Pharmaceuticals and Medical Devices Safety Information

No. 399 March 2023

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Available information is listed here

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Pharmaceuticals and Medical Devices Safety Information

No. 399 March 2023

Ministry of Health, Labour and Welfare
Pharmaceutical Safety and Environmental Health 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 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, please 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.

Please utilize the Report Reception Site for reporting.
(This service is only available in Japanese.)
https://www.pmda.go.jp/safety/reports/hcp/0002.html

Abbreviations

ADR	Adverse Drug Reaction
EBV	Epstein-Barr Virus
EPPV	Early Post-marketing Phase Vigilance
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
PED	Pharmaceutical Evaluation Division
PMDA	Pharmaceuticals and Medical Devices Agency
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
SD	Safety Division

1
Safety Control Measures for Generic Lenalidomide Preparations

1. Introduction

Lenalidomide (brand name: Revlimid Capsules) and pomalidomide (brand name: Pomalyst Capsules) are drugs for the treatment of multiple myeloma, etc. Because they have a similar chemical structure to thalidomide and teratogenicity, implementation of strict control procedures (Proper Control Procedures for Revlimid/Pomalyst (RevMate)) is mandated in order to prevent fetal exposure to these drugs.

For the prescription and dispensing of lenalidomide and pomalidomide based on RevMate, prescribing physicians, responsible pharmacists, and patients all need to be well informed of and understand the control procedures before they are registered in the RevMate Center. In order to confirm the adherence status of RevMate, when these drugs are prescribed or dispensed, patients should fill in the periodic check sheets at the instructed frequencies, and prescribing physicians and pharmacists should check them based on the adherence check sheets.

Generic drugs of lenalidomide preparation were approved on February 15, 2023 and are expected to be put on the market after being listed on the Japanese National Health Insurance drug price list. RevMate will be revised for the post-marketing safety control of generic drugs, and it is scheduled to take effect in June of this year. This section will provide an outline of the safety control measures.

2. Main outline of safety control measures

(1) Sharing of safety control procedures

In principle, generic lenalidomide preparations will also be subject to strict controls to prevent fetal exposure to the drugs based on RevMate, and the brand name drug manufacturer and each generic drug manufacturer will share a safety management system and work closely together in the operation of the system.

(2) Cooperation system among the companies

Of the tasks related to RevMate, those that are common to each product and that are considered reasonable and efficient to be carried out in a concentrated manner (management and operation of the database, training of prescribing physicians and responsible pharmacists, regular visits to medical institutions, etc.) will be implemented by the representative company, and those that are considered reasonable to be implemented by each company including companies of generic drugs under their own responsibility (provision of materials based on RevMate, handling individual deviation cases, etc.) will be implemented by each company.

(3) Third-party Assessment Committee and RevMate Committee

As before, the Third-party Assessment Committee, as an organization independent from the company, will review and make proposals regarding the compatibility between preventing fetal exposure to drugs and ensuring patient access to drugs.

The purpose of the RevMate Committee is to operate and manage RevMate properly as before. In order to achieve this purpose, the RevMate Joint Steering Committee will be established and operated by the companies that share RevMate, and the knowledge and experience gained through the operation of RevMate will be shared among the companies.

(4) Consent form

Since personal information will be shared with other companies due to the marketing of the generic drugs, the consent form will be revised to clearly state that personal information will be provided to the companies that operate the RevMate Center as well as to the companies of the drug product being taken. In addition, each company should prepare explanatory materials on the details of the handling of personal information, and physicians or pharmacists should provide an

explanation based on the materials.

For patients for whom consent has been obtained using the new form, additional consent is not required, even if they switch to another company's lenalidomide preparation. However, when a change is made, physicians or pharmacists should provide a sufficient explanation to patients using explanatory materials, and they should state in the adherence check sheets that the explanation has been given.

For patients who have continued treatment with the brand name drug since before the marketing of generic drugs, i.e., for patients whose consent was obtained using the current form, consent should be obtained again using the new form when switching to generic drugs. After consent is obtained using the new form, even if patients switch to a lenalidomide preparation of a different company, it will not be necessary to obtain additional consent.

(5) Management of information, etc.

Regarding the handling of the shared data, the database that records registered information, adherence status, etc. based on RevMate will be a single common database, and it will be centrally managed at the data center of the representative company.

The information registered in the database should be used only for the operations of RevMate, and it is strictly prohibited to be used for sales activities. For this reason, those involved in RevMate operations and those involved in sales activities should be clearly distinguished and should not hold both positions concurrently.

3. Closing remark

Revised RevMate will take effect on June 1, 2023, after information provision activities are conducted by the companies. In addition, the name of RevMate will be changed to "Lenalidomide/Pomalidomide Proper Control Procedures," using the nonproprietary name.

