Pharmaceuticals and Medical Devices Safety Information

No. 385 August 2021

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Available information is listed here

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Pharmaceuticals and Medical Devices Safety Information

No. 385 August 2021

Ministry of Health, Labour and Welfare & Pharmaceutical Safety and Environmental Health Bureau, Labour and Welfare, 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, 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
ALP	Alkaline phosphatase
CT	Computed tomography
EPPV	Early Post-marketing Phase Vigilance
MAH	Marketing authorization holder
MHLW	Ministry of Health, Labour and Welfare
MR	Medical representative
MRI	Magnetic resonance imaging
PMDA	Pharmaceuticals and Medical Devices Agency
PTH	Parathyroid hormone
VitD	Vitamin D
X-p	X-ray photograph

1

Revision of Proper Control Procedures for Revlimid/Pomalyst (RevMate)

1. Introduction

Lenalidomide (branded name: Revlimid Capsules) and pomalidomide (branded 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 foetal 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. When these drugs are prescribed or dispensed, prescribing physicians and pharmacists should check with patients for their medication adherence based on the adherence check sheet and patients should complete and submit their periodic check sheet at the instructed frequencies. Please refer to the summary diagram below for the details.

RevMate was revised on July 1, 2021. This section will introduce the details of the revision and other relevant information.

2. Key components of revision

(1) Establishment of RevMate Representative as a role that is separate from promotional activities.

It was decided to newly establish RevMate Representatives for the task of confirming the implementation status of RevMate, which had been carried out by medical representatives (MRs) of the MAH. Since the task involves handling patient information, the decision was made to clearly distinguish the task from promotion activities by removing it from the duties of MRs. RevMate Representative is a role dedicated to confirming the implementation status of RevMate and other relevant tasks. They handle patient information registered in RevMate independent of promotion activities.

The table shows the duties of RevMate Representatives and MRs in the revised RevMate. MRs will continue their proper use promotion activities as well as collection of adverse reactions data under RMP. Registration of prescribing physicians and responsible pharmacists, and training and education for them will be mainly carried out by RevMate Representatives, while responses to any deviations from the procedures encountered and monitoring of facilities will be solely the responsibility of RevMate Representatives with no involvement of MRs. Please note that RevMate Representatives and MRs will visit healthcare institutions in accordance with their respective roles.

(2) Change of corporate name associated with integration of marketing authorization holder

