Capsules 5, 10, 20 mg (Recordati Rare Diseases Japan KK)

Drug Interactions
Contraindications for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Moderate CYP3A inhibitors (aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil, miconazole (gel/ injections), tofisopam)	The blood concentration of this drug may increase markedly.	These drugs inhibit CYP3A and thereby inhibit metabolism of lomitapide mesilate.

Precautions for Co-Administration

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Weak CYP3A inhibitors (atorvastatin, cimetidine, cilostazol, oral contraceptives, istradefylline, etc.)	The blood concentration of this drug may increase. Co-administered with weak CYP3A inhibitors requires caution. The dosage of this drug should be reduced and patients should be closely monitored.	These drugs inhibit CYP3A and thereby inhibit metabolism of lomitapide mesilate.

3

List of Products Subject to Early Post-marketing Phase Vigilance

Early Post-marketing Phase Vigilance (EPPV) was established in 2001. This unique system for newly-approved drug products refers to any safety assurance activities that are conducted within a period of 6 months just after marketing of a new drug. The MAH responsible for a new drug in the EPPV period is required to collect adverse drug reactions (ADRs) data from all medical institutions where the drug is used and to take safety measures as appropriate. The aim of EPPV is to promote the rational and appropriate use of drugs in medical treatments and to facilitate prompt action for the prevention of serious ADRs. EPPV is specified as a condition of product approval.

(As of 31 August 2021)
◎: Products for which EPPV was initiated after August 1, 2021

	Nonproprietary name Branded name	Name of the MAH	Date of EPPV initiate
◎	Fremanezumab (genetical recombination) Ajovy Syringes for S.C. Injection 225 mg	Otsuka Pharmaceutical Co., Ltd.	August 30, 2021
◎	Givosiran sodium Givlaari Subcutaneous Injection 189 mg	Alnylam Japan K.K.	August 30, 2021
◎	Upadacitinib hydrate[*1] Rinvoq Tablets 7.5 mg, 15 mg	AbbVie GK	August 25, 2021
◎	Dapagliflozin propylene glycolate hydrate[*2] Forxiga 5 mg, 10 mg tablets	AstraZeneca K.K.	August 25, 2021
◎	Selexipag[*3] Uptravi Tablets 0.2 mg, 0.4 mg	Nippon Shinyaku Co., Ltd.	August 25, 2021
◎	Fentanyl citrate[*4] Fentos Tapes 0.5 mg, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg	Hisamitsu Pharmaceutical Co., Inc.	August 25, 2021
◎	Upacicalcet sodium hydrate Upasita IV Injection Syringe for Dialysis 25 μg, 50 μg, 100 μg, 150 μg, 200 μg, 250 μg, 300 μg	Sanwa Kagaku Kenkyusho Co., Ltd.	August 20, 2021
◎	Teduglutide (genetical recombination) Revestive 3.8 mg for S.C. Injection	Takeda Pharmaceutical Company Limited.	August 18, 2021
◎	COVID-19 (SARS-CoV-2) Vaccine (recombinant chimpanzee adenovirus vector) Vaxzevria Intramuscular Injection	AstraZeneca K.K.	August 16, 2021
◎	Erenumab (genetical recombination) Aimovig Subcutaneous injection Pens 70 mg	Amgen K.K.	August 12, 2021
◎	Risdiplam Evrysdi Dry Syrup 60 mg	Chugai Pharmaceutical Co., Ltd.	August 12, 2021
◎	Tazemetostat hydrobromide Tazverik tablets 200 mg	Eisai Co., Ltd.	August 16, 2021
◎	Larotrectinib sulfate Vitrakvi oral solution 20 mg/mL	Bayer Yakuhin Ltd.	August 6, 2021