Healthcare professionals are requested to understand the purpose of this content and implement safety management according to RevMate. Their continued cooperation would be much appreciated.

[References]

• Safety Control Measures for Generic Lenalidomide Preparations
https://www.mhlw.go.jp/stf/shingi2/0000070175_00001.html (only in Japanese)

• Revisions to Safety Control Procedures for Use of Lenalidomide Preparations
(request for precaution and dissemination of information to medical institutions) (PSEHB/PED Notification No. 0131-1 and PSEHB/SD Notification 0131-1 dated January 31,2023)
https://www.mhlw.go.jp/content/001047576.pdf (only in Japanese)

• RMP materials such as RevMate Ver 7.0
https://www.pmda.go.jp/PmdaSearch/iyakuDetail/GeneralList/4291024 (only in Japanese)

Figure 1. RevMate Ver.6.2 (before revision)

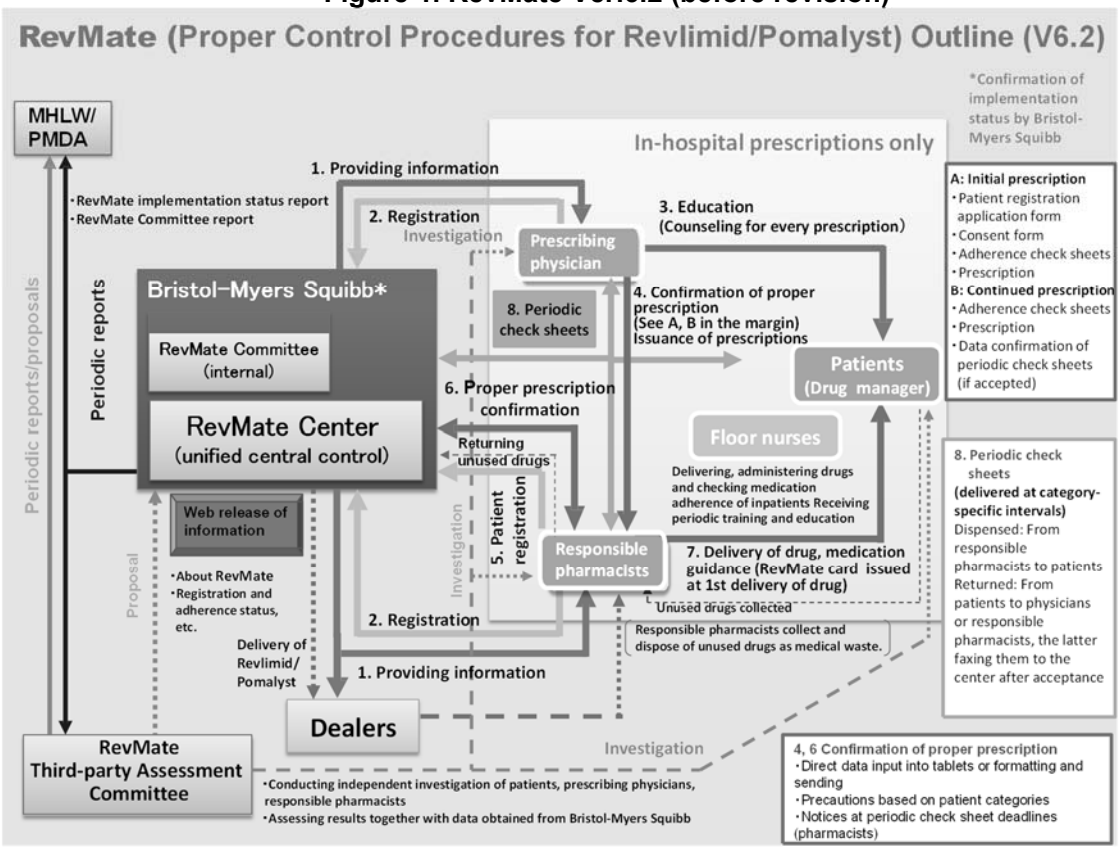
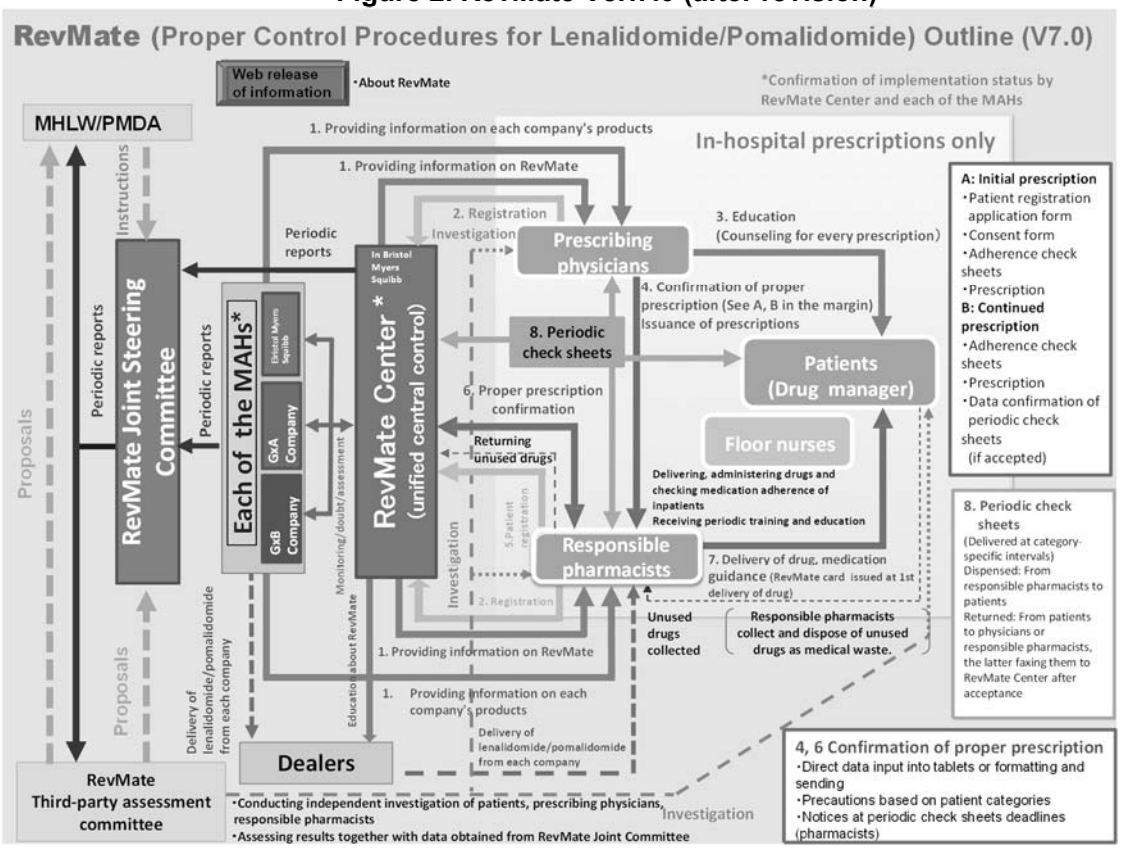