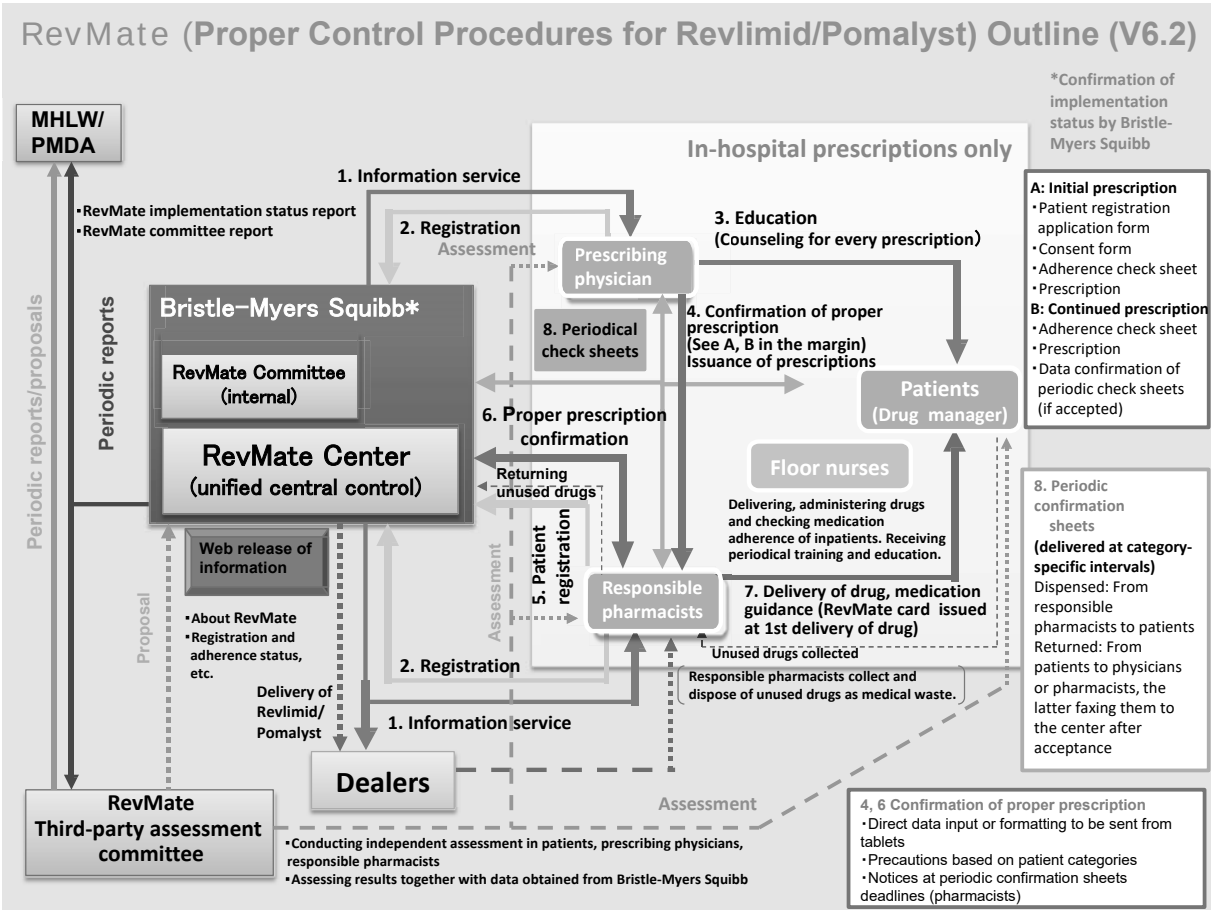
Celgene K.K., the MAH of Revlimid Capsules and Pomalyst Capsules was integrated into Bristle-Myers Squibb K.K. on July 1, 2021 following the acquisition of Celgene Corporation by Bristol-Myers Squibb Company, both in the US. In line with the integration, the patient consent form was revised. Please use the consent form with the new corporate name for patients for whom consent should be newly obtained to initiate treatment or for changes of categories or drugs. Consent obtained in the past is nonetheless valid. It need not be obtained again. For the change in the corporation that handles their information, please inform the patients with the patient leaflet prepared by the corporation.

3. In conclusion

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

[References]

- RevMate Ver 6.2
  https://www.revmate-japan.jp/ver6/professional/pdf/RevMate_Management_v6.2.pdf
  (only in Japanese)
- RevMate Ver 6.2 Key Components of Revision
  https://www.revmate-japan.jp/upload/RevMate%E6%94%B9%E8%A8%82%E3%81%AE%E3%83%9D%E3%82%A4%E3%83%B3%E3%83%88_Ver.6.2.pdf (only in Japanese)



RevMate Representatives Post-launch activities

Current

Preparation for RevMate registration	MR	Field Nurse
1. Healthcare staff registration	✓	
2. Facility arrangement at healthcare institutions	✓	
3. Ensuring cooperation in post-marketing survey	✓	
4. Confirmation of distributors' bookkeeping	✓	

Activities at RevMate-registered facilities	MR	Field Nurse
1. Addition/change of healthcare staff registration	✓	
2. Continuing healthcare staff training	✓ (HCP)	✓(Nurse)
3. Responses in equipment failure	✓	
4. Material replenishment	✓	
5. Provision of RevMate registration data	✓	
6. Monitoring or audit	✓	
7. Precautions regarding unused drug collection	✓	
8. Proper use promotion activities by MRs	✓	

Post-RevMate Rep.-launch (✓: Main duties)

Preparation for RevMate registration	MR	RevMate Rep.
1. Healthcare staff registration		✓
2. Facility arrangement at healthcare institutions		✓
3. Ensuring cooperation in post-marketing survey	✓	
4. Confirmation of distributors' bookkeeping	✓	

Activities at RevMate-registered facilities	MR	RevMate Rep.
1. Addition/change of healthcare staff registration		✓
2. Continuing healthcare staff training		✓
3. Responses in equipment failure	N/A	✓
4. Material replenishment		✓
5. Provision of RevMate registration data	N/A	✓
6. Monitoring or audit	N/A	✓
7. Precautions regarding unused drug collection	N/A	✓
8. Proper use promotion activities based on RMP, etc.	✓	

N/A…No personal data related duties by MRs

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Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated July 20, 2021, this section will present the details of important revisions as well as the case summaries serving as the basis for these revisions.

