Pharmaceuticals and Medical Devices Safety Information

No. 398 February 2023

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Pharmaceuticals and Medical Devices Safety Information

No. 398

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, 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
EPPV	Early Post-marketing Phase Vigilance
FY	Fiscal Year
HES	Hydroxyethylated Starch
JDIIP	Japan Drug Information Institute in Pregnancy
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
PMDA	Pharmaceuticals and Medical Devices Agency
PSD	Pharmaceutical Safety Division
PSEHB	Pharmaceutical Safety and Environmental Health Bureau
SOFA	Sequential [Sepsis-Related] Organ Failure Assessment
TIA	Transient Ischaemic Attack
WG	Working Group

1
Revisions of Precautions for 2 Calcium Channel Blockers (Amlodipine Besilate and Nifedipine)

1. Introduction

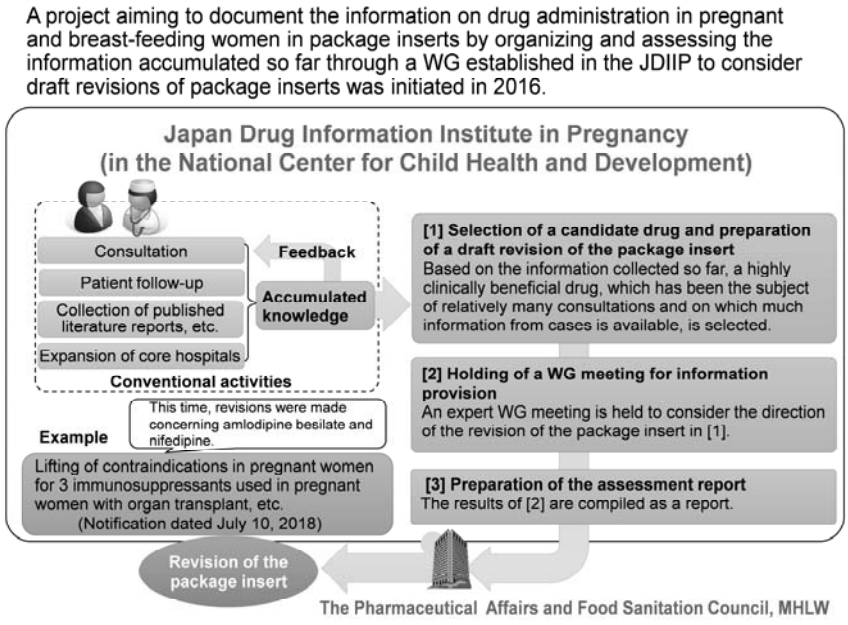
When drugs are used during pregnancy, attention must be paid to the effects on the fetus as well as on the mother. On the other hand, due to difficulties with obtaining safety information on drug use during pregnancy, women who are receiving drug therapy for pre-existing diseases may choose to avoid pregnancy or to discontinue taking prescribed necessary medications, which is an undesirable behavior. In addition, there are cases in which women who used drugs without realizing that they are pregnant become concerned about continuation of the pregnancy.

In 2005, the Japan Drug Information Institute in Pregnancy (hereinafter referred to as “JDIIP”) was established in the National Center for Child Health and Development by the MHLW to collect and assess the latest scientific evidence on the effects of drugs on mothers and fetuses. Based on these data, the JDIIP has provided consultations for women who are pregnant or who wish to become pregnant.

Since 2016, a project aiming to promote the documentation of information on drug use in pregnant women, etc. in package inserts by organizing and assessing the information accumulated so far by the JDIIP has been underway. In this project, a working group (hereinafter referred to as “WG”) composed of experts has been established. The WG selects a candidate drug, organizes and evaluates the information accumulated so far, and compiles the draft revision of the package insert for the drug as a report (Figure 1).

Recently, the language concerning contraindications, etc. for 2 calcium channel blockers (amlodipine besilate and nifedipine) has been revised based on the deliberation in the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (hereinafter referred to as “the Subcommittee on Drug Safety”). This section will introduce the details of the revision.

Figure 1 Proper Use Promotion Project for Pregnant and Breast-feeding Women



2. Details of the review by the WG

Amlodipine besilate was approved for marketing with the indication for hypertension and angina pectoris. Administration of amlodipine besilate to “pregnant women or women who may be pregnant” is contraindicated because prolongation of both the gestational period and the duration of labor was observed from administration to rats in late pregnancy, which was evaluated at the initial application for market approval of the brand name product.

Nifedipine was approved for marketing with the indication for hypertension, angina pectoris, etc. Administration of nifedipine to “pregnant women or women who may be pregnant” has been contraindicated since the market approval of the brand name product, due to teratogenicity observed in toxicity studies using rats, mice, etc. As a result of reviewing the contraindications in 2011, the language was revised to “pregnant women (less than 20 weeks of pregnancy) or women who may be pregnant.”

Recently, given the increasing need in clinical settings for strict blood pressure control during the entire gestational age, the appropriateness of contraindicating amlodipine besilate and nifedipine to pregnant women, etc. in the package inserts was investigated by the WG, taking into account that these drugs have a high prescription rate in clinical settings among calcium channel blockers, which are considered as the first line drugs for hypertension without compelling indications. A report was compiled stating that pregnant women or women who may be pregnant may be deleted from the CONTRAINDICATIONS sections in the package inserts for both drugs and that it is appropriate to add precautions that these drugs should be administered to pregnant women or women who may be pregnant only if the potential therapeutic benefits are considered to outweigh the potential risks.

3. Deliberation by the Subcommittee on Drug Safety

Based on the deliberation by the WG and the investigation results by the PMDA in response to the WG report, the 19th fiscal year (FY) 2022 Subcommittee on the Drug Safety held on November 22, 2022, concluded that the package inserts of amlodipine besilate and nifedipine may be revised as follows:

- For amlodipine besilate, “pregnant women or women who may be pregnant” may be deleted from the CONTRAINDICATIONS section in the package insert, and this drug may be administered to pregnant women or women who may be pregnant if the potential therapeutic benefits are considered to outweigh the potential risks.
- For nifedipine, “pregnant women (less than 20 weeks of pregnancy) or women who may be pregnant” may be deleted from the CONTRAINDICATIONS section in the package insert, and this drug may be administered to pregnant women or women who may be pregnant if the potential therapeutic benefits are considered to outweigh the potential risks.