Figure 2. RevMate Ver.7.0 (after revision)



2

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated February 14, 2023, this section will present the details of important revisions as well as the case summary serving as the basis for these revisions.

1 Preparations containing GLP-1 receptor agonists and tirzepatide
[1] Liraglutide (genetical recombination)
[2] Exenatide
[3] Lixisenatide
[4] Dulaglutide (genetical recombination)
[5] Semaglutide (genetical recombination)
[6] Insulin degludec (genetical recombination)/liraglutide (genetical recombination)
[7] Insulin glargine (genetical recombination)/lixisenatide
[8] Tirzepatide

Brand name (name of company)	[1] Victoza Subcutaneous Injection 18 mg (Novo Nordisk Pharma Ltd.) [2] Byetta Subcutaneous Injection 5 μg Pen 300, 10 μg Pen 300 Bydureon Subcutaneous Injection 2 mg Pen (AstraZeneca K.K.) [3] Lyxumia S.C. Injection 300 μg (Sanofi K.K.) [4] Trulicity Subcutaneous Injection 0.75 mg Ateos (Eli Lilly Japan K.K.) [5] Ozempic Subcutaneous Injection 0.25 mg SD, 0.5 mg SD, 1.0 mg SD, Ozempic Subcutaneous Injection 2 mg, Rybelsus tablets 3 mg, 7 mg, 14 mg (Novo Nordisk Pharma Ltd.) [6] Xultophy combination injection FlexTouch (Novo Nordisk Pharma Ltd.) [7] Soliqua Injection SoloStar (Sanofi K.K.) [8] Mounjaro Subcutaneous Injection 2.5 mg Ateos, 5 mg Ateos, 7.5 mg Ateos, 10 mg Ateos, 12.5 mg Ateos, 15 mg Ateos (Eli Lilly Japan K.K.)
Therapeutic category	Other hormone preparations (including antihormone preparations) Antidiabetic agents
Indications	[1] Type 2 diabetes mellitus [2] •Byetta Subcutaneous Injection Type 2 diabetes mellitus The use is limited to patients who have not adequately responded to treatment with sulfonylureas (including concomitant use with biguanides or thiazolidines) in addition to diet and exercise therapy. •Bydureon Subcutaneous Injection Type 2 diabetes mellitus The use is limited to patients who have not adequately responded to treatment with sulfonylureas, biguanides, and thiazolidines (including monotherapy or combination therapy with each drug) in addition to diet and exercise therapy. [3] to [5], [8] Type 2 diabetes mellitus [6], [7] Type 2 diabetes mellitus for which insulin therapy is indicated

PRECAUTIONS (Revised language is underlined.)