1 [1] Magnesium sulfate hydrate/glucose
[2] Magnesium sulfate hydrate

Branded name (name of company)	[1] Magsent Injection 100 mL, Magsent Injection Syringe 40 mL, Magnesol for Intravenous Injection 20 mL (Aska Pharmaceutical Co., Ltd.) [2] Magnesium Sulfate Hydrate "NikP" (Nichi-Iko Pharmaceutical Co., Ltd.)
Therapeutic category	[1] Antispasmodics, [2] Purgatives and clysters
Indications	[1] Inhibition of uterine contractions in threatened premature labour, prophylaxis and treatment of eclampsia in severe hypertensive disorders of pregnancy [2] Constipation (oral dosage form), cholelithiasis (infusion via duodenal tube), hypomagnesaemia (injection), eclampsia (injection), tachyarrhythmia (injection)

PRECAUTIONS (revised language is underlined)

[Under old instructions]

Use during Pregnancy, Delivery or Lactation (newly added)	With prolonged administration of this drug during pregnancy, rickets-like bone lesion may be identified in neonates at birth. (The shortest duration of administration with magnesium sulfate hydrate/glucose (injections) to the mother was 18 days as confirmed among the cases reported after the product launch in Japan.)
Use during Pregnancy, Delivery or Lactation	When administering this drug for eclampsia, caution should be exercised for the following: ・With administration of this drug during pregnancy, hypokinesia in foetuses as well as heart failure, hyperkalaemia, or hypocalcaemia in neonates may occur. ・With prolonged administration of this drug during pregnancy, rickets-like bone lesion may be identified in neonates at birth. (The shortest duration of administration with magnesium sulfate hydrate/glucose (injections) to the mother was 18 days as confirmed among the cases reported after the product launch in Japan.)

[Under new instructions]

9. PRECAUTIONS CONCERNING PATIETS WITH SPECIFIC BACKGROUNDS **9.5 Pregnant Women**	With administration of this drug during pregnancy, hypokinesia in foetuses as well as heart failure, hyperkalaemia, or hypocalcaemia in neonates may occur.
(newly added)	With prolonged administration of this drug during pregnancy, rickets-like bone lesion may be identified in neonates at birth. (The shortest duration of administration with magnesium sulfate

	hydrate/glucose (injections) to the mother was 18 days as confirmed among the cases reported after the product launch in Japan.)
Reference information	Number of cases (for which a causal relationship between the drug and event is reasonably possible) reported during the previous approximately 3-year period (April 2018 to March 2021) Cases involving rickets: [1] 1 (No patient mortalities) [2] 0 Number of patients using the drug as estimated by the MAH during the previous 1-year period: [1] Magsent Injection 100 mL: Approximately 77 000, Magsent Injection Syringe 40 mL: Approximately 600, Magnesol for Intravenous Injection 20 mL: Approximately 2 300 [2] Approximately 132 600 Japanese market launch: [1] Magsent Injection 100 mL: June 2006, Magsent Injection Syringe 40 mL: November 2011, Magnesol for Intravenous Injection 20 mL: January 1946 [2] January 2006

Case Summary

No.	Patient		Daily dose/ administration duration	Adverse reaction
	Sex/ age	Reason for use (complication)		Clinical course and treatment
1	Female 0 year old	Threatened premature labour (None)	19.2 g 3 days ↓ 16.8-28.8 g 2 days ↓ 21.6 g 14 days ↓ 19.2-24.0 g 9 days ↓ 19.2-28.8 g 9 days	**Craniotabes, rickets, hypermagnesaemia** 62 days before administration: At 25 weeks and 1 day pregnant, the patient's mother had abdominal pain since early morning and was admitted to the hospital due to threatened premature labour. Ritodrine hydrochloride and piperacillin sodium were administered. During hospitalization, the patient's mother had gastralgia and vomited. Day 1 of administration: The patient's mother had uterine tension. Administration of magnesium sulfate hydrate was initiated. Day 37 of Administration (Day of final administration): Administration of magnesium sulfate hydrate was terminated. 2 days after termination (Day of birth): The patient was delivered via cesarean section. Body weight: 1 896 g The patient had extensive craniotabes in the skull at birth, developing rickets and hypermagnesaemia concurrently. 6 days after termination: Systemic X-ray photograph (x-p): There was cupping in the lower end of humerus, bilateral radius, distal end of ulna. Provisional calcification layers were unclear. 14 days after termination: Head CT: The bone cortex was thin, and the intensity of its whiteness was faint. 15 days after termination: Oral administration of alfacalcidol 0.05 μg/kg/day was initiated. 33 days after termination: Upper limb x-p: The cupping in the epiphysis disappeared. Rickets was resolved. 54 days after termination: Head MRI: Craniotabes persisted. 112 days after termination: Sagittal suture was sclerotic on palpation. 168 days after termination: No sagittal suture separation was noted on palpation. Large fontanelle was 1 cm x 1 cm. Craniotabes was resolved.