4. Closing remark

The present revisions of the package inserts are not intended to allow the unconditional use of amlodipine besilate or nifedipine in “pregnant women or women who may be pregnant” or “pregnant women (less than 20 weeks of pregnancy) or women who may be pregnant,” respectively, which has previously been uniformly prohibited. Physicians prescribing these drugs must carefully decide whether to administer these drugs or not while closely monitoring the condition of the patient’s disease and weighing the expected therapeutic benefits against the possible risks associated with the treatment. Healthcare professionals are requested to understand the purpose of the present revisions, and continued cooperation for proper use of this drug would be appreciated.

5. [References]

·Materials 1-1 to 1-3 of the 19th FY 2022 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on November 22, 2022)

https://www.mhlw.go.jp/stf/newpage_29305.html (only in Japanese)

·Revision of Precautions (PSEHB/PSD Notification No. 1205-1 dated December 5, 2022)
https://www.mhlw.go.jp/content/11120000/001019980.pdf (in Japanese)
English translation by the PMDA (December 5, 2022)
https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0010.html

2
Revision of Precautions for Hydroxyethylated Starch

1. Introduction

Hydroxyethylated starch 70000 (brand name: Salinhes fluid solution 6%), hydroxyethylated starch 70000/sodium chloride/potassium chloride/calcium chloride hydrate/sodium lactate (brand name: Hespander fluid solution) (hereinafter referred to as “HES70”), and hydroxyethylated starch 130000 (brand name: Voluven 6% solution for infusion) (hereinafter referred to as “HES130”) are blood substitutes that increase the plasma volume based on colloid osmotic effects. HES70 was approved for marketing in Japan for the indication of “excessive bleeding in various therapeutic areas” and “haemodilution in extracorporeal circulation,” and HES130 for the indication of “maintenance of circulating blood volume.”

Recently, the revisions of Precautions have been made including the addition of "patients with severe sepsis" in the contraindication of HES70 and HES130 (hereinafter referred to as "HES preparations") based on the deliberation in the 22nd FY 2022 Subcommittee on Drug Safety held on Dec 27, 2022. This section will introduce the details of the revision.

2. Background

The clinical studies have shown that HES preparations increased mortality when administered to patients with sepsis and critically ill patients, and measures were taken in 2013 in the EU including contraindication of HES preparations in patients such as those with sepsis and those admitted to the intensive care unit, and a revision was made to the package insert in Japan as follows:

- For HES130, it was considered appropriate to retain the possibility of its use in relative decreased blood volume during the management of critically ill patients including those with severe sepsis under unavoidable circumstances, and a revision was made including the addition of the statement that “HES preparations should be administered only if the therapeutic benefits outweigh the risks because it may exacerbate the condition of patients when used in relative decreased blood volume for the management of critically ill patients including those with severe sepsis.” to the WARNINGS section.
- The indication for HES70 was “excessive bleeding in various therapeutic areas” and “haemodilution in extracorporeal circulation,” and it was not expected to be used in patients with relative decreased blood volume without bleeding. Based on these, a revision was made including the addition of the statement that “HES70 should not be used in relative decreased blood volume during the management of critically ill patients including those with severe sepsis.” to the Precautions for Indications section.

In the EU, the European Medicines Agency (EMA) recommended the suspension of the marketing authorization in February 2022 with reasons such as continued clinical use of the HES preparations in the population of patients who are contraindicated for the preparations, and the suspension of the marketing authorization was decided by the European Commission (EC) in May 2022. In response to this, it was decided to review the necessity of revising precautions based on the status of use in Japan and the scientific knowledge regarding the safety of HES preparations after the measures taken in 2013.

3. Investigation results

The investigation results by the PMDA are described as follows.

- The major patient population in clinical studies currently showing the risk with the administration of HES preparations is patients with severe sepsis, and the risk with HES preparations in other patients with sepsis is unknown.
- Both the drug use-results survey of HES130 and the spontaneous reports on HES70 and HES130 revealed no use of HES preparations in patients with sepsis, and no literature reports on the use of HES preparations in patients with sepsis were identified in Japan.
- The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020 state as follows, “Sepsis is a pathological condition showing a great diversity depending on its cause, severity, stage, comorbidities, complications, etc. In clinical settings, clinician’s decisions must be made on an individual patient basis, taking into account not only the patient's condition, but also the availability and resources of healthcare professionals and the wishes of the patient and family or caregivers.” It is therefore considered that the severity of sepsis should be judged appropriately in clinical settings not only by the sequential (sepsis-related) organ failure assessment (SOFA) score and the quick SOFA (qSOFA) score, which are recommended in the current guidelines.
- The major published literature on the risk with the administration of HES preparations to patients with sepsis includes the overseas clinical studies which are cited in the current package inserts, and 3 publications reporting the effect of HES on the mortality risk in patients with sepsis published after the measures taken in the EU in 2013. Of the latter 3 publications, 2 are systematic reviews and 1 is a study in patients with shock in which the definition of sepsis was not clearly described. It is considered that overseas clinical studies which are cited in the current package inserts may be most helpful in identifying patients with severe sepsis in clinical settings.

Based on the above, the report stating the necessity of the following revisions for "Precautions" of HES preparations was prepared by the PMDA.

- Regarding sepsis, based on “the mortality risk reported in the literature after the review in 2013,” "patients with severe sepsis" should be added to the CONTRAINDICATIONS section and “patients with sepsis (excluding those with severe sepsis)” should be added to the Careful Administration section in the package insert of HES70 and HES130.
- As the reference information to identify "patients with severe sepsis” in clinical settings, to whom administration of HES preparations is to be contraindicated, the definition of the target patient populations, which was used in the clinical studies evaluating the risk with the administration of HES preparations whose results are currently described in the package insert, will be provided in the package insert.

4. Deliberation by the Subcommittee on Drug Safety

Based on the above investigation results, it was concluded that revision of “Precautions” for HES preparations as proposed by the PMDA was necessary.

5. Closing remark

Other than "patients with severe sepsis," which was added in the contraindication this time, there are some patients who have been listed as a contraindication for HES preparations since before this revision. In addition, the precautionary statement has been added that "HES preparations should be administered only if the therapeutic benefits outweigh the risks because it may exacerbate the condition of patients when used in relative decreased blood volume for the management of critically ill patients." for HES130, and that "HES preparations should not be used for relative decreased blood volume during the management of critically ill patients." for HES70.

Healthcare professionals are requested to understand the gist of the revision this time and to carefully check the electronic package inserts for a careful decision on the use of hydroxyethylated starch. Continued cooperation by healthcare professionals for proper use of these drugs would be appreciated.