[1] – [7]

[Under new instructions]

8. IMPORTANT PRECAUTIONS (newly added)	Cholelithiasis, cholecystitis, cholangitis, or cholestatic jaundice may occur. If abdominal symptoms such as abdominal pain are observed, appropriate measures should be taken with consideration given to close examination of the cause by imaging tests, etc., if necessary.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Cholecystitis, cholangitis, cholestatic jaundice

[8]

[Under new instructions]

8. IMPORTANT PRECAUTIONS	Cholelithiasis, cholecystitis, cholangitis, or cholestatic jaundice may occur. If abdominal symptoms such as abdominal pain are observed, appropriate measures should be taken with consideration given to close examination of the cause by imaging tests, etc., if necessary.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Cholecystitis, cholangitis, cholestatic jaundice
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving cholecystitis, cholangitis, cholestatic jaundice: [1] 8 (No patient mortalities) [2] 1 (No patient mortalities) [3] 1 (No patient mortalities) [4] 6 (No patient mortalities) [5] 1 (No patient mortalities) No cases have been reported to date for [6] to [8]. Number of patients using the drug as estimated by the MAH during the previous 1-year period: [1] Approximately 73 000 [2] Approximately 1 893 [3] Approximately 3 000 [4] Approximately 229 000 [5] Subcutaneous Injection: Approximately 70 000, Tablets: 185 000 [6] Approximately 78 000 [7] Approximately 20 000 [8] Not marketed (as of February 2023) Japanese market launch: [1] June 2010 [2] Byetta Subcutaneous Injection: December 2010, Bydureon Subcutaneous Injection: May 2015 [3] September 2013 [4] September 2015 [5] Subcutaneous Injection 0.25 mg SD, 0.5 mg SD, 1.0 mg SD: June

2020, Subcutaneous Injection 2 mg: May 2022, Tablets: February 2021
[6] September 2019
[7] June 2020
[8] Not listed in the Japanese National Health Insurance Drug Price List (as of February 2023)

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Patient</th><th rowspan="2">Daily dose/ administration duration</th><th>Adverse reaction</th></tr>
<tr><th>Sex/ age</th><th>Reason for use (complication)</th><th>Clinical course and treatment</th></tr>
<tr><td>1</td><td>Male
70s</td><td>Type 2 diabetes mellitus (hypertension, emphysema)</td><td>0.75 mg/week
Unknown (The actual dosing frequency is unknown.)</td><td>Cholecystitis
16 days before administration: ALT: 30 IU/L, AST: 30 IU/L, ALP: 264 IU/L, T-Bil: 0.5 mg/dL, γ-GTP: 39 IU/L, LDH: 210 IU/L, WBC: 4 600/μL
Before initiation of administration: The patient was admitted to the hospital for the purpose of education in glycaemia control. No gallstones or cholecystitis was noted at that time.
Day 1 of administration: For type 2 diabetes, administration of 0.75 mg of dulaglutide was initiated.
After initiation of administration: After initiating administration of dulaglutide, γ-GTP tended to increase.
47 days after administration (day of discontinuation): Administration of dulaglutide was discontinued, and it was switched to linagliptin.
8 days after discontinuation: The patient complained of abdominal pain. A CT confirmed biliary sludge.
10 days after discontinuation: The patient was admitted to the hospital due to cholecystitis. A percutaneous transhepatic biliary drainage procedure was performed. Administration of linagliptin, insulin glargine, and metformin was discontinued. T-Bil: 1.2 mg/dL, D-Bil: 0.6 mg/dL, γ-GTP: 1 028 IU/L, WBC: 19 900/μL
11 days after discontinuation: ALT: 70 IU/L, AST: 121 IU/L, ALP: 687 IU/L, LDH: 332 IU/L, CRP: 30.01 mg/L
25 days after administration: ALT: 27 IU/L, AST: 31 IU/L, ALP: 337 IU/L, T-Bil: 0.5 mg/dL, D-Bil: 0.2 mg/dL, γ-GTP: 238 IU/L, LDH: 252 IU/L, CRP: 3.63 mg/L, WBC: 4 300/μL
28 days after discontinuation: Cholecystitis was resolving, and the patient is being followed up.</td></tr>
<tr><td></td><td colspan="4">Laboratory test value
<table>
<tr><th></th><th>16 days before administration</th><th>10 days after discontinuation</th><th>11 days after discontinuation</th><th>25 days after discontinuation</th></tr>
<tr><td>ALT (IU/L)</td><td>30</td><td>-</td><td>70</td><td>27</td></tr>
<tr><td>AST (IU/L)</td><td>30</td><td>-</td><td>121</td><td>31</td></tr>
<tr><td>ALP (IU/L)</td><td>264</td><td>-</td><td>687</td><td>337</td></tr>
<tr><td>T-Bil (mg/dL)</td><td>0.5</td><td>1.2</td><td>-</td><td>0.5</td></tr>
<tr><td>D-Bil (mg/dL)</td><td>-</td><td>0.6</td><td>-</td><td>0.2</td></tr>
<tr><td>γ-GTP (IU/L)</td><td>39</td><td>1 028</td><td>-</td><td>238</td></tr>
<tr><td>LDH (IU/L)</td><td>210</td><td>-</td><td>332</td><td>252</td></tr>
<tr><td>WBC (/μL)</td><td>4 600</td><td>19 900</td><td>-</td><td>4 300</td></tr>
<tr><td>CRP (mg/L)</td><td>-</td><td>-</td><td>30.01</td><td>3.63</td></tr>
</table></td></tr>
<tr><td></td><td colspan="4">Concomitant drugs: Linagliptin, insulin glargine, metformin</td></tr>
</table>