Laboratory test value

	2 days after termination	5 days after termination	6 days after termination	11 days after termination	17 days after termination	25 days after termination	33 days after termination
Serum Mg (mg/dl)	3.8	3.8	-	-	-	-	-
Serum Ca (mg/dl)	8.3	8.4	-	10.1	10.1	10.2	10.2
25(OH)VitD (ng/dl)	-	-	8	-	-	-	-
intact PTH (pg/ml)	-	-	245	-	-	-	-
ALP (IU/L)	1 900	1 884		2 818	1 978	1 412	1 666

Concomitant drugs: Ritodrine Hydrochloride, piperacillin sodium, thiamine disulfide phosphate/B6/B12, ascorbic acid, famotidine, saccharated ferric oxide, flomoxef sodium

3
Revision of Precautions (No.325)

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 June 21, July 7, 20, 2021.

1 Other antitumor agents
Nivolumab (genetical recombination)

Branded name	Opdivo Intravenous Infusion 20 mg, 100 mg, 120 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)
[Under New instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	<Unresectable advanced or recurrent non-small cell lung cancer> Febrile neutropenia may occur when this drug is co-administered with carboplatin, paclitaxel, and bevacizumab (genetical recombination). The condition of patients should be carefully monitored through methods such as performing blood tests if necessary.
11. ADVERSE REACTIONS **11.1. Clinically Significant Adverse Reactions**	Serious blood disorder Serious blood disorder such as immune thrombocytopenic purpura, haemolytic anaemia, agranulocytosis, or febrile neutropenia may occur. In addition, febrile neutropenia may occur when this drug is co-administered with carboplatin, paclitaxel, and bevacizumab (genetical recombination).

2 Vaccines
Coronavirus modified uridine RNA vaccine (SARS-CoV-2)

Branded name	[1] Comirnaty intramuscular injection (Pfizer Japan Inc.) [2] COVID-19 Vaccine Moderna Intramuscular Injection (Takeda Pharmaceutical Company Limited.)
[Under New instructions]	
8. IMPORTANT PRECAUTIONS (newly added)	Although the causal relationship with this vaccine is unknown, cases of myocarditis and pericarditis have been reported following inoculation with this vaccine. Vaccinees or their caregivers should be instructed in advance to seek medical attention immediately if they experience or notice any symptoms that could suggest myocarditis or pericarditis (such as chest pain, palpitation, oedema, dyspnoea, and tachypnoea).
(newly added)	15. OTHER PRECAUTIONS 15.1 Information Based On Clinical Use Although the causality is unknown, cases of myocarditis and pericarditis have been reported overseas following inoculation with coronavirus modified uridine RNA vaccine (SARS-CoV-2). Reported cases have occurred predominantly in male adolescents and young adults and onset was typically within several days after second vaccination. It has also been reported that in most cases, patients had improvement of symptoms by resting in a supine position in hospital.

3 Antispasmodics
Magnesium sulfate hydrate/glucose (preparations indicated for prophylaxis and treatment of eclampsia in severe hypertensive disorders of pregnancy)

Branded name	Magsent Injection 100 mL, Magsent Injection Syringe 40 mL, Magnesol for Intravenous Injection 20 mL (Aska Pharmaceutical Co., Ltd.)

[Under Old instructions]

Use during Pregnancy, Delivery or Lactation (newly added)	With prolonged administration of this drug during pregnancy, rickets-like bone lesion may be identified in neonates at birth. (The shortest duration of administration with magnesium sulfate hydrate/glucose (injections) to the mother was 18 days as confirmed among the cases reported after the product launch in Japan.)

