Pharmaceuticals and Medical Devices Safety Information

No. 414 November 2024

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

Available information is listed here

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

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

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Pharmaceuticals and Medical Devices Safety Information

No. 414 November 2024

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

[Outline of Information]

E: Distribution of Dear Healthcare Professional Letters of Emergency Communications, *R:* Distribution of Dear

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

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

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

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

Abbreviations

ADEM	Acute Disseminated Encephalomyelitis
ADR	Adverse Drug Reaction
AGEP	Acute Generalised Exanthematous Pustulosis
CI	Confidence Interval
DIDPC	Department of Infectious Disease Prevention and Control
EPPV	Early Post-marketing Phase Vigilance
FDA	Food and Drug Administration
JCS	Japanese Circulation Society
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
NDB	National Database of Health Insurance Claims and Specific Health Checkups of Japan
NSAIDs	Non-steroidal Anti-inflammatory Drugs
OTC	Over-the-Counter
PMDA	Pharmaceuticals and Medical Devices Agency
PMD Act	Act on Securing Quality, Efficacy and Safety of Pharmaceuticals and Medical Devices
PSB	Pharmaceutical Safety Bureau
PSD	Pharmaceutical Safety Division
PV Law	Preventive Vaccination Law
RS virus	Respiratory Syncytial virus
SOC	System Organ Class

1

Suspected Adverse Reactions to Influenza Vaccines in the 2023 Season

1. Introduction

This section describes the status of instances of suspected adverse reactions to influenza vaccines reported from October 1, 2023 through March 31, 2024 (hereinafter referred to as the "2023 season").

Medical institutions are required to report to the MHLW when they encounter symptoms from influenza vaccines that they decide meet the Suspected Adverse Reaction Reporting Criteria regardless of causality. Reports by medical institutions, together with those by the marketing authorization holders (MAHs), are compiled and evaluated by the PMDA. For serious cases, including fatal cases, the PMDA performs causality assessment and/or considers the necessity of safety measures in consultation with experts.

Joint meetings of the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council and the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs Council (hereinafter referred to as the "Joint Meeting") are convened periodically for the purpose of investigating and reviewing these reports of suspected adverse reactions to influenza vaccines and to discuss the necessity of safety measures[1)2)].

2. Reports of suspected adverse reactions to influenza vaccines (2023 season)

(1) Numbers and frequencies of suspected adverse reactions reported

Table 1 shows the numbers of reported suspected adverse reactions to the influenza vaccines and frequencies calculated from the estimated numbers of vaccinated persons based on the number of vaccines distributed to medical institutions.

Table 1 Numbers of suspected adverse reactions reported and estimated number of vaccinated persons

	Reports by MAHs (serious reports)*		Reports by medical institutions**		
Estimated number of vaccinated persons (number of vaccinations)	Number of serious cases reported (frequency)	Number of patient mortalities reported	Number of reports (frequency)	Number of serious cases reported (frequency)	Number of patient mortalities reported
49,058,485 (as of March 31, 2024)	24 (0.000049%)	3 (0.0000061%)	75 (0.00015%)	43 (0.00009%)	7 (0.0000143%)

* Reports by the MAHs were on cases determined to be "serious" under Article 68-10, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act). Reports by the MAHs may duplicate some cases reported by medical institutions, and such duplicated cases are included in the number for reports by medical institutions.

** Reports by medical institutions were submitted under Article 12, Paragraph 1 of the Preventive Vaccination Law (PV Law) or Article 68-10, Paragraph 2 of the PMD Act.

(2) Reports of suspected adverse reactions by sex and age group

The numbers of reported suspected adverse reactions to influenza vaccines are shown by sex and age group in Table 2 and Table 3, respectively.

Table 2 Number of reports by sex

Sex	Number of Reports by MAHs (serious cases)	Number of reports by medical institutions
Male	16	35
Female	7	40
Unknown	1	0
Total	24	75

Table 3 Number of reports by age group

	Number of Reports by MAHs		Number of reports by medical institutions		
Age group	Number of serious cases reported		Number of reports	Number of serious cases reported	
		Number of patient mortalities reported			Number of patient mortalities reported
0 - 9	3	0	28	16	0
10 - 19	1	0	3	2	0
20 - 29	2	0	3	1	0
30 - 39	1	0	4	1	0
40 - 49	1	0	7	5	0
50 - 59	2	0	6	2	0
60 - 69	2	0	3	2	0
70 - 79	4	0	11	6	1
80 or older	5	1	10	8	6
Unknown	3	2	0	0	0
Total	24	3	75	43	7

(3) Details of reported symptoms

Suspected adverse reactions to influenza vaccines reported during the 2023 season are outlined by System Organ Class (SOC) in the right-hand side columns of Table 4.