2 Tazobactam/piperacillin hydrate

Brand name (name of company)	Zosyn I.V. injection 2.25, 4.5, Zosyn I.V. infusion bag 4.5 (TAIHO Pharmaceutical Co., Ltd.), and the others
Therapeutic category	Antibiotic preparations acting mainly on gram-positive and gram-negative bacteria
Indications	•Common infection <Applicable microorganisms> Tazobactam/piperacillin hydrate-susceptible strains of genus *Staphylococcus*, genus *Streptococcus*, genus *Pneumococcus*, genus *Enterococcus*, *Moraxella (Branhamella) catarrhalis*, *Escherichia coli*, genus *Citrobacter*, genus *Klebsiella*, genus *Enterobacter*, genus *Serratia*, genus *Proteus*, genus *Providencia*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, genus *Acinetobacter*, genus *Peptostreptococcus*, genus *Clostridium* (excluding *Clostridium difficile*), genus *Bacteroides*, and genus *Prevotella* <Applicable conditions> Sepsis, deep-seated skin infections, secondary infections following erosion or ulcer, pneumonia, pyelonephritis, complicated cystitis, peritonitis, intra-abdominal abscess, cholecystitis, and cholangitis •Febrile neutropenia

PRECAUTIONS (Revised language is underlined.)

[Under old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Haemophagocytic lymphohistiocytosis (haemophagocytic syndrome): Haemophagocytic lymphohistiocytosis may occur. Patients should be carefully monitored, and if any abnormalities such as pyrexia, rash, neurological symptoms, splenomegaly, swollen lymph nodes, cytopenia, increased LDH, hyperferritinaemia, hypertriglyceridaemia, hepatic impairment, or coagulation abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
[Under new instructions]	
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Haemophagocytic lymphohistiocytosis (haemophagocyticsyndrome) If any abnormalities such as pyrexia, rash, neurological symptoms, splenomegaly, swollen lymph nodes, cytopenia, increased LDH, hyperferritinaemia, hypertriglyceridaemia, hepatic impairment, or coagulation abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) collected in the PMDA's database for adverse drug reactions, etc. reports Cases involving haemophagocytic lymphohistiocytosis (haemophagocytic syndrome): 5 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 128 020 Japanese market launch I.V. injection: October 2008, I.V. infusion bag: June 2015

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Female under 10 years old	Bacterial nephritis, renal abscess (escherichia infection)	6.75 g 16 days ↓ discontinuation	**Haemophagocytic lymphohistiocytosis**	
				Day 1 of administration	Administration of tazobactam/piperacillin hydrate (2.25 g × 3/day) and amikacin sulfate was initiated.
				Day 3 of administration	The patient's body temperature returned to normal, and the symptoms were resolving.
				Day 5 of administration	Administration of amikacin sulfate was discontinued.
				Day 7 of administration	Patient's body temperature: 36.0°C
				Day 13 of administration	The patient's body temperature was 39.2°C.
				Day 14 of administration	Administration of tosufloxacin tosilate hydrate was initiated in the evening (until Day 16 of administration).
				Day 15 of administration	Maculo-papular rash developed systemically and covered less than 50% of the body surface area. A bone marrow aspirate revealed excessive bone marrow cells associated with haemophagocytosis at multiple sites. However, there was no definite proof of malignant tumour. Guttural viral cultures were negative. Serum IgM antibodies against herpes simplex virus (HSV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) were all negative. White blood cell (WBC) and bacteria were not detected in the urine, and blood cultures were negative. An intensive search for an infectious, neoplastic, or autoimmune cause of haemophagocytic syndrome was negative. Clinical features (pyrexia) and assessment of the tests (hypofibrinogenaemia, increased serum ferritin and increased interleukin-2 receptor, deficiencies in natural killer cell activity, haemophagocytosis in the bone marrow) met the criteria of haemophagocytic syndrome.
				Day 16 of administration (day of discontinuation)	Hyperthermia persisted, and the marked aggravation of laboratory values was noted. Patient's body temperature: 40.5°C EBV: Negative Administration of tazobactam/piperacillin hydrate was discontinued. Since haemophagocytosis was noted in a myelogram, steroid pulse therapy was performed. The patient was transferred to another hospital. Thereafter, she recovered from haemophagocytic syndrome and disseminated intravascular coagulation.
				904 days after discontinuation	A drug-induced lymphocyte stimulation test (DLST) was performed. Tazobactam/piperacillin hydrate: Positive (measured value 4 094, control 495, S.I. = 891)