[Reference]

- Materials 3-1 to 3-2 of the 22nd FY 2022 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (held on December 27, 2022)
  https://www.mhlw.go.jp/stf/newpage_29975.html (only in Japanese)
- Revisions of Precautions (PSEHB/PSD 0112 No.1 dated January 12, 2023)
  https://www.mhlw.go.jp/content/11120000/001036270.pdf (in Japanese)
  English translation by the PMDA (January 12, 2023)
  https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0010.html
- Proper use of hydroxyethylated starch-containing preparations (HES preparations) (Fresenius Kabi Japan K.K.)
  https://www.pmda.go.jp/files/000249767.pdf (only in Japanese)

3
Revision of the Package Insert for Hypothyroidism and Request for Adverse Drug Reaction Reports, etc.

1. Revision of the package insert for hypothyroidism

Roxadustat (hereinafter referred to as “this drug”) is a drug indicated for "nephrogenic anaemia" and the marketing was initiated in November 2019. Precaution for hypothyroidism has been in place in the "Other Adverse Reactions" section of the package insert for this drug since the time of approval because its occurrence had been observed in clinical studies conducted in Japan evaluated at the time of the review of marketing authorization.

Recently, several cases of serious hypothyroidism in which a causal relationship with this drug was reasonably possible have been reported in Japan. All of them were central hypothyroidism caused by hypofunction of the pituitary or hypothalamus. For these reasons, the MHLW considered it necessary to add a cautionary statement for "central hypothyroidism" in the "8. IMPORTANT PRECAUTIONS" and "11.1 Clinically Significant Adverse Reactions" sections, and instructed the revision of the Precautions on November 16, 2022.

2. Hypothyroidism

Hypothyroidism is a disease with clinical symptoms based on energy hypometabolism due to low blood thyroid hormone levels and can be broadly divided into the following two types. When it occurs as an adverse drug reaction of a drug with any of the laboratory findings or clinical symptoms listed in the table below, the causative drug is discontinued or supplementation of thyroid hormone preparations is performed after careful consideration of the therapeutic effect of the causative drug and the adverse effects of discontinuation.

(1) Primary hypothyroidism
It occurs when a drug inhibits the synthesis/secretion of thyroid hormones, either directly or through the immune system.

(2) Central hypothyroidism
It occurs when a drug acts on the hypothalamus/pituitary and suppresses TSH secretion.

Table Laboratory findings and clinical symptoms of hypothyroidism

		Primary hypothyroidism	Central hypothyroidism
Laboratory findings	Blood free T4 concentration	Low	
	Blood TSH concentration	High	Low or within normal range
Clinical symptoms		Symptoms based on energy hypometabolism such as lack of motivation, fatiguability, eyelid oedema, cold intolerance, increased weight, bradykinesia, lethargy, hypomnesia, constipation, hoarseness	

3. Request for cooperation in reporting adverse drug reactions, etc.

Several cases have been reported in which supplementation of thyroid hormone preparations was discontinued or reduced in patients who had been administered with thyroid hormone preparations prior to the administration of this drug, despite the fact that both TSH and free T4 were low and central hypothyroidism developed, and the condition seemed to have worsened.

Healthcare professionals are requested to take into consideration the possibility of central

hypothyroidism when assessing thyroid gland function during administration of drugs (including preparations for which "hypothyroidism" has been alerted) and to check not only TSH but also other thyroid function test values before taking measures. When such an event occurs, it would be appreciated if the information such as test values and clinical courses, as well as whether the event is primary or central could be reported to the PMDA or provided to the MAHs of the drug concerned.

[References]

- Revision of Precautions (PSEHB/PSD Notification No. 1116-1 dated November 16, 2022)
  https://www.mhlw.go.jp/content/11120000/001013423.pdf (in Japanese)
  English translation by the PMDA (November 16, 2022)
  https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0010.html
- Guidelines for the diagnosis of thyroid disease 2021, Japan Thyroid Association
  https://www.japanthyroid.jp/doctor/guideline/japanese.html#teika (only in Japanese)
- The Manuals for Management of Various Serious Adverse Drug Reactions Hypothyroidism: MHLW
  https://www.mhlw.go.jp/topics/2006/11/dl/tp1122-1d37.pdf (only in Japanese)

4

Important Safety Information

Regarding the revision of the Precautions of package inserts of drugs in accordance with the Notification dated January 17, 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 acetaminophen ([1] acetaminophen (oral dosage form), [2] acetaminophen (suppositories), [3] acetaminophen (injections), [4] pyrazolone-based antipyretics, analgesics and anti-inflammatory combination drug (4), [5] tramadol hydrochloride/acetaminophen, [6] diprophylline/dihydrocodeine phosphate/dl-methylephedrine hydrochloride/diphenhydramine salicylate/acetaminophen/ bromovalerylurea, [7] non-pyrine common cold medicine (2), [8] non-pyrine common cold medicine (3), [9] non-pyrine common cold medicine (4), [10] non-pyrine common cold medicine (5), [11] acetaminophen (oral dosage form, suppositories) (OTC drugs))

Brand name (name of company)	[1] Calonal powder, Calonal tablets 200, 300, 500, Calonal Fine Gran. 20%, 50%, Calonal Syrup 2%, and the others (AYUMI Pharmaceutical Corporation, and the others) [2] Alpiny Suppositories 50, 100, 200, and the others (Hisamitsu Pharmaceutical Co., Inc., and the others) [3] acelio Bag for Intravenous Injection 1000 mg (Terumo Corporation) [4] SG Combination Granules (Shionogi Pharma Co., Ltd.) [5] Tramcet Combination Tablets, and the others (Janssen Pharmaceutical K.K., and the others) [6] Coughcode-N Combination Tablets (Mylan EPD G.K.) [7] Pelex combination granule (TAIHO Pharmaceutical Co., Ltd.) [8] Pediatric Pelex combination granule (TAIHO Pharmaceutical Co., Ltd.) [9] PL Combination Granules, and the others (Shionogi Pharma Co., Ltd., and the others) [10] PL Combination Granules for Infants (Shionogi Pharma Co., Ltd.) [11] Tylenol A (TOA Pharmaceuticals Co., Ltd.), Kio Fever (Hiya Pharmaceutical Co., Ltd.), and the other OTC drugs
Therapeutic category	Antipyretics, analgesics and anti-inflammatory agents, agents used for common cold, antitussives, cold medicines, antipyretics and analgesics
Indications	[1] <Powder, tablets, granules> · Analgesia for the following diseases and symptoms: Headache, ear pain, symptomatic neuralgia, lumbago, myalgia, bruising pain, sprain pain, painful menses, postpartum pain, pain

