Pharmaceuticals and Medical Devices Safety Information

No. 410 June 2024

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This *Pharmaceuticals and Medical Devices Safety Information (PMDSI)* publication is issued reflective of safety information collected by the Ministry of Health, Labour and Welfare (MHLW). It is intended to facilitate safer use of pharmaceuticals and medical devices by healthcare providers. The PMDSI is available on the Pharmaceuticals and Medical Devices Agency (PMDA) web page (https://www.pmda.go.jp/english/safety/info-services/drugs/medical-safety-information/0002.html) and on the MHLW website (https://www.mhlw.go.jp/, only in Japanese).

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 the 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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No. 410 June 2024

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

[Outline of Information]

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 healthcare professionals.

If healthcare professionals such as physicians, dentists, and pharmacists detect adverse reactions, infections, or malfunctions associated with drugs, medical devices, or regenerative medical products, please report them to the Minister of Health, Labour and Welfare directly or through the marketing authorization holder. As healthcare professionals, drugstore and pharmacy personnel are also required to report adverse reactions, etc.

Please utilize the Report Reception Site for reporting.
(This service is available only in Japanese.)

https://www.pmda.go.jp/safety/reports/hcp/0002.html

Abbreviations

ADR	Adverse Drug Reaction
DIES	Drug-induced Enterocolitis Syndrome
EPPV	Early Post-marketing Phase Vigilance
FPIES	Food Protein-induced Enterocolitis Syndrome
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PSB	Pharmaceutical Safety Bureau
PSD	Pharmaceutical Safety Division

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Drug-induced Enterocolitis Syndrome

1. Introduction

The MHLW issued a notification on May 8, 2024 instructing the addition of a cautionary statement regarding “drug-induced enterocolitis syndrome (DIES)” to the PRECAUTIONS of the package insert for preparations containing amoxicillin hydrate (hereinafter referred to as “these preparations”). This revision is based on several reported cases of DIES in which a causal relationship with these preparations was reasonably possible.

2. Drug-induced enterocolitis syndrome

Descriptions regarding DIES in the literature are summarized as shown below.

(1) Disease concept

DIES is, according to the literature, a non-IgE-mediated hypersensitivity reaction involving the gastrointestinal system that occurs several hours after drug administration.[i, ii] IgE-mediated immediate-type hypersensitivity reaction is known for gastrointestinal symptoms including vomiting occurring after drug administration. It is characteristic to DIES that gastrointestinal symptoms occur several hours (1 to 4 hours in many cases) after drug administration in the absence of allergic skin and respiratory symptoms.[i] It is considered that DIES presents with symptoms that typically resemble those of food protein-induced enterocolitis syndrome (FPIES), which is a kind of food allergies.

(2) Epidemiology

Only a limited number of cases of DIES have been reported in the literature. It is assumed that gastrointestinal symptoms after drug administration have been diagnosed as anaphylaxis or antibiotic-induced enterocolitis, and it is discussed in the literature that the actual number of patients may be higher than that of the reported cases. In addition, it is mainly reported in children.[i]

(3) Causes

The pathophysiology of DIES is unknown. It is considered that a drug reactive metabolite or drug-protein complex may affect the gastrointestinal epithelium directly or indirectly through immunological reactions.[i, iii] In addition, drugs other than these preparations have been reported to be the presumed causative drugs of DIES.[iv]

(4) Diagnosis

There are no established diagnostic criteria for DIES. As of May 2024, no descriptions regarding DIES are identified in Japanese and overseas guidelines. However, clinical symptoms including repetitive vomiting, severe abdominal pain, and diarrhoea occurring several hours after drug administration have been reported to be related to the diagnosis. Cases with dehydration, extreme lethargy, facial pallor, hypotension, and hypothermia have also been reported. Of note, DIES does not necessarily occur at the time of the first dose. Increased neutrophil count has been known as a laboratory finding, and increased platelet count and increased methaemoglobin values have also been reported. In addition, a finding of intestinal oedema revealed by a CT scan during the acute phase has been reported. For a definitive diagnosis, a drug provocation test (drug challenge) is useful. However, extreme caution should be exercised when performing the test.[i, ii]