4 Purgatives and clysters

Magnesium sulfate hydrate (preparations indicated for eclampsia)

Branded name	Magnesium Sulfate Hydrate "NikP" (Nichi-Iko Pharmaceutical Co., Ltd.)

[Under Old instructions]

Use during Pregnancy, Delivery or Lactation	When administering this drug for eclampsia, caution should be exercised for the following: ・With administration of this drug during pregnancy, hypokinesia in foetuses as well as heart failure, hyperkalaemia, or hypocalcaemia in neonates may occur. ・With prolonged administration of this drug during pregnancy, rickets-like bone lesion may be identified in neonates at birth. (The shortest duration of administration with magnesium sulfate hydrate/glucose (injections) to the mother was 18 days as confirmed among the cases reported after the product launch in Japan.)

[Under New instructions]

9. PRECAUTIONS CONCERNING PATIETS WITH SPECIFIC BACKGROUNDS **9.5 Pregnant Women**	With administration of this drug during pregnancy, hypokinesia in foetuses as well as heart failure, hyperkalaemia, or hypocalcaemia in neonates may occur.
(newly added)	With prolonged administration of this drug during pregnancy, rickets-like bone lesion may be identified in neonates at birth. (The shortest duration of administration with magnesium sulfate hydrate/glucose (injections) to the mother was 18 days as confirmed among the cases reported after the product launch in Japan.)

5 Adrenal hormone preparations

[1] Hydrocortisone
[2] Hydrocortisone sodium succinate
[3] Hydrocortisone sodium phosphate

Branded name	[1] Cortril Tablets 10 mg (Pfizer Japan Inc.) [2] Solu-Cortef Injection 100 mg, and the others, Solu-Cortef for Intravenous Use 250 mg, 500 mg, 1000 mg, and the others (Pfizer Japan Inc.) [3] Hydrocortone Injection (Aqueous) 100 mg, 500 mg, and the others (Nichi-Iko Pharmaceutical Co., Ltd.)

[Under Old instructions]

Pediatric Use (newly added)	Occurrence of transient hypertrophic cardiomyopathy in neonates and infants has been reported. Neonates and infants should be carefully monitored by cardiac function tests (such as echocardiogram) as necessary prior to and during administration of this drug.

[Under New instructions]

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS	Occurrence of transient hypertrophic cardiomyopathy in neonates and infants has been reported. Neonates and infants should be carefully monitored by cardiac function tests (such as echocardiogram) as necessary prior to and during administration of this

9.7 Pediatric Use (newly added)	drug.

6 Other agents for uro-genital and anal organ

Magnesium sulfate hydrate/glucose (preparations indicated for inhibition of uterine contractions in threatened premature labour, and prophylaxis and treatment of eclampsia in severe hypertensive disorders of pregnancy)

Branded name	Magnesol for Intravenous Injection 20 mL (Aska Pharmaceutical Co., Ltd.)
[Under New instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.5 Pregnant Women (newly added)**	With prolonged administration of this drug during pregnancy, rickets-like bone lesion may be identified in neonates at birth. (The shortest duration of administration with magnesium sulfate hydrate/glucose (injections) to the mother was 18 days as confirmed among the cases reported after the product launch in Japan.)

7 Agents affecting metabolism, n.e.c. (not elsewhere classified)

[1] Alendronate sodium hydrate
[2] Zoledronic acid hydrate
[3] Pamidronate disodium hydrate
[4] Minodronic acid hydrate
[5] Sodium risedronate hydrate