A total of 10 cases of post-vaccination deaths were reported for this season. Among them, 9 cases excluding 1 case under investigation were evaluated by experts. The assessment by experts determined that the causality between the vaccination and death could not be assessed due to lack of information for these cases.

A total of 5 cases [Note 1)] of possible Guillain-Barré syndrome or acute disseminated encephalomyelitis (ADEM) were reported for this season. The assessment by experts determined that a causal relationship between the respective diseases and vaccination was reasonably possible for 1 case.

A total of 8 cases [Note 2)] were reported as possible anaphylaxis. Experts concluded that 3 cases (including 2 serious cases) were assessed as Level 3 or higher anaphylaxis using the Brighton Criteria. Regarding the number of reports from the MAHs by manufacturing lot, no distinct increases in the number of cases reported as possible anaphylaxis were attributed to any of the specific lots.

At the Joint Meeting held in July 2024, it was concluded that there were no new concerns

regarding the safety of the vaccines, including other reported symptoms than anaphylaxis, with no safety measures such as revision of package inserts required at present, but reporting of suspected adverse reactions and their details should be carefully monitored.

Note 1) Cases reported with the symptom name “Guillain-Barré syndrome” or “acute disseminated encephalomyelitis”
Note 2) Cases reported with the symptom name “anaphylactic reaction,” “anaphylactic shock,” “anaphylactoid reaction”

Table 4 Comparison of the number of suspected adverse reaction reports between the 2022 and 2023 seasons (by SOC)

	2022 season†		2023 season††	
SOC of symptom	Reports by MAHs (serious cases)	Reports by medical institutions (serious cases)	Reports by MAHs (serious cases)	Reports by medical institutions (serious cases)
Gastrointestinal disorders	3	4	1	5
General disorders and administration site conditions	13	12	8	16
Infections and infestations	1	7	2	8
Haepatobiliary disorders	0	1	1	1
Eye disorders	2	0	1	6
Musculoskeletal and connective tissue disorders	1	3	5	2
Blood and lymphatic system disorders	0	4	1	5
Vascular disorders	0	5	1	3
Respiratory, thoracic and mediastinal disorders	1	9	2	3
Injury, poisoning and procedural complications	1	1	0	0
Cardiac disorders	1	6	2	6
Nervous system disorder	8	23	6	15
Renal and urinary disorders	3	1	1	3
Mental disorder	0	1	1	0
Metabolic and nutritional disorders	0	3	0	1
Endocrine disorders	1	1	0	1
Skin and subcutaneous tissue disorders	5	4	0	4
Immune system disorders	4	5	2	7
Investigations	0	9	4	3
Total	44	99	38	89

† Reported from October 1, 2022 to September 30, 2023
†† Reported from October 1, 2023 to March 31, 2024

3. Future safety measures

As detailed in the “Reporting Suspected Adverse Reactions for Routine Vaccination, etc.” notification[3)], medical institutions are urged to promptly report when they encounter symptoms that they believe meet the Suspected Adverse Reaction Reporting Criteria even if the causality is

unclear.

In addition to the conventional reporting by fax, electronic reporting is available through the website since April 1, 2021.

[Report Reception Site (electronic report system)]

https://www.pmda.go.jp/safety/reports/hcp/0002.html (only in Japanese)

The MHLW/PMDA will continue their efforts to gather information concerning the safety of influenza vaccines including suspected adverse reaction reports, etc. and to implement safety measures based on such information. Continued cooperation is requested in alerting vaccine recipients to adverse reactions and reporting them when suspected.

[References]

1) MHLW: The Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council (the 102nd meeting) and the 2024 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs Council (the 4th meeting) (Joint Meeting)
   ・Material 2-29 Reports of Suspected Adverse Reactions to Influenza Vaccines
   https://www.mhlw.go.jp/content/11120000/001280878.pdf (only in Japanese)
   ・Material 2-34 List of reports of fatal cases after vaccination
   https://www.mhlw.go.jp/content/11120000/001280826.pdf (only in Japanese)

2) MHLW: The Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council (the 101st meeting) and the 2024 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs Council (the 1st meeting) (Joint Meeting)
   ・Material 2-31 List of reports of fatal cases after vaccination
   https://www.mhlw.go.jp/content/11120000/001244848.pdf (only in Japanese)

3) "Partial Amendment of Reporting Suspected Adverse Reactions for Routine Vaccinations, etc." dated August 8, 2024, Joint DIDPC Notification No.0808-5 and PSB Notification No.0808-1 by the Director of the Department of Infectious Disease Prevention and Control and the Director-General of the Pharmaceutical Safety Bureau, Ministry of Health, Labor and Welfare
   https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/kanrentuuti.html (only in Japanese)

   Report form
   https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/dl/r04youshiki_02.pdf (only in Japanese)

   Entry instructions
   https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou20/hukuhannou_houkoku/dl/r04youshiki_03.pdf (only in Japanese)