(5) Treatment

Treatment of DIES is based on the relief of gastrointestinal symptoms (vomiting, abdominal

pain, etc.) and intravenous fluid for dehydration.[i]

3. Request for cooperation

DIES is considered to be an event that occurs potentially with any drugs causing an allergic reaction. Healthcare professionals encountering a suspected case of this event caused by a drug are requested to cooperate in reporting to the PMDA pursuant to the Drugs and Medical Devices Safety Information Reporting System or in providing the information to the marketing authorization holder (MAH) of the drug.

[References]
•Revisions of PRECAUTIONS (PSB/PSD Notification No.0508-1 dated May 8, 2024)
https://www.mhlw.go.jp/content/001252456.pdf (in Japanese)
English translation by the PMDA (May 8, 2024)
https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0012.html

•Drugs and Medical Devices Safety Information Reporting System
https://www.pmda.go.jp/safety/reports/hcp/0002.html (only in Japanese)

<Literature>

i Mori F, et al. :Drug-induced enterocolitis syndrome: Similarities and differences compared with food protein-induced enterocolitis syndrome. Pediatr Allergy Immunol. 32: 1165–72(2021).
ii Van Thuijl AOJ, et al. Drug-induced enterocolitis syndrome (DIES): A clinical entity that deserves more awareness. Ann Allergy Asthma Immunol. 122: 538-9(2019).
iii Elio Novembre, et al. The history of the drug-induced enterocolitis syndrome. Pediatr Allergy Immunol. 33: 54–7(2022).
iv Barroso B, et al. Reply to "Management of Patients with Suspected or Confirmed Antibiotic Allergy". J Investig Allergol Clin Immunol. 33(6): 500-501(2023).

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Revisions of PRECAUTIONS (No. 350)

This section presents details of revisions to the PRECAUTIONS and brand names of drugs that have been revised in accordance with the Notifications dated May 8, 2024.

1 Anticoagulants
Rivaroxaban

Brand name

Xarelto tablets 2.5 mg, 10 mg, 15 mg, Xarelto OD tablets 10 mg, 15 mg, Xarelto fine granules 10 mg, 15 mg, Xarelto dry syrup for pediatric 51.7 mg, 103.4 mg (Bayer Yakuhin, Ltd.)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)

Patients receiving oral dosage form or injections of azoles (itraconazole, voriconazole, miconazole, posaconazole, ketoconazole)

10. INTERACTIONS
10.1 Contraindications for Co-administration (Do not co-administer with the following.)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
The following azoles (oral dosage form or injections) Itraconazole Voriconazole Miconazole Posaconazole Ketoconazole (not marketed in Japan)	The blood concentration of this drug may increase, resulting in the enhancement of the anticoagulant effect and concerns about an increased risk of haemorrhage.	The clearance of this drug is decreased by the potent inhibition of CYP3A4 and inhibition of P-glycoprotein.

2 Antibiotic preparations acting mainly on gram-negative bacteria
Colistin sodium methanesulfonate (injections)

Brand name

Aldreb for Injection 150 mg (GlaxoSmithKline K.K.)

8. IMPORTANT PRECAUTIONS (newly added)

Hypokalaemia, hypomagnesaemia, and hypocalcaemia may occur. Periodic tests should be performed.

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)

Hypokalaemia, hypomagnesaemia, hypocalcaemia, metabolic alkalosis

3 Antibiotic preparations acting mainly on gram-positive and gram-negative bacteria

[1] Amoxicillin hydrate
[2] Potassium clavulanate/amoxicillin hydrate

Brand name
[1] Sawacillin Capsules 125, 250, Sawacillin Fine Granules 10%, Sawacillin Tablets 250 (LTL Pharma Co., Ltd), and the others
[2] Augmentin Combination Tablets 125SS, 250RS, Clavamox Combination Dry Syrup for Pediatric (GlaxoSmithKline K.K.)