	due to cancer, toothache, pain after dental treatment, osteoarthritis · Antipyresis and analgesia for the following diseases: Acute upper respiratory inflammation (including acute upper respiratory inflammation associated with acute bronchitis) · Antipyresis and analgesia in the field of pediatrics <Syrup> Antipyresis and analgesia in the field of pediatrics [2] Antipyresis and analgesia in the field of pediatrics [3] Pain and pyrexia when administration of oral preparations and suppositories is difficult [4] Antipyresis for common cold, ear pain, sore throat, painful menses, headache, toothache, symptomatic neuralgia, traumatic pain [5] Analgesia for the following diseases that cannot be managed by treatment with non-opioid analgesics: · Non-cancerous chronic pain · Pain after tooth extraction [6] Antitussive, pain relief, and antipyresis in common cold syndrome Antitussive in bronchitis [7] Improvement and alleviation in the following symptoms accompanying common cold or upper respiratory inflammation: Nasal discharge, nasal congestion, pharyngeal/laryngeal pain, cough, sputum, headache, arthralgia, myalgia, pyrexia [8] Improvement and alleviation in the following symptoms accompanying common cold or upper respiratory inflammation: Nasal discharge, nasal congestion, pharyngeal/laryngeal pain, cough, sputum, headache, arthralgia, myalgia, pyrexia [9] Improvement and alleviation in the following symptoms accompanying common cold or upper respiratory inflammation: Nasal discharge, nasal congestion, pharyngeal/laryngeal pain, headache, arthralgia, myalgia, pyrexia [10] Improvement and alleviation in the following symptoms accompanying common cold or upper respiratory inflammation: Nasal discharge, nasal congestion, pharyngeal/laryngeal pain, headache, arthralgia, myalgia, pyrexia [11] Oral dosage form: · Analgesia for headache, painful menses (period pains), toothache, pain after tooth extraction, sore throat, ear pain, arthralgia, neuralgia, low back pain, myalgia, pain associated with shoulder muscle stiffness, bruising pain, fracture pain, sprain pain, and traumatic pain · Antipyresis of chills or pyrexia Suppositories: Temporal antipyresis of pyrexia in children

PRECAUTIONS (revised language is underlined)

[1] – [10]

[Under old instructions]

Adverse Reactions	Drug-induced hypersensitivity syndrome:
Clinically Significant	Initial symptoms of rash and pyrexia, followed by serious delayed
Adverse Reactions	symptoms of hypersensitivity accompanied by hepatic impairment,
(newly added)	swollen lymph nodes, increased white blood cell, eosinophilia, and

appearance of atypical lymphocytes may occur. Symptoms are often accompanied by virus reactivation, such as human herpes virus type 6 (HHV-6). Caution is required for recurrence or prolongation of rash, pyrexia, and hepatic impairment, etc. that may occur even after discontinuation of administration.

[Under new instructions]

11. ADVERSE REACTIONS

11.1 Clinically Significant Adverse Reactions (newly added)

Drug-induced hypersensitivity syndrome
Initial symptoms of rash and pyrexia, followed by serious delayed symptoms of hypersensitivity accompanied by hepatic impairment, swollen lymph nodes, increased white blood cell, eosinophilia, and appearance of atypical lymphocytes may occur. Symptoms are often accompanied by virus reactivation, such as human herpes virus type 6 (HHV-6). Caution is required for recurrence or prolongation of rash, pyrexia, and hepatic impairment, etc. that may occur even after discontinuation of administration.

[11] Consultation (newly added)

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.

Name of symptoms	Symptoms
Drug-induced hypersensitivity syndrome	Some symptoms, such as redness over large part of the skin, generalised exanthema, pyrexia, malaise, swollen lymph nodes (neck, armpits, groin, etc.) may occur.

*The highlighted part should be listed only in the preparations containing ibuprofen among antipyretics and analgesics.

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 drug-induced hypersensitivity syndrome:
[1] to [3] 6 (No patient mortalities)
No cases have been reported to date for [4] to [10].
[11] 1 (No patient mortalities)
Number of patients using the drug as estimated by the MAH during the previous 1-year period: Because there are many preparations, the descriptions are omitted.
Japanese market launch: Please refer to the electronic package insert for each drug.

Case summary

No.	Patient		Daily dose/ administration duration	Adverse reaction	
	Sex/ age	Reason for use (complication)		Clinical course and treatment	
1	Male 40s	Fatigue, pyrexia (fulminant type 1 diabetes mellitus)	Unknown For 3 days ↓ Discontinuation of administration	**Drug-induced hypersensitivity syndrome**	
				Day 1 of administration	Administration of multiple drugs including preparations containing acetaminophen was initiated due to pyrexia and fatigue.
				Day 4 of administration (Day of discontinuation)	The patient developed red rashes on the extremities and the trunk. Administration of preparations containing acetaminophen was discontinued because drug eruption was suspected. Treatment with prednisolone 20 mg/day was initiated.
				4 days after discontinuation	The patient developed erythematous lesion over his entire skin. His body temperature rose to over 40°C, and swollen cervical lymph nodes were noted. White blood cell (WBC) count was 16 300/μL with 12.9% eosinophils, 6% atypical lymphocytes. ALT was 820 IU/L, AST was 297 IU/L, IgG was 430 mg/dL, and RegiSCAR score used for the diagnosis of drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) was 7. Oral prednisolone 1 mg/kg/day was administered followed by methylprednisolone pulse therapy 1 g/day for 3 days. The drug-induced lymphocyte stimulation test with preparations containing acetaminophen was positive. He had concurrent fulminant type 1 diabetes mellitus. Methylprednisolone pulse therapy 1 g/day was resumed for 3 days. Treatment with ciclosporin was also attempted. However, there was no improvement. At the time of visiting another hospital, previous cytomegalovirus infection was positive. Cytomegalovirus antibody changed to immunoglobulin (Ig) M dominant within 3 months after the initiation of prednisolone therapy.
				12 months after discontinuation	The patient was under medical treatment with prednisolone 20 mg and ciclosporin 50 mg. Diffuse pruritic erythematous plaques were noted on the patient's entire body. WBC count was 9 490 /μL with 0.1% eosinophils and no atypical lymphocytes. ALT was 46 IU/L, AST was 21 IU/L, IgG was 995 mg/dL, and LDH was 611 IU/L.
				15 months after discontinuation	Administration of ciclosporin was discontinued. The dose of prednisolone was gradually tapered. During prednisolone therapy, severe itching persisted despite treatment with antihistamines and corticosteroid. After tapering prednisolone to 7.5 mg, the skin lesion improved.
				19 months after discontinuation	The patient developed infection with herpes zoster virus.
				2 years after discontinuation	Administration of prednisolone was discontinued.