Branded name	[1] Bonalon Tablet 5 mg, 35 mg, Bonalon Oral Jelly 35mg, Bonalon Bag for I.V. Infusion 900 μg (Teijin Pharma Limited.), Fosamac Tablets 5, 35 mg and the others (MSD K.K.) and the others [2] ZOMETA for i.v. infusion 4 mg/5 mL, 4 mg/100 mL, and the others (Novartis Pharma K.K.), and the others, Reclast for I.V. Injection 5 mg (Asahi Kasei Pharma Corporation) [3] Pamidronate Disodium intravenous for drip use 15 mg "F", 30 mg "F", and the others (Fuji Pharma Co., Ltd.), and the others [4] Bonoteo Tablets 1 mg, 50 mg, and the others (Astellas Pharma Inc.), Recalbon Tablets 1 mg, 50 mg, and the others (ONO Pharmaceutical Co., Ltd.), and the others [5] Actonel Tablets 2.5 mg, 17.5 mg, 75 mg (EA Pharma Co., Ltd.), Benet Tablets 2.5 mg, 17.5 mg, 75 mg and the others (Takeda Pharmaceutical Company Limited.) and the others
[Under Old instructions]	
Important Precautions	Cases of atypical fracture of subtrochanteric femur, proximal femoral shaft, proximal ulnar shaft, or other sites that is associated with no trauma or induced by mild external force have been reported in patients on long-term treatment with bisphosphonates. In some of the cases, prodromal pain in the femur, inguinal, forearm, or other sites started several weeks to months before complete fracture occurred. If such symptoms are observed, X-ray examination, etc. should be performed and appropriate measures should be taken. In addition, bilateral fracture may occur. If unilateral atypical fracture occurs, patients should be carefully monitored by checking symptoms of the sites on the other side and performing an X-ray examination. Characteristic findings noted in X-rays such as a thickened bone lateral cortex have been reported. If such signs are observed, appropriate measures should be taken.
Adverse Reactions	Atypical fracture of subtrochanteric femur, proximal femoral shaft,

Clinically Significant Adverse Reactions	proximal ulnar shaft, or other sites: Atypical fracture of subtrochanteric femur, proximal femoral shaft, proximal ulnar shaft, or other sites may occur. Patients should be carefully monitored and appropriate measures should be taken if any abnormalities are observed, such as discontinuing administration of this drug.
[Under New instructions]	
8. IMPORTANT PRECAUTIONS	Cases of atypical fracture of subtrochanteric femur, proximal femoral shaft, proximal ulnar shaft, or other sites that is associated with no trauma or induced by mild external force have been reported in patients on long-term treatment with bisphosphonates. In some of the cases, prodromal pain in the femur, inguinal, forearm, or other sites started several weeks to months before complete fracture occurred. If such symptoms are observed, X-ray examination, etc. should be performed and appropriate measures should be taken. In addition, bilateral fracture may occur. If unilateral atypical fracture occurs, patients should be carefully monitored by checking symptoms of the sites on the other side and performing an X-ray examination. Characteristic findings noted in X-rays such as a thickened bone lateral cortex have been reported. If such signs are observed, appropriate measures should be taken.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Atypical fracture of subtrochanteric femur, proximal femoral shaft, proximal ulnar shaft, or other sites

8 Agents affecting metabolism, n.e.c. (not elsewhere classified)

[1] Ibandronate sodium hydrate
[2] Etidronate disodium

Branded name	[1] Bonviva Tablets 100 mg, Bonviva Syringes for Intravenous Injection 1 mg (Chugai Pharmaceutical Co., Ltd.) [2] Didronel Tablets 200 (Sumitomo Dainippon Pharma Co., Ltd.)
[Under New instructions]	
8. IMPORTANT PRECAUTIONS	Cases of atypical fracture of subtrochanteric femur, proximal femoral shaft, proximal ulnar shaft, or other sites that is associated with no trauma or induced by mild external force have been reported in patients on long-term treatment with bisphosphonates. In some of the cases, prodromal pain in the femur, inguinal, forearm, or other sites started several weeks to months before complete fracture occurred. If such symptoms are observed, X-ray examination, etc. should be performed and appropriate measures should be taken. In addition, bilateral fracture may occur. If unilateral atypical fracture occurs, patients should be carefully monitored by checking symptoms of the sites on the other side and performing an X-ray examination. Characteristic findings noted in X-rays such as a thickened bone lateral cortex have been reported. If such signs are observed, appropriate measures should be taken.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Atypical fracture of subtrochanteric femur, proximal femoral shaft, proximal ulnar shaft, or other sites

9 Agents affecting metabolism, n.e.c. (not elsewhere classified)

Denosumab (genetical recombination)