8. IMPORTANT PRECAUTIONS
No methods are currently available for predicting onset of shock, anaphylaxis, acute coronary syndrome accompanying allergic reaction, or drug-induced enterocolitis syndrome with reasonable certainty. A thorough medical interview on information including the patient's medical history of these events, etc. should be conducted in advance. In addition, it should be ensured that a history of allergy to antibiotics was checked.

11. ADVERSE REACTIONS
11.1 Clinically Significant Adverse Reactions (newly added)
Drug-induced enterocolitis syndrome
Allergic gastroenteritis (drug-induced enterocolitis syndrome) similar to food protein-induced enterocolitis accompanied by diarrhoea, lethargy, facial pallor, hypotension, abdominal pain, increased neutrophils, etc., with recurrent vomiting within several hours after administration as a main symptom, may occur. Cases have been reported mainly in children.

4 Antibiotic preparations acting mainly on mold

Posaconazole

Brand name
Noxafil Tablets 100 mg, Noxafil for Intravenous Infusion 300 mg (MSD K.K.)

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
Patients receiving the following drugs: Ergotamine tartrate/anhydrous caffeine/isopropylantipyrine, dihydroergotamine, methylergometrine, ergometrine, simvastatin, atorvastatin, pimozide, quinidine, venetoclax [during its dose escalation phase for relapsed or refractory chronic lymphocytic leukemia (including small lymphocytic lymphoma)], suvorexant, lurasidone hydrochloride, blonanserin, triazolam, rivaroxaban

10. INTERACTIONS
10.1 Contraindications for Co-administration (Do not co-administer with the following.) (newly added)

Drugs	Signs, symptoms, and treatment	Mechanism/risk factors
Rivaroxaban	The anticoagulant effect of rivaroxaban may be enhanced, and a risk of haemorrhage may be increased.	The plasma concentration of rivaroxaban is expected to rise due to the inhibition of CYP3A4, as well as the possible inhibition of P-gp, by co-administration with posaconazole.

5 Other antibiotic preparations

[1] Vonoprazan fumarate/amoxicillin hydrate/clarithromycin
[2] Vonoprazan fumarate/amoxicillin hydrate/metronidazole
[3] Rabeprazole sodium/amoxicillin hydrate/clarithromycin
[4] Rabeprazole sodium/amoxicillin hydrate/metronidazole

Brand name	[1] Vonosap Pack 400, 800 (Takeda Pharmaceutical Company Limited) [2] Vonopion Pack (Takeda Pharmaceutical Company Limited) [3] Rabecure Pack 400, 800 (Eisai Co., Ltd.) [4] Rabefine Pack (Eisai Co., Ltd.)
8. IMPORTANT PRECAUTIONS	<Amoxicillin hydrate> No methods are currently available for predicting onset of shock, anaphylaxis, acute coronary syndrome accompanying allergic reaction, or drug-induced enterocolitis syndrome with reasonable certainty. A thorough medical interview on information including the patient's medical history of these events, etc. should be conducted in advance. In addition, it should be ensured that a history of allergy to antibiotics was checked.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	<Amoxicillin hydrate> Drug-induced enterocolitis syndrome Allergic gastroenteritis (drug-induced enterocolitis syndrome) similar to food protein-induced enterocolitis accompanied by diarrhoea, lethargy, facial pallor, hypotension, abdominal pain, increased neutrophils, etc., with recurrent vomiting within several hours after administration as a main symptom, may occur. Cases have been reported mainly in children.