Laboratory test value

	4 days after discontinuation	12 months after discontinuation
ALT (IU/L)	820	46
AST (IU/L)	297	21
LDH (U/L)	-	611
IgG (mg/dL)	430	995
WBC (/μL)	16 300	9 490
Eosinophils (%)	12.9	0.1
Atypical lymphocytes (%)	6	not detected

Concomitant drugs: Clarithromycin, lysozyme hydrochloride, L-carbocisteine, maoto extract
Note: Literature report (Higashi Y, et al. J Dermatol. 2020 47(2):174-177.)

2 Preparations containing clopidogrel sulfate
[1] Clopidogrel sulfate
[2] Clopidogrel sulfate/aspirin

Brand name (name of company)	[1] Plavix Tablets 25 mg, 75 mg (Sanofi K.K.), and the others [2] ComPlavin Combination Tablets (Sanofi K.K.), and the others
Therapeutic category	Other agents relating to blood and body fluids
Indications	[1] Clopidogrel sulfate ·Prevention of recurrence following ischaemic cerebrovascular disorder (except cardioembolic stroke) ·The following ischaemic heart diseases for which percutaneous coronary intervention (PCI) is indicated: Acute coronary syndromes (unstable angina, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction) Stable angina pectoris, old myocardial infarction ·Prevention of thrombus/embolus formation in peripheral arterial disease [2] Clopidogrel sulfate/aspirin The following ischaemic heart diseases for which percutaneous coronary intervention (PCI) is indicated: ·Acute coronary syndromes (unstable angina, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction) ·Stable angina pectoris, old myocardial infarction

PRECAUTIONS (revised language is underlined)

[Under old instructions]	
Adverse reactions Clinically Significant Adverse Reactions (newly added)	Insulin autoimmune syndrome: Severe hypoglycaemia may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures, such as discontinuation of administration, should be taken.
Other Precautions	It has been reported that the occurrence of insulin autoimmune syndrome is strongly correlated with HLA-DR4 (DRB1*0406). In addition, it has been reported that patients with HLA DR4 subtype are more frequent in the Japanese population.
[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Insulin autoimmune syndrome Severe hypoglycaemia may occur.
15. OTHER PRECAUTIONS **15.1 Information Based on Clinical Uses**	It has been reported that the occurrence of insulin autoimmune syndrome is strongly correlated with HLA-DR4 (DRB1*0406). In addition, it has been reported that patients with HLA DR4 subtype are more frequent in the Japanese population.
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 insulin autoimmune syndrome: [1] 8 (No patient mortalities) [2] No cases have been reported to date. Number of patients using the drug as estimated by the MAH during

the previous 1-year period:
[1] Tablets 25 mg: Approximately 27 900, Tablets 75 mg: Approximately 175 700
[2] Approximately 17 300
Japanese market launch:
[1] May 2006
[2] December 2013

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>Transient ischaemic attack
(none)</td><td>75 mg
5 months</td><td>Insulin autoimmune syndrome
Before start of administration: (Date unknown)
The patient was hospitalized due to transient ischaemic attack (TIA). He had no history of diabetes mellitus.
Day 1 of administration
Administration of clopidogrel sulfate was started for the treatment of TIA.
6 months after administration (Day of transfer to a hospital)
The patient was transferred to a nearby hospital because he had a light-headed feeling upon waking and disturbed consciousness. A markedly low blood glucose level of 33 mg/dL was observed when he was transferred. Blood test results were 14 mg/dL for fasting blood glucose level and 127.5 μIU/mL for insulin concentration on the next day, indicating excessive secretion of insulin. The anti-insulin antibody concentration was ≥5 000 nU/mL and the anti-insulin antibody binding was 89.8%, both showing a markedly high value.
In addition, a Scatchard analysis revealed the characteristics of a high binding ability and low affinity. Thus he was diagnosed with low blood glucose due to insulin autoimmune syndrome.
7 days after transfer to a hospital
After discontinuation of clopidogrel sulfate (date unknown), improving tendencies in blood glucose levels and antibody concentrations were observed.</td></tr>
<tr><td></td><td colspan="4">Laboratory test value
<table><tr><th></th><th>At the onset of adverse reaction (6 months after administration)</th></tr><tr><td>Blood glucose level (mg/dL)</td><td>33</td></tr><tr><td>Fasting blood glucose level (mg/dL)</td><td>14</td></tr><tr><td>Insulin (μIU/mL)</td><td>127.5</td></tr><tr><td>Anti-insulin antibody concentration (nU/mL)</td><td>≥ 5 000</td></tr><tr><td>Anti-insulin antibody binding rate (%)</td><td>89.8</td></tr></table></td></tr>
<tr><td></td><td colspan="4">Concomitant drugs: Unknown</td></tr>
</table>

3 Oral live attenuated human rotavirus vaccine

Brand name (name of company)	Rotarix oral liquid formulation (GlaxoSmithKline K.K.)
Therapeutic category	Vaccines
Indications	Prevention of gastroenteritis caused by rotavirus

PRECAUTIONS (revised language is underlined)

[Under new instructions]

11. ADVERSE REACTIONS (newly added)	11.1 Clinically Significant Adverse Reactions Anaphylaxis
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 anaphylaxis: 2 (No patient mortalities) Number of patients using the drug as estimated by the MAH during the previous 1-year period: Approximately 538 560 Japanese market launch: November 2011

Case summary

<table>
<tr><th rowspan="2">No.</th><th colspan="2">Vaccine recipient</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>Female
Under 1 year old</td><td>Prevention of gastroenteritis caused by rotavirus
(none)</td><td>1.5 mL
(2 oral inoculations at least 4 weeks apart)</td><td>Anaphylactic reaction
Body temperature before vaccination: 37.3 degrees
There were no notes on the prevaccination screening questionnaire (underlying diseases, allergies, vaccinations or illnesses within the last month, drugs being taken, history of past adverse drug reactions, developmental status, etc.).
Day of vaccination: After inoculation with the suspected concomitant vaccines, the patient began to develop a body rash and wheezing during the first administration of this vaccine. She became somewhat listless, and wheezing was heard on auscultation. SpO_2 was unstable, ranging from 94-97%. The symptoms were considered to be anaphylaxis, and she was transferred to the hospital.
She visited the emergency department. On examination at the time of visit, her symptoms had peaked, and the skin rash had almost disappeared. She was observed for approximately 2 hours, and she was sent home after confirming that there was no recurrence.</td></tr>
<tr><td></td><td colspan="4">Laboratory test value
<table><tr><th></th><th>Post inoculation</th></tr><tr><td>Oxygen saturation (%)</td><td>94 - 97</td></tr></table></td></tr>
<tr><td></td><td colspan="4">Suspected concomitant vaccines: Haemophilus influenzae type b conjugate vaccine (tetanus toxoid conjugate), pneumococcal 13-valent conjugate vaccine (diphtheria CRM197 protein), recombinant adsorbed hepatitis B vaccine (prepared from yeast)
Concomitant drugs: None</td></tr>
</table>

5
Revision of Precautions (No.338)

This section presents details of revisions to the Precautions and brand names of drugs that have been revised in accordance with the Notifications dated December 5, 2022, January 12, January 17, 2023.