Laboratory test value

	Day 1 of administration	Day 4 of administration	Day 9 of administration	Day 14 of administration	Day 15 of administration	Day 16 of administration
WBC(/μL)	19 800	6 600	6 400	4 200	6 700	5 700
Neutrophil count (/μL)	15 630	-	-	-	-	-
Haemoglobin (g/dL)	11.6	12.2	12.9	13.1	13.7	13.3
Platelet count ($\times10^4$/μL)	29.7	45.2	56.9	18.1	12.3	11.4
Prothrombin time (%)	64	78	82	-	-	41
Blood fibrinogen (mg/dL)	743	649	318	-	173	173
LDH(IU/L)	233	223	217	632	8 406	7 100
AST(IU/L)	20	47	32	79	1 639	1 574
ALT(IU/L)	18	75	39	45	337	399
Al-P(IU/L)	553	597	656	673	-	879
Blood triglycerides (mg/dL)	73	-	-	-	155	145
IL-2 receptor	923.1	725.8	711.0	-	3 812	3 506.4
Serum ferritin (ng/mL)	-	-	-	-	108 638	118 261.0
Natural killer cell activity (%)	-	-	-	-	1	-
CRP (mg/dL)	26.9	8.4	0.6	4.1	-	7.6

Suspected concomitant drugs: None
Concomitant drugs: Amikacin sulfate, tosufloxacin tosilate hydrate
Note: Miyabayashi H, et al. Tohoku J Exp Med. 2018; 245(1): 55-59.

3
Revision of Precautions (No.339)

This section presents details of revisions to the Precautions and brand names of drugs that have been revised in accordance with the Notifications dated February 14, 2023

1 Other hormone preparations (including antihormone preparations), antidiabetic agents

[1] Exenatide
[2] Semaglutide (genetical recombination)
[3] Dulaglutide (genetical recombination)
[4] Lixisenatide
[5] Liraglutide (genetical recombination)
[6] Insulin glargine (genetical recombination)/lixisenatide
[7] Insulin degludec (genetical recombination)/liraglutide (genetical recombination)

Brand name	[1] Byetta Subcutaneous Injection 5 μg Pen 300, 10 μg Pen 300, Bydureon Subcutaneous Injection 2 mg Pen (AstraZeneca K.K.) [2] Ozempic Subcutaneous Injection 0.25 mg SD, 0.5 mg SD, 1.0 mg SD, Ozempic Subcutaneous Injection 2 mg, Rybelsus tablets 3 mg, 7 mg, 14 mg (Novo Nordisk Pharma Ltd.) [3] Trulicity Subcutaneous Injection 0.75 mg Ateos (Eli Lilly Japan K.K.) [4] Lyxumia S.C. Injection 300 μg (Sanofi K.K.) [5] Victoza Subcutaneous Injection 18 mg (Novo Nordisk Pharma Ltd.) [6] Soliqua Injection SoloStar (Sanofi K.K.) [7] Xultophy combination injection FlexTouch (Novo Nordisk Pharma Ltd.)
[Under new instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	Cholelithiasis, cholecystitis, cholangitis, or cholestatic jaundice may occur. If abdominal symptoms such as abdominal pain are observed, appropriate measures should be taken with consideration given to close examination of the cause by imaging tests, etc., if necessary.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Cholecystitis, cholangitis, cholestatic jaundice