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 April 30, 2024)
◎: Products for which EPPV was initiated after April 1, 2024

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Talazoparib tosilate / (1) Talzenna capsules 0.1 mg, (2)Talzenna capsules 0.25 mg, (3) Talzenna capsules 1 mg	Pfizer Japan Inc.	April 23, 2024
◎	Evinacumab (genetical recombination) / Evkeeza for Intravenous Infusion 345 mg	Ultragenyx Japan K.K.	April 17, 2024
◎	Danicopan / Voydeya tablets 50 mg	Alexion Pharma Godo Kaisha	April 17, 2024
◎	Aflibercept (genetical recombination) / Eylea 8mg solution for IVT inj. 114.3 mg/mL	Bayer Yakuhin, Ltd.	April 17, 2024
◎	Efgartigimod alfa (genetical recombination)/ vorhyaluronidase alfa (genetical recombination) / Vyvdura Combination Subcutaneous Injection	argenx Japan K.K.	April 17, 2024
◎	Perampanel hydrate / Fycompa for intravenous infusion 2 mg	Eisai Co., Ltd.	April 17, 2024
	Benralizumab (genetical recombination) / Fasenra Subcutaneous Injection 30 mg Syringe	AstraZeneca K.K.	March 26, 2024
	Rifaximin / Rifxima Tablets 200 mg	Aska Pharmaceutical Co., Ltd.	March 26, 2024
	Fenfluramine hydrochloride[*1] / Fintepla oral solution 2.2 mg/mL	UCB Japan Co. Ltd.	March 26, 2024

	Efgartigimod alfa (genetical recombination)[*2] Vyvgart for Intravenous Infusion 400 mg	argenx Japan K.K.	March 26, 2024
	Baricitinib[*3] (1) Olumiant tablets 2 mg, (2) Olumiant tablets 4 mg	Eli Lilly Japan K.K.	March 26, 2024
	Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio-*Haemophilus* type b conjugate combined vaccine Gobik Aqueous Suspension Syringes	The Research Foundation for Microbial Diseases of Osaka University	March 15, 2024
	Adsorbed diphtheria-purified pertussis-tetanus-inactivated polio-*Haemophilus* type b conjugate combined vaccine Quintovac Aqueous Suspension Injection	KM Biologics Co., Ltd.	March 14, 2024
	Semaglutide (genetical recombination)[*4] (1) Wegovy Subcutaneous Injection 0.25 mg SD, (2) Wegovy Subcutaneous Injection 0.5 mg SD, (3) Wegovy Subcutaneous Injection 1.0 mg SD, (4) Wegovy Subcutaneous Injection 1.7 mg SD, (5) Wegovy Subcutaneous Injection 2.4 mg SD	Novo Nordisk Pharma Ltd.	February 22, 2024
	Tenapanor hydrochloride Phozevel Tablets 5mg, 10 mg, 20 mg, 30 mg	Kyowa Kirin Co., Ltd.	February 20, 2024
	Zilucoplan sodium Zilbrysq Syringe for S.C. Injections 16.6 mg, 23.0 mg, 32.4 mg	UCB Japan Co. Ltd.	February 16, 2024
	Concizumab (genetical recombination) Alhemo Subcutaneous Injection 15 mg, 60 mg, 150 mg, 300 mg	Novo Nordisk Pharma Ltd.	February 16, 2024
	Sacubitril valsartan sodium hydrate[*5] (1) Entresto Tablets 50 mg, (2) Entresto Tablets 100 mg, (3) Entresto Tablets 200 mg	Novartis Pharma K.K.	February 9, 2024
	Empagliflozin[*6] Jardiance Tablets 10 mg	Nippon Boehringer Ingelheim Co., Ltd.	February 9, 2024
	pH4-treated acidic normal human immunoglobulin (subcutaneous injection) Cuvitru 20% S.C. Injection 2 g/10 mL, 4 g/20 mL, 8 g/40 mL	Takeda Pharmaceutical Company Limited	January 24, 2024
	Recombinant respiratory syncytial virus vaccine Arexvy Intramuscular Injection	GlaxoSmithKline K.K.	January 15, 2024
	Glucarpidase (genetical recombination) Megludase for Intravenous Use 1000	Ohara Pharmaceutical Co., Ltd.	January 4, 2024
	Bimekizumab (genetical recombination)[*7] Bimzelx Syringe for S.C. injection 160 mg, Bimzelx Autoinjector for S.C. injection 160 mg	UCB Japan Co. Ltd.	December 22, 2023