1 Vasodilators
Amlodipine besilate

Brand name	Norvasc Tablets 2.5 mg, 5 mg, 10 mg, Norvasc OD Tablets 2.5 mg, 5 mg, 10 mg (Viatris Pharmaceuticals Japan Inc.), and the others
[Under old instructions]	
Contraindications	(deleted)
Use during Pregnancy, Delivery or Lactation	Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks. [Prolongation of both the gestational period and the duration of labor was observed when this drug was administered to rats in late pregnancy.]
[Under new instructions]	
2. CONTRAINDICATIONS	(deleted)
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.5 Pregnant Women	Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are considered to outweigh the potential risks. Prolongation of both the gestational period and the duration of labor was observed when this drug was administered to rats in late pregnancy.

2 Vasodilators
Nifedipine

Brand name	Adalat-CR10, CR20, CR40, Adalat-L10, L20 (Bayer Yakuhin Ltd.), and the others
[Under old instructions]	
Contraindications	(deleted)
Use during Pregnancy, Delivery, or Lactation	(deleted) This drug should be administered to pregnant women or women who may be pregnant only if the potential therapeutic benefits are considered to outweigh the potential risks. [Teratogenicity and foetal toxicity have been reported in animal studies.] Prior to administration, the latest relevant guidelines, etc. should be referred to. In order to avoid acute and excessive decrease in blood pressure, basically, long-acting preparations of this drug should be administered with a full understanding of the characteristics of each preparation. In addition, mothers, foetuses, and neonates should be carefully monitored. If any abnormalities such as excessive decrease in blood pressure and decrease in foetal placental circulation are observed, appropriate measures should be taken. [In cases of administration to pregnant women, excessive decrease in blood pressure, etc. have been reported.]
[Under new instructions]	
2. CONTRAINDICATIONS	(deleted)

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS	(deleted)
9.5 Pregnant Women	This drug should be administered to pregnant women or women who may be pregnant only if the potential therapeutic benefits are considered to outweigh the potential risks. Teratogenicity and foetal toxicity have been reported in animal studies. Prior to administration, the latest relevant guidelines, etc. should be referred to. In order to avoid acute and excessive decrease in blood pressure, basically, long-acting preparations of this drug should be administered with a full understanding of the characteristics of each preparation. In addition, mothers, foetuses, and neonates should be carefully monitored. If any abnormalities such as excessive decrease in blood pressure and decrease in foetal placental circulation are observed, appropriate measures should be taken. In cases of administration to pregnant women, excessive decrease in blood pressure, etc. have been reported.

3 Blood substitutes

[1] Hydroxyethylated starch 70000
[2] Hydroxyethylated starch 70000/sodium chloride/potassium chloride/calcium chloride hydrate/sodium lactate

Brand name	[1] Salinhes fluid solution 6% (Fresenius Kabi Japan K.K.) [2] Hespander fluid solution (Fresenius Kabi Japan K.K.)
[Under old instructions]	
Contraindications (newly added)	Patients with severe sepsis [The condition of patients may be exacerbated.]
Precautions for Indications	This drug should not be used for relative decreased blood volume during the management of critically ill patients.
Careful Administration (newly added)	Patients with sepsis (excluding patients with severe sepsis) [If the disease becomes severe, the condition of patients may be exacerbated.]
Other Precautions	In overseas clinical studies, it has been reported that the use of HES preparations note) in patients with severe sepsis (having infection, meeting the systemic inflammatory response syndrome (SIRS) criteria, and having at least one organ dysfunction [= SOFA score of 3 or more]) was associated with a higher mortality risk at 90 days after administration and a higher percentage of patients requiring renal replacement therapy, as compared with the use of acetated Ringer's solution. It has been also reported that the use of HES preparations in patients admitted to the ICU including patients with sepsis was associated with a higher percentage of patients requiring renal replacement therapy, as compared with the use of saline, although the mortality risk up to 90 days after administration did not increase. note) HES preparations with different molecular weights or degrees of substitution, etc. from those of this drug

4 Blood substitutes

Hydroxyethylated starch 130000

Brand name	Voluven 6% solution for infusion (Fresenius Kabi Japan K.K.)
[Under old instructions]	
Warning	The condition of patients may be exacerbated when this drug is used in relative decreased blood volume during the management of critically ill patients. This drug should be administered only if the therapeutic benefits outweigh the risks.
Contraindications	Patients with severe sepsis [The condition of patients may be

(newly added)	exacerbated.]
Careful Administration (newly added)	Patients with sepsis (excluding patients with severe sepsis) [If the disease becomes severe, the condition of patients may be exacerbated.]
Other Precautions	In overseas clinical studies, it has been reported that the use of HES preparations in patients with severe sepsis (having infection, meeting the systemic inflammatory response syndrome (SIRS) criteria, and having at least one organ dysfunction [= SOFA score of 3 or more]) was associated with a higher mortality risk at 90 days after administration and a higher percentage of patients requiring renal replacement therapy, as compared with the use of acetated Ringer's solution. It has been also reported that the use of HES preparations in patients admitted to the ICU including patients with sepsis was associated with a higher percentage of patients requiring renal replacement therapy, as compared with the use of saline, although the mortality risk up to 90 days after administration did not increase.
[Under new instructions]	
1. WARNINGS	The condition of patients may be exacerbated when this drug is used in relative decreased blood volume during the management of critically ill patients. This drug should be administered only if the therapeutic benefits outweigh the risks.
2. CONTRAINDICATIONS (newly added)	Patients with severe sepsis [The condition of patients may be exacerbated.]
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.1 Patients with Complication or History of Diseases, etc. (newly added)	Patients with sepsis (excluding patients with severe sepsis) If the disease becomes severe, the condition of patients may be exacerbated.
15. OTHER PRECAUTIONS 15.1 Information Based on Clinical Uses	In overseas clinical studies, it has been reported that the use of HES preparations in patients with severe sepsis (having infection, meeting the systemic inflammatory response syndrome (SIRS) criteria, and having at least one organ dysfunction [= SOFA score of 3 or more]) was associated with a higher mortality risk at 90 days after administration and a higher percentage of patients requiring renal replacement therapy, as compared with the use of acetated Ringer's solution. It has been also reported that the use of HES preparations in patients admitted to the ICU including patients with sepsis was associated with a higher percentage of patients requiring renal replacement therapy, as compared with the use of saline, although the mortality risk up to 90 days after administration did not increase.