2 Other hormone preparations (including antihormone preparations)

Tirzepatide

Brand name	Mounjaro Subcutaneous Injection 2.5 mg Ateos, 5 mg Ateos, 7.5 mg Ateos, 10 mg Ateos, 12.5 mg Ateos, 15 mg Ateos (Eli Lilly Japan K.K.)
[Under new instructions]	
8. IMPORTANT PRECAUTIONS	Cholelithiasis, cholecystitis, cholangitis, or cholestatic jaundice may occur. If abdominal symptoms such as abdominal pain are observed, appropriate measures should be taken with consideration given to close examination of the cause by imaging tests, etc., if necessary.
11. ADVERSE REACTIONS	Cholecystitis, cholangitis, cholestatic jaundice

11.1 Clinically Significant Adverse Reactions (newly added)	

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

Tazobactam/piperacillin hydrate

Brand name	Zosyn I.V. injection 2.25, 4.5, Zosyn I.V. infusion bag 4.5 (TAIHO Pharmaceutical Co., Ltd.), and the others
[Under old instructions]	
Adverse reactions Clinically Significant Adverse Reaction (newly added)	Haemophagocytic lymphohistiocytosis (haemophagocytic syndrome): Haemophagocytic lymphohistiocytosis may occur. Patients should be carefully monitored, and if any abnormalities such as pyrexia, rash, neurological symptoms, splenomegaly, swollen lymph nodes, cytopenia, increased LDH, hyperferritinaemia, hypertriglyceridaemia, hepatic impairment, or coagulation abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.
[Under new instructions]	
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Haemophagocytic lymphohistiocytosis (haemophagocytic syndrome) If any abnormalities such as pyrexia, rash, neurological symptoms, splenomegaly, swollen lymph nodes, cytopenia, increased LDH, hyperferritinaemia, hypertriglyceridaemia, hepatic impairment, or coagulation abnormalities are observed, administration of this drug should be discontinued, and appropriate measures should be taken.

The Revision of Precautions notified by PSEHB/PSD Notification No. 0117-1 by the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated January 17, 2023 has been partially corrected as follows.

Correction	Current	Corrected
Current statement and proposed revision for preparations containing acetaminophen (oral dosage form, suppositories) (OTC drugs)	Consultation If the following symptoms are observed after taking this drug, these may be adverse reactions. In such a case, the use of this drug should be immediately discontinued, and a physician, dentist or pharmacist should be consulted with this document. The following serious symptoms may occur rarely. In such a case, medical attention should be sought immediately. (N/A)	Consultation If the following symptoms are observed after taking this drug, these may be adverse reactions. In such a case, the use of this drug should be immediately discontinued, and a physician, dentist, pharmacist or registered sales clerk should be consulted with this document. The following serious symptoms may occur rarely. In such a case, medical attention should be sought immediately. (N/A) *The highlighted part should be listed only in the preparations containing ibuprofen among antipyretics and analgesics.

*Corrected language is underlined.

4

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 January 31, 2023)
◎: Products for which EPPV was initiated after January 1, 2023

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	Abaloparatide acetate / Ostabalo Subcutaneous Injection Cart 1.5 mg	Teijin Pharma Limited.	January 30, 2023
◎	Risankizumab (genetical recombination) / Skyrizi Intravenous infusion 600 mg	AbbVie GK	January 13, 2023
	Caplacizumab (genetical recombination) / Cablivi Injection 10 mg	Sanofi K.K.	December 23, 2022
	Valemetostat tosilate / Ezharmia Tablets 50 mg, 100 mg	Daiichi Sankyo Co., Ltd.	December 20, 2022
	Ozoralizumab (genetical recombination) / Nanozora 30 mg Syringes for S.C. Injection	Taisho Pharmaceutical Co., Ltd.	December 1, 2022
	Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) / Spikevax Intramuscular Injection (Bivalent: Original/Omicron BA.4-5)	Moderna Japan Co., Ltd.	November 28, 2022
	Ensitrelvir fumaric acid / Xocova Tablets 125 mg	Shionogi & Co., Ltd.	November 24, 2022
	Human C1-inactivator / Berinert S.C. Injection 2000	CSL Behring K.K.	November 21, 2022
	Vutrisiran sodium / Amvuttra Subcutaneous Injection 25 mg Syringe	Alnylam Japan K.K.	November 18, 2022
	Deucravacitinib / Sotyktu tablets 6 mg	Bristol-Myers Squibb K.K.	November 16, 2022
	Tezepelumab (genetical recombination) / Tezspire Subcutaneous Injection 210 mg	AstraZeneca K.K.	November 16, 2022
	Spesolimab (genetical recombination) / Spevigo 450 mg for I.V. Infusion	Nippon Boehringer Ingelheim Co., Ltd.	November 16, 2022
	Fenfluramine hydrochloride		