	Eltrombopag olamine Revolade Tablets 12.5 mg, 25 mg	Novartis Pharma K.K.	December 22, 2023
	Brexpiprazole[*8] Rexulti tablets 1 mg, 2 mg, Rexulti OD tablets 0.5 mg, 1 mg, 2 mg	Otsuka Pharmaceutical Co., Ltd.	December 22, 2023
	Cefiderocol tosilate sulfate hydrate Fetroja for Intravenous Drip Infusion 1 g	Shionogi & Co., Ltd.	December 20, 2023
	Lecanemab (genetical recombination) Leqembi for Intravenous Infusion 200 mg, 500 mg	Eisai Co., Ltd.	December 20, 2023
	Difelikefalin acetate Korsuva IV Injection Syringe for Dialysis 17.5 μg, 25.0 μg, 35.0 μg	Maruishi Pharmaceutical Co., Ltd.	December 13, 2023
	Coronavirus (SARS-CoV-2) RNA vaccine[*9] Daichirona for Intramuscular Injection	Daiichi Sankyo Co., Ltd.	December 1, 2023
	Rozanolixizumab (genetical recombination) Rystiggo for S.C. Injection 280 mg	UCB Japan Co. Ltd.	November 28, 2023
	Rivaroxaban[*10] [1] Xarelto tablets 10 mg, [2] Xarelto fine granules 10 mg, [3] Xarelto OD tablets 10 mg, [4] Xarelto dry syrup for pediatric 51.7 mg, [5] Xarelto dry syrup for pediatric 103.4 mg, [6] Xarelto tablets 2.5 mg	Bayer Yakuhin, Ltd.	November 24, 2023
	Epcoritamab (genetical recombination) Epkinly Subcutaneous Injection 4 mg, 48 mg	Genmab K.K.	November 22, 2023
	Efanesoctocog alfa (genetical recombination) Altuviiio Intravenous 250, 500, 1000, 2000, 3000, 4000	Sanofi K.K.	November 22, 2023
	Inclisiran sodium Leqvio for s.c. injection syringe 300 mg	Novartis Pharma K.K.	November 22, 2023
	Pertuzumab (genetical recombination)/ trastuzumab (genetical recombination)/ vorhyaluronidase alfa (genetical recombination) Phesgo Combination for Subcutaneous Injection MA, Phesgo Combination for Subcutaneous Injection IN	Chugai Pharmaceutical Co., Ltd.	November 22, 2023
	Coronavirus (SARS-CoV-2) RNA vaccine Spikevax Intramuscular Injection	Moderna Japan Co., Ltd.	November 1, 2023

*1 Concomitant therapy with antiepileptic drugs for epileptic seizures in patients with Lennox-Gastaut syndrome who are not sufficiently responsive to other antiepileptic drugs

*2 Chronic idiopathic thrombocytopenic purpura

*3 Polyarticular-course juvenile idiopathic arthritis in patients who have not responded sufficiently to conventional treatments

*4 Treatment of obesity
The use is limited to patients with either hypertension, dyslipidaemia, or type 2 diabetes mellitus who have not adequately responded to treatment with diet and exercise therapy and meet the following conditions:
・BMI of 27 kg/m^2 or greater in the presence of at least two obesity-related comorbidities
・BMI of 35 kg/m^2 or greater

*5 Addition of pediatric dosage indicated for chronic heart failure

*6 Chronic kidney disease

*7 Psoriatic arthritis (PsA), ankylosing spondylitis (AS), and non-radiographic axial spondyloarthritis (nr-axSpA) in patients who have not sufficiently responded to conventional therapies

*8 Depression/depressed state (for use only in patients who have not sufficiently responded to conventional antidepressant therapies)

*9 Prevention of infectious disease caused by SARS-CoV-2

*10 Prevention of thrombus/embolization formation in patients who have undergone the Fontan procedure