5 Antipyretics, analgesics and anti-inflammatory agents, agents used for common cold, antitussives

[1] Acetaminophen (oral dosage form, suppositories)
[2] Tramadol hydrochloride/acetaminophen
[3] Salicylamide/acetaminophen/anhydrous caffeine/chlorpheniramine maleate

[4] Salicylamide/acetaminophen/anhydrous caffeine/promethazine methylenedisalicylate
[5] Diprophylline/dihydrocodeine phosphate/dl−methylephedrine hydrochloride/diphenhydramine salicylate/ acetaminophen/bromovalerylurea

Brand name	[1] Calonal powder, Calonal tablets 200, 300, 500, Calonal Fine Gran. 20%, 50%, Calonal Syrup 2%, and the others (AYUMI Pharmaceutical Corporation and the others), Alpiny Suppositories 50, 100, 200, and the others (Hisamitsu Pharmaceutical Co., Inc. and the others), Anhiba pediatric suppository 50 mg, 100 mg, 200 mg, and the others (Mylan EPD G.K. and the others), Calonal Supp. 50 for Pediatric, Calonal Supp. 100, 200, 400, and the others (AYUMI Pharmaceutical Corporation and the others) [2] Tramcet Combination Tablets, and the others (Janssen Pharmaceutical K.K. and the others) [3] Pelex combination granule (TAIHO Pharmaceutical Co., Ltd.) [4] Pediatric Pelex combination granule (TAIHO Pharmaceutical Co., Ltd.) [5] Coughcode-N Combination Tablets (Mylan EPD G.K.)
[Under old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Drug-induced hypersensitivity syndrome: Initial symptoms of rash and pyrexia, followed by serious delayed symptoms of hypersensitivity accompanied by hepatic impairment, swollen lymph nodes, increased white blood cell, eosinophilia, and appearance of atypical lymphocytes may occur. Symptoms are often accompanied by virus reactivation, such as human herpes virus type 6 (HHV-6). Caution is required for recurrence or prolongation of rash, pyrexia, and hepatic impairment, etc. that may occur even after discontinuation of administration.
[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Drug-induced hypersensitivity syndrome Initial symptoms of rash and pyrexia, followed by serious delayed symptoms of hypersensitivity accompanied by hepatic impairment, swollen lymph nodes, increased white blood cell, eosinophilia, and appearance of atypical lymphocytes may occur. Symptoms are often accompanied by virus reactivation, such as human herpes virus type 6 (HHV-6). Caution is required for recurrence or prolongation of rash, pyrexia, and hepatic impairment, etc. that may occur even after discontinuation of administration.

6 Antipyretics, analgesics and anti-inflammatory agents

[1] Acetaminophen (injections)
[2] Isopropylantipyrine/acetaminophen/allylisopropylacetylurea/ anhydrous caffeine

Brand name	[1] acelio Bag for Intravenous Injection 1000 mg (Terumo Corporation) [2] SG Combination Granules (Shionogi Pharma Co., Ltd.)
[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Drug-induced hypersensitivity syndrome Initial symptoms of rash and pyrexia, followed by serious delayed symptoms of hypersensitivity accompanied by hepatic impairment, swollen lymph nodes, increased white blood cell, eosinophilia, and appearance of atypical lymphocytes may occur. Symptoms are often

(newly added)	accompanied by virus reactivation, such as human herpes virus type 6 (HHV-6). Caution is required for recurrence or prolongation of rash, pyrexia, and hepatic impairment, etc. that may occur even after discontinuation of administration.

7 Other agents relating to blood and body fluids

[1] Clopidogrel sulfate
[2] Clopidogrel sulfate/aspirin

Brand name	[1] Plavix Tablets 25 mg, 75 mg (Sanofi K.K.), and the others [2] ComPlavin Combination Tablets (Sanofi K.K.), and the others
[Under old instructions]	
Adverse Reactions **Clinically Significant Adverse Reactions (newly added)**	Insulin autoimmune syndrome: Severe hypoglycaemia may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures, such as discontinuation of administration, should be taken.
Other Precautions	It has been reported that the occurrence of insulin autoimmune syndrome is strongly correlated with HLA-DR4 (DRB1*0406). In addition, it has been reported that patients with HLA DR4 subtype are more frequent in the Japanese population.
[Under new instructions]	
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Insulin autoimmune syndrome Severe hypoglycaemia may occur.
15. OTHER PRECAUTIONS **15.1 Information Based on Clinical Uses**	It has been reported that the occurrence of insulin autoimmune syndrome is strongly correlated with HLA-DR4 (DRB1*0406). In addition, it has been reported that patients with HLA DR4 subtype are more frequent in the Japanese population.

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

Alendronate sodium hydrate

Brand name	Fosamac Tablets 5, 35 mg (Organon K.K.), Bonalon Tablet 5 mg, 35 mg, Bonalon Oral Jelly 35 mg, Bonalon Bag for I.V. Infusion 900 μg (Teijin Pharma Limited.), and the others
[Under old instructions]	
Careful Administration	Patients with serious renal impairment [Safety has not been established due to the small number of cases in which this drug has been administered. In addition, in an epidemiological study conducted in Japan using a medical information database, among patients with renal impairment who used bisphosphonates for the treatment of osteoporosis, particularly in those with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), an increased risk of hypocalcaemia (corrected serum calcium level less than 8 mg/dL) has been reported compared with those with normal renal function.]
[Under new instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.2 Patients with renal impairment**	Patients with serious renal impairment (1) Clinical trials have not been conducted in patients with serious renal impairment. (2) In an epidemiological study conducted in Japan using a medical information database, among patients with renal impairment who used bisphosphonates for the treatment of osteoporosis, particularly in those with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), an

	increased risk of hypocalcaemia (corrected serum calcium level less than 8 mg/dL) has been reported compared with those with normal renal function.