	Nonproprietary name Branded name	Name of the MAH	Date of EPPV initiate
◎	Simoctocog alfa (genetical recombination) Nuwiq For I.V. Injection 250, 500, 1000, 2000, 2500, 3000, 4000	Fujimoto Pharmaceutical Corporation	August 2, 2021
	Lyophilized human alpha1-proteinase inhibitor concentrate Lynspad for Intravenous Infusion 1000 mg	Grifols Therapeutics LLC.	July 27, 2021
	Casirivimab (genetical recombination), Imdevimab（genetical recombination） Ronapreve for Intravenous Infusion Set 300, 1332	Chugai Pharmaceutical Co., Ltd.	July 22, 2021
	Rivaroxaban[*5] Xarelto dry syrup for pediatric 51.7 mg, 103.4 mg	Bayer Yakuhin Ltd.	July 12. 2021
	Amikacin sulfate Arikayce (amikacin liposome inhalation suspension) 590 mg/8.4 mL	Insmed Incorporated.	July 7, 2021
	Larotrectinib sulfate Vitrakvi capsules 25 mg, 100 mg	Bayer Yakuhin Ltd.	July 7, 2021
	Osilodrostat phosphate Isturisa tablets 1 mg, 5 mg	Recordati Rare Diseases Japan KK	June 30, 2021
	Incobotulinumtoxin A[*6] Xeomin 50 units/100 units/200 units for Intramuscular injection	Teijin Pharma Limited.	June 23, 2021
	Pemigatinib Pemazyre Tablets 4.5 mg	Incyte Biosciences Japan G.K.	June 1, 2021
	Inebilizumab (genetical recombination) Uplizna for Intravenous Infusion 100 mg	Mitsubishi Tanabe Pharma Corporation	June 1, 2021
	Upadacitinib hydrate[*7] Rinvoq Tablets 7.5 mg, 15 mg	AbbVie GK	May 27, 2021
	Palonosetron hydrochloride Aloxi I.V. injection 0.75 mg, Aloxi I.V. infusion bag 0.75 mg	Taiho Phamaceutical Co., Ltd.	May 27, 2021
	Coronavirus modified uridine RNA vaccine (SARS-CoV-2) COVID-19 Vaccine Moderna Intramuscular Injection	Takeda Pharmaceutical Company Limited.	May 24, 2021
	Ofatumumab (genetical recombination) [*8] Kesimpta for s.c. injection 20 mg pen	Novartis Pharma K.K.	May 24, 2021
	Polatuzumab vedotin (genetical recombination) Polivy for Intravenous Infusion 140 mg, 30 mg	Chugai Pharmaceutical Co., Ltd.	May 19, 2021
	Pabinafusp alfa (genetical recombination) Izcargo for I.V. infusion 10 mg	JCR Pharmaceuticals Co., Ltd.	May 19, 2021
	Denileukin diftitox (genetical recombination) Remitoro for Intravenous Drip Infusion 300	Eisai Co., Ltd.	May 19, 2021

Nonproprietary name Branded name	Name of the MAH	Date of EPPV initiate
μg		
Diclofenac etalhyaluronate sodium Joyclu 30 mg intra-articular injection	Seikagaku Corporation	May 19, 2021
Anhydrous sodium sulfate/potassium sulfate/magnesium sulfate hydrate Sulprep Combination Solution	Nihon Pharmaceutical Co., Ltd.	May 19, 2021
Galcanezumab (genetical recombination) Emgality Subcutaneous Injection 120 mg Autoinjectors, Emgality Subcutaneous Injection 120 mg Syringe	Eli Lilly Japan K.K.	April 26, 2021
Idursulfase beta (genetical recombination) Hunterase ICV Injection 15 mg	Clinigen K.K.	April 26, 2021
Baricitinib*9 Olumiant tablets 2 mg, 4 mg	Eli Lilly Japan K.K.	April 23, 2021
Brigatinib Alunbrig Tablets 30 mg, 90 mg	Takeda Pharmaceutical Company Limited.	April 23, 2021
Berotralstat hydrochloride Orladeyo Capsules 150 mg	OrphanPacific, Inc.	April 23, 2021
Molidustat sodium Musredo tablets 5 mg, 12.5 mg, 25 mg, 75 mg	Bayer Yakuhin Ltd.	April 22, 2021
Dimethyl sulfoxide Zymso Intravesical Solution 50%	Kyorin Pharmaceutical Co., Ltd.	April 21, 2021
Anamorelin hydrochloride Adlumiz Tablets 50 mg	Ono Pharmaceutical Co., Ltd.	April 21, 2021
Acalabrutinib Calquence capsules 100 mg	AstraZeneca K.K.	April 21, 2021
Delgocitinib [1] Corectim Ointment 0.25% [2] Corectim Ointment 0.5%	Japan Tobacco Inc.	March 23, 2021
Ferric citrate hydrate*10 Riona Tab. 250 mg	Japan Tobacco Inc.	March 23, 2021
Lascufloxacin hydrochloride Lasvic Intravenous Drip Infusion Kit 150 mg	Kyorin Pharmaceutical Co., Ltd.	March 1, 2021

*1 Atopic dermatitis that has not responded adequately to conventional treatments

*2 Chronic kidney disease

*3 Chronic thromboembolic pulmonary hypertension inoperable or persistent/recurrent after interventional treatment

*4 Pain relief in cancers accompanied by moderate to severe pain difficult to treat with non-opioid analgesics (limited to use as a switch from other opioid analgesics)

*5 Treatment and reduction in the risk of recurrence of venous thromboembolism

*6 Leg spasm

*7 Psoriatic arthritis in patients who have responded inadequately to conventional therapy

*8 Prevention of relapse and delaying the accumulation of physical disability in patients with relapsing-remitting multiple sclerosis and patients with active secondary progressive multiple sclerosis

*9 SARS-CoV2 pneumonia (limited to patients requiring supplemental oxygen)

*10 Iron deficiency anaemia