   Report entry application (National Institute of Infectious Diseases)
   http://www.nih.go.jp/niid/ja/vaccine-j/6366-vaers-app.html (only in Japanese)

Reference: Suspected Adverse Reaction Reporting Criteria
<Routine vaccination>

Symptoms	Time to onset after inoculation
Anaphylaxis	4 hours
Hepatic impairment	28 days
Interstitial pneumonia	28 days
Acute disseminated encephalomyelitis (ADEM)	28 days
Acute generalised exanthematous pustulosis (AGEP)	28 days
Guillain-Barré syndrome	28 days
Convulsion	7 days
Vasculitis	28 days
Thrombocytopenic purpura	28 days
Optic neuritis	28 days
Myelitis	28 days
Asthmatic attack	24 hours
Nephrotic syndrome	28 days
Encephalitis or encephalopathy	28 days
Oculomucocutaneous syndrome	28 days
Other reactions (symptoms suspected to be associated with the vaccination and either (1) requiring hospital admission or (2) resulting in, or associated with a risk of death or persistent incapacity)	Time frame in which the event was considered by the physician to be associated with the vaccination

Except for “other reactions,” any event occurring within the specified time frame is subject to mandatory reporting to the MHLW regardless of causality under the PV Law and related rules.

<Voluntary vaccination>

Adverse reactions or infections associated with voluntary vaccinations should be reported when reporting is considered necessary to prevent the occurrence and spread of health hazards. Refer to the following for specific cases subject to reporting. Adverse reactions and infections for which causality with vaccinations is unclear may also be subject to reporting.

(1) Death
(2) Disability
(3) Events that may result in death
(4) Events that may result in disability
(5) Symptoms that require admission or prolonged hospitalization at medical institutions for treatment [excluding events in (3) and (4)]
(6) Serious events corresponding to those in items (1) to (5)
(7) Congenital diseases or anomalies in the next generation
(8) Onset of infections suspected of being caused by use of the applicable pharmaceutical
(9) Onset of unknown events which are not mild and could not be predicted based on the package insert, other than those listed in (1) to (8)

2

Revision of PRECAUTIONS for Non-steroidal Anti-inflammatory Drugs Regarding Myocardial Infarction and Cerebrovascular Disorder

1. Introduction

Non-steroidal anti-inflammatory drugs (hereinafter referred to as "NSAIDs") are used for antipyretic, analgesic, and anti-inflammatory purposes in various diseases as prescription drugs, guidance-mandatory drugs, and over-the-counter drugs.

To clarify the risk of myocardial infarction and cerebrovascular disorder in patients treated with NSAIDs for which systemic effects are expected, a pharmacoepidemiological study (hereinafter referred to as the "NDB study") was conducted using the National Database of Health Insurance Claims and Specific Health Checkups of Japan (hereinafter referred to as "NDB"). As a result of reviewing the results of the NDB study including the opinions of expert advisors, the MHLW determined that it was necessary to call attention to myocardial infarction and cerebrovascular disorder in administration of NSAIDs for which systemic effects are expected, and instructed the MAHs to revise the PRECAUTIONS on October 8, 2024. The details of the review are described in this section.

2. Background

In Europe and the United States, the product labeling includes precautions on the risk of myocardial infarction and cerebrovascular disorder as a class effect of NSAIDs excluding aspirin, based on the results of pharmacoepidemiological studies, etc.