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

Ibandronate sodium hydrate

Brand name	Bonviva Tablets 100 mg, Bonviva Syringes for Intravenous Injection 1 mg (Chugai Pharmaceutical Co., Ltd.), and the others
[Under new instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.2 Patients with renal impairment	Patients with severe renal disorder (1) Excretion may be delayed. (2) In an epidemiological study conducted in Japan using a medical information database, among patients with renal impairment who used bisphosphonates for the treatment of osteoporosis, particularly in those with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), an increased risk of hypocalcaemia (corrected serum calcium level less than 8 mg/dL) has been reported compared with those with normal renal function.

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

Etidronate disodium

Brand name	Didronel Tablets 200 (Sumitomo Pharma Co., Ltd.)
[Under new instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.2 Patients with renal impairment	Patients with serious renal disorder (1) This drug should not be administered. Excretion may be inhibited. (2) In an epidemiological study conducted in Japan using a medical information database, among patients with renal impairment who used bisphosphonates for the treatment of osteoporosis, particularly in those with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), an increased risk of hypocalcaemia (corrected serum calcium level less than 8 mg/dL) has been reported compared with those with normal renal function.

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

Zoledronic acid hydrate (indicated for osteoporosis)

Brand name	Reclast for i.v. infusion 5 mg (Asahi Kasei Pharma Corporation)
[Under new instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.2 Patients with renal impairment	Patients with severe renal impairment (creatinine clearance less than 35 mL/min) (1) This drug should not be administered. Acute kidney injury may occur. (2) In an epidemiological study conducted in Japan using a medical information database, among patients with renal impairment who used bisphosphonates for the treatment of osteoporosis, particularly in those with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), an increased risk of hypocalcaemia (corrected serum calcium level less than 8 mg/dL) has been reported compared with those with normal renal function.

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

Hydroxychloroquine sulfate

Brand name	Plaquenil Tablets 200 mg (Sanofi K.K.)
[Under new instructions]	

11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, erythroderma (exfoliative dermatitis), drug-induced hypersensitivity syndrome, acute generalised exanthematous pustulosis, acute febrile neutrophilic dermatosis (Sweet's syndrome)

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

Minodronic acid hydrate

Brand name	Recalbon Tablets 1 mg, 50 mg (Ono Pharmaceutical Co., Ltd.), Bonoteo Tablets 1 mg, 50 mg (Astellas Pharma Inc.), and the others
[Under old instructions]	
Careful Administration	Patients with serious renal disorder [Excretion may be delayed. In addition, in an epidemiological study conducted in Japan using a medical information database, among patients with renal impairment who used bisphosphonates for the treatment of osteoporosis, particularly in those with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), an increased risk of hypocalcaemia (corrected serum calcium level less than 8 mg/dL) has been reported compared with those with normal renal function.]
[Under new instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.2 Patients with renal impairment**	Patients with serious renal disorder (1) Excretion may be delayed. (2) In an epidemiological study conducted in Japan using a medical information database, among patients with renal impairment who used bisphosphonates for the treatment of osteoporosis, particularly in those with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), an increased risk of hypocalcaemia (corrected serum calcium level less than 8 mg/dL) has been reported compared with those with normal renal function.

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

Sodium risedronate hydrate

Brand name	Actonel Tablets 2.5 mg, 17.5 mg, 75 mg (EA Pharma Co., Ltd.), Benet Tablets 2.5 mg, 17.5 mg, 75 mg (Takeda Pharmaceutical Company Limited.), and the others
[Under old instructions]	
Careful Administration	Patients with renal disorder [Excretion may be delayed. In addition, in an epidemiological study conducted in Japan using a medical information database, among patients with renal impairment who used bisphosphonates for the treatment of osteoporosis, particularly in those with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), an increased risk of hypocalcaemia (corrected serum calcium level less than 8 mg/dL) has been reported compared with those with normal renal function.]
[Under new instructions]	
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.2 Patients with renal impairment**	Patients with severe renal impairment (1) This drug should not be administered. Excretion may be delayed in patients with a creatinine clearance value less than approximately 30 mL/min. (2) In an epidemiological study conducted in Japan using a medical information database, among patients with renal impairment who used bisphosphonates for the treatment of osteoporosis, particularly in those with severe renal impairment (eGFR less than 30 mL/min/1.73

m^2), an increased risk of hypocalcaemia (corrected serum calcium level less than 8 mg/dL) has been reported compared with those with normal renal function.

15 Other antitumor agents
Imatinib mesilate

Brand name	Glivec Tablets 100 mg (Novartis Pharma K.K.), and the others
[Under old instructions]	
Adverse Reactions Clinically Significant Adverse Reactions (newly added)	Pemphigus: Pemphigus may occur. If blister, erosion, scab or other signs/symptoms are observed, a dermatologist should be consulted.
[Under new instructions]	
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Pemphigus If blister, erosion, scab or other signs/symptoms are observed, a dermatologist should be consulted.

16 Vaccines
Oral live attenuated human rotavirus vaccine

Brand name	Rotarix oral liquid formulation (GlaxoSmithKline K.K.)
[Under new instructions]	
11. ADVERSE REACTIONS (newly added)	11.1 Clinically Significant Adverse Reactions Anaphylaxis

17 Cold medicines, antipyretics and analgesics
Preparations containing acetaminophen (oral dosage form, suppositories) (OTC drugs)

Brand name	Tylenol A (TOA Pharmaceuticals Co., Ltd.), Kio Fever (Hiya Pharmaceutical Co., Ltd.), and the others
Consultation (newly added)	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.

Name of symptoms	Symptoms
Drug-induced hypersensitivity syndrome	Some symptoms, such as redness over large part of the skin, generalised exanthema, pyrexia, malaise, swollen lymph nodes (neck, armpits, groin, etc.) may occur.

*The highlighted part should be listed only in the preparations containing ibuprofen among antipyretics and analgesics.

6

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 December 31, 2022)
◎: Products for which EPPV was initiated after December 1, 2022

	Nonproprietary name / Brand name	Name of the MAH	Date of EPPV initiate
◎	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 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

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiate
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 Infusion 1100 mg/11 mL	Alexion Pharma Godo Kaisha	August 24, 2022
Landiolol hydrochloride[*8] Onoact for I. V. Infusion 50 mg, 150 mg	Ono Pharmaceutical Co., Ltd.	August 24, 2022

Nonproprietary name / Brand name		Name of the MAH	Date of EPPV initiate
	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