Branded name	Ranmark Subcutaneous Injection 120 mg, Pralia Subcutaneous Injection 60 mg Syringe (Daiichi Sankyo Co., Ltd.)
[Under New instructions]	
8. IMPORTANT PRECAUTIONS	Cases of atypical fracture of subtrochanteric femur, proximal femoral shaft, proximal ulnar shaft, or other sites that is associated with no trauma or induced by mild external force have been reported in patients on long-term treatment with this drug or bisphosphonates. In some of the cases, prodromal pain in the femur, inguinal, forearm, or other sites started several weeks to months before complete fracture occurred. If such symptoms are observed following initiation of this drug, X-ray examination, etc. should be performed and appropriate measures should be taken. In addition, bilateral fracture may occur. If unilateral atypical fracture occurs, patients should be carefully monitored by checking symptoms of the sites on the other side and performing an X-ray examination. Characteristic findings noted in X-rays such as a thickened bone lateral cortex have been reported. If such signs are observed, appropriate measures should be taken.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Atypical fracture of subtrochanteric femur, proximal femoral shaft, proximal ulnar shaft, or other sites

10 Agents affecting metabolism, n.e.c. (not elsewhere classified)

Romosozumab (genetical recombination)

Branded name	Evenity Subcutaneous Injection 105 mg Syringes (Amgen K.K.)
[Under New instructions]	
8. IMPORRANT PRECAUTIONS	Cases of atypical fracture of subtrochanteric femur, proximal femoral shaft, proximal ulnar shaft, or other sites that is associated with no trauma or induced by mild external force have been reported in patients on long-term treatment bisphosphonates which have antiresorptive effects. In some of the cases, prodromal pain in the femur, inguinal, forearm, or other sites started several weeks to months before complete fracture occurred. If such symptoms are observed, X-ray examination, etc. should be performed and appropriate measures should be taken. In addition, bilateral fracture may occur. If unilateral atypical fracture occurs, patients should be carefully monitored by checking symptoms of the sites on the other side and performing an X-ray examination. Characteristic findings noted in X-rays such as a thickened bone lateral cortex have been reported. If such signs are observed, appropriate measures should be taken.

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 30 June 2021)
◎: Products for which EPPV was initiated after June 1, 2021

	Nonproprietary name / Branded name	Name of the MAH	Date of EPPV initiate
◎	Osilodrostat phosphate / Isturisa tablets 1 mg, 5 mg[*1]	Recordati Rare Diseases Japan KK	June 30, 2021
◎	Incobotulinumtoxin A / Xeomin 50 units/100 units/200 units for Intramuscular injection[*2]	Teijin Pharma Limited.	June 23, 2021
◎	Pemigatinib / Pemazyre Tablets 4.5 mg[*3]	Incyte Biosciences Japan G.K.	June 1, 2021
◎	Inebilizumab (genetical recombination) / Uplizna for Intravenous Infusion 100 mg[*4]	Mitsubishi Tanabe Pharma Corporation	June 1, 2021
	Upadacitinib hydrate / Rinvoq Tablets 7.5 mg, 15 mg[*5]	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[*6]	Takeda Pharmaceutical Company Limited.	May 24, 2021
	Ofatumumab (genetical recombination) / Kesimpta for s.c. injection 20 mg pen[*7]	Novartis Pharma K.K.	May 24, 2021
	Polatuzumab vedotin (genetical recombination) / Polivy for Intravenous Infusion 140 mg, 30 mg[*8]	Chugai Pharmaceutical Co., Ltd.	May 19, 2021
	Pabinafusp alfa (genetical recombination) / Izcargo for I.V. infusion 10 mg[*9]	JCR Pharmaceuticals Co., Ltd.	May 19, 2021
	Denileukin diftitox (genetical recombination) / Remitoro for Intravenous Drip Infusion 300 μg[*10]	Eisai Co., Ltd.	May 19, 2021
	Diclofenac etalhyaluronate sodium	Seikagaku Corporation	May 19,