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
Fintepla oral solution 2.2 mg/mL	UCB Japan Co. Ltd.	November 16, 2022
Selumetinib sulfate Koselugo Capsules 10 mg, 25 mg	Alexion Pharma Godo Kaisha	November 16, 2022
Rivaroxaban[*1] Xarelto tablets 2.5 mg	Bayer Yakuhin Ltd.	October 24, 2022
Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) Comirnaty intramuscular injection for 6 months to 4 years old	Pfizer Japan Inc.	October 19, 2022
Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2) COMIRNATY RTU intramuscular injection (Bivalent: Original/Omicron BA.4-5)	Pfizer Japan Inc.	October 7, 2022
Fesoterodine fumarate[*2] Toviaz Tablets 4 mg, 8 mg	Pfizer Japan Inc.	September 26, 2022
Aflibercept (genetical recombination) [*3] Eylea solution for IVT inj. 40 mg/mL	Bayer Yakuhin Ltd.	September 26, 2022
Upadacitinib hydrate[*4] [1] Rinvoq Tablets 7.5 mg, [2] 15 mg, [3] 30 mg, [4] 45 mg	AbbVie GK	September 26, 2022
Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2)[*5] Spikevax Intramuscular Injection (Bivalent: Original/Omicron BA.1)	Moderna Japan Co., Ltd.	September 20, 2022
Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2)[*6] Comirnaty RTU intramuscular injection (Bivalent: Original/Omicron BA.1)	Pfizer Japan Inc.	September 14, 2022
Ethyl icosapentate Epadel EM Capsules 2 g	Mochida Pharmaceuticals Co. Ltd.	September 12, 2022
Sutimlimab (genetical recombination) Enjaymo for I.V. infusion 1.1 g	Sanofi K.K.	September 8, 2022
Tixagevimab (genetical recombination) and cilgavimab (genetical recombination) Evusheld Intramuscular Injection Set	AstraZeneca K.K.	August 31, 2022
Pimitespib Jeselhy tablets 40 mg	TAIHO Pharmaceutical Co., Ltd.	August 30, 2022
Icatibant acetate Firazyr subcutaneous injection 30 mg syringes	Takeda Pharmaceutical Company Limited.	August 24, 2022
Ravulizumab (genetical recombination) [*7] Ultomiris for Intravenous Infusion 300 mg, 300 mg/3 mL, Ultomiris for Intravenous	Alexion Pharma Godo Kaisha	August 24, 2022

Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
Infusion 1100 mg/11 mL		
Landiolol hydrochloride[*8] / Onoact for I. V. Infusion 50 mg, 150 mg	Ono Pharmaceutical Co., Ltd.	August 24, 2022
Darinaparsin / Darvias Injection 135 mg	Solasia Pharma K.K.	August 22, 2022
Vestronidase alfa (genetical recombination) / Mepsevii Intravenous Infusion 10 mg	Ultragenyx Japan K.K.	August 22, 2022
Vosoritide (genetical recombination) / Voxzogo for Subcutaneous Injection 0.4 mg, 0.56 mg, 1.2 mg	BioMarin Pharmaceutical Japan K.K.	August 19, 2022
Nemolizumab (genetical recombination) / Mitchga 60 mg Syringes	Maruho Co., Ltd.	August 8, 2022
Freeze-dried Smallpox Vaccine Prepared in Cell Culture[*9] / Freeze-dried Smallpox Vaccine Prepared in Cell Culture LC16 “KMB”	KM Biologics Co., Ltd.	August 2, 2022

*1 Prevention of thrombus/embolus formation in patients with peripheral arterial disease after lower extremity revascularization

*2 A drug with a new additional pediatric dosage indicated for urinary management in patients with neurogenic bladder

*3 Retinopathy of prematurity

*4 [1] [2] [3] Remission induction and maintenance therapy for moderate to severe ulcerative colitis (only for patients who have not adequately responded to conventional treatments), [4] remission induction therapy for moderate to severe ulcerative colitis (only for patients who have not adequately responded to conventional treatments)

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

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

*7 Treatment of generalized myasthenia gravis (only for patients whose symptoms are difficult to control with high-dose intravenous immunoglobulin therapy or plasmapheresis)

*8 A drug with a new additional pediatric dosage indicated for the treatment of tachyarrhythmia (supraventricular tachycardia, atrial fibrillation and atrial flutter) in patients with low cardiac function

*9 Monkeypox

<Errata, Brand name of 5 antipyretics, analgesics and anti-inflammatory agents, agents used for common cold, antitussives on page 26 in the English version of PMDSI No.398>

Original	Revised
[3] Pelex combination granule (TAIHO Pharmaceutical Co., Ltd.) [4] Pediatric Pelex combination granule (TAIHO Pharmaceutical Co., Ltd.)	[3] Pelex combination granule, Pediatric Pelex combination granule (TAIHO Pharmaceutical Co., Ltd.) [4] PL Combination Granules, PL Combination Granules for Infants, and the others (Shionogi Pharma Co., Ltd. and the others)