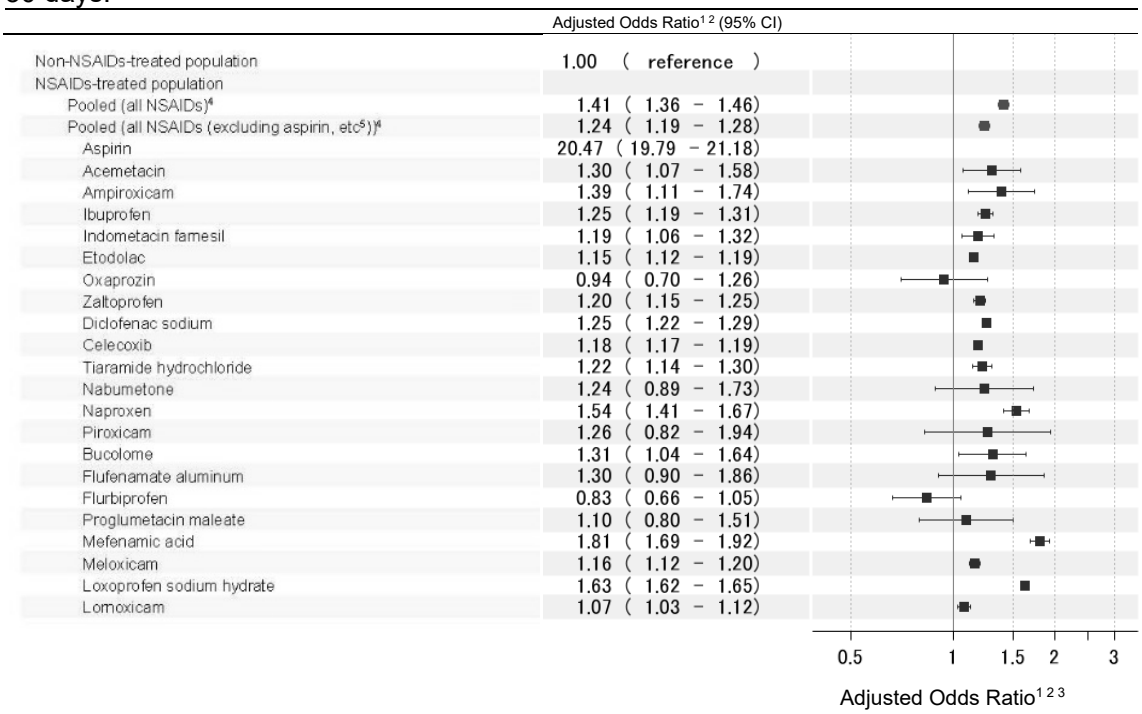
In Japan, precautions were included in the electronic package inserts for only some of the NSAIDs (celecoxib and diclofenac sodium), for which cases of myocardial infarction and cerebrovascular disorder had been reported, because the risks of myocardial infarction and cerebrovascular disorder had been reported to differ between Japanese and Western populations [1)] and reference pharmacoepidemiological studies in Japanese population are limited. Thus, the status of precautions differed among NSAIDs.

For this reason, the PMDA conducted the NDB study to clarify the risk of myocardial infarction and cerebrovascular disorder due to NSAIDs for which systemic effects are expected, and reviewed the necessity of taking safety measures for NSAIDs regarding myocardial infarction and cerebrovascular disorder.

3. Details of the review

In the NDB study, a case-control study was conducted in patients with chronic diseases such as rheumatoid arthritis and osteoarthritis by matching patients with cardiovascular events (composite outcome of acute coronary syndrome, cerebral infarction, and cerebral haemorrhage) and patients without them using the claims data stored in the NDB between April 1, 2012 and March 31, 2020. The adjusted odds ratio (95% confidence interval) for cardiovascular events in the population who used NSAIDs in the past 14 days (hereinafter referred to as "NSAIDs-treated population") was 1.41 (1.36−1.46) for all NSAIDs in comparison with the population who did not use NSAIDs in the past 180 days (hereinafter referred to as "non-NSAIDs-treated population"), and the adjusted odds ratio (95% CI) for all NSAIDs was 1.24 (1.19−1.28) when aspirin, etc., for which evaluation in the NDB study was considered to be difficult, were excluded. Moreover, the point

estimates of the adjusted odds ratios for each NSAID were mostly higher than 1.00 (Figure 1). As a result of evaluation by duration of use of NSAIDs, an increased risk of cardiovascular events was suggested also in the population of short-term use whose duration of use of NSAIDs was less than 30 days.



Results for the use of multiple NSAIDs and those for NSAIDs for which marketing was discontinued or transitional measures were completed are not shown.

1 Estimated using a conditional logistic regression model
2 Adjusted with the matching pairs (age, sex, starting year of follow-up, and history of cardiovascular events) as stratification factors and with hypertension, diabetes mellitus, dyslipidaemia, arrhythmia, antiplatelet drugs, anticoagulant drugs, heart failure, chronic kidney disease, chronic obstructive pulmonary disease, and rheumatoid arthritis as covariates
3 The adjusted odds ratio for aspirin is not shown.
4 Estimated using a contrast method
5 Aspirin and multiple use of NSAIDs

Figure 1 Adjusted odds ratios for cardiovascular events in NSAIDs-treated population compared to non-NSAIDs-treated population

The adjusted odds ratio (95% confidence interval) for aspirin was remarkably high at 20.47 (19.79−21.18). However, an additional analysis suggested that aspirin may have been prescribed to treat myocardial infarction or cerebrovascular disorder or to prevent the onset of myocardial infarction or cerebrovascular disorder in patients at high risk of onset. Based on this, the PMDA determined that it was not necessary to take safety measures for aspirin regarding myocardial infarction and cerebrovascular disorder at this point for the following reasons: It was considered to be difficult to evaluate the risk of myocardial infarction and cerebrovascular disorder due to aspirin based on the NDB study; no precautions for myocardial infarction and cerebrovascular disorder are included in the product labeling of aspirin in Europe and the United States. For details of the results of the NDB study, please refer to "Evaluation of the risk of cardiovascular events due to non-steroidal anti-