Nonproprietary name Branded name	Name of the MAH	Date of EPPV initiate
Joyclu 30 mg intra-articular injection*11		2021
Anhydrous sodium sulfate/potassium sulfate/magnesium sulfate hydrate Sulprep Combination Solution*12	Nihon Pharmaceutical Co., Ltd.	May 19, 2021
Galcanezumab (genetical recombination) Emgality Subcutaneous Injection 120 mg Autoinjectors, Emgality Subcutaneous Injection 120 mg Syringe*13	Eli Lilly Japan K.K.	April 26, 2021
Idursulfase beta (genetical recombination) Hunterase ICV Injection 15 mg*14	Clinigen K.K.	April 26, 2021
Baricitinib Olumiant tablets 2 mg, 4 mg*15	Eli Lilly Japan K.K.	April 23, 2021
Brigatinib Alunbrig Tablets 30 mg, 90 mg*16	Takeda Pharmaceutical Company Limited.	April 23, 2021
Berotralstat hydrochloride Orladeyo Capsules 150 mg*17	OrphanPacific, Inc.	April 23, 2021
Molidustat sodium Musredo tablets 5 mg, 12.5 mg, 25 mg, 75 mg*18	Bayer Yakuhin Ltd.	April 22, 2021
Dimethyl sulfoxide Zymso Intravesical Solution 50%*19	Kyorin Pharmaceutical Co., Ltd.	April 21, 2021
Anamorelin hydrochloride Adlumiz Tablets 50 mg*20	Ono Pharmaceutical Co., Ltd.	April 21, 2021
Acalabrutinib Calquence capsules 100 mg*21	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*22 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
Recombinant adsorbed 9-valent human papillomavirus virus-like particles vaccine (yeast origin) Silgard 9 Aqueous Suspension for Intramuscular Injection Syringes	MSD K.K.	February 24, 2021
Thalidomide*23 Thaled Capsules 25, 50, 100	Fujimoto Pharmaceutical Corporation	February 24, 2021
Coronavirus modified uridine RNA vaccine (SARS-CoV-2) Comirnaty intramuscular injection	Pfizer Japan Inc.	February 16, 2021
Semaglutide (genetical recombination) Rybelsus tablets 3 mg, 7 mg, 14 mg	Novo Nordisk Pharma Ltd.	February 5, 2021
Rivaroxaban*24 Xarelto tablets 15 mg, 10 mg, Xarelto fine granules 15 mg, 10 mg, Xarelto OD tablets	Bayer Yakuhin Ltd.	January 22, 2021

Nonproprietary name / Branded name		Name of the MAH	Date of EPPV initiate
	15 mg, 10 mg		
	Cetuximab sarotalocan sodium (genetical recombination)	Rakuten Medical Japan K.K.	January 1, 2021
	Akalux IV Infusion 250 mg		

*1 Cushing's syndrome (when pituitary surgery is not an option or has not been curative)

*2 Leg spasm

*3 Unresectable biliary tract cancer (BTC) with a fibroblast growth factor receptor 2 (FGFR2) fusion gene, worsening after cancer chemotherapy

*4 Prevention of relapses of neuromyelitis optica spectrum disorder (including neuromyelitis optica)

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

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

*7 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

*8 Relapsed or refractory diffuse large B-cell lymphoma

*9 Mucopolysaccharidosis II

*10 Relapsed or refractory peripheral T-cell lymphoma and relapsed or refractory cutaneous T-cell lymphoma

*11 Osteoarthritis (in the knee and hip joints)

*12 Elimination of intestinal contents as pretreatment prior to colonoscopy

*13 Preventive treatment of migraine

*14 Mucopolysaccharidosis II

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

*16 Unresectable, advanced or recurrent ALK fusion gene-positive non-small cell lung cancer

*17 Suppression of the onset of attacks in acute hereditary angioedema

*18 Nephrogenic anaemia

*19 Improvement of symptoms of interstitial cystitis (Hunner type) (chronic pelvic pain, pressure and discomfort associated with the bladder, lower urinary tract symptoms such as increased urgency or pollakiuria)

*20 Cancer cachexia in malignant tumors of non-small cell lung cancer, gastric cancer, pancreatic cancer, or colorectal cancer

*21 Relapsed or refractory chronic lymphocytic leukaemia (including small lymphocytic lymphoma).

*22 Iron deficiency anaemia

*23 Crow-Fukase (POEMS) syndrome

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

＜Errata, List of Products Subject to Early Post-marketing Phase Vigilance in the English version of PMDSI No.381, 382, 383, 384>

Original

	Lascufloxacin hydrochloride Lasvic Intravenous Drip Infusion Kit 150 mg	Kyorin Pharmaceutical Co., Ltd.	March 1, 2021
	Thalidomide Thaled Capsules 25, 50, 100	Fujimoto Pharmaceutical Corporation	February 24, 2021

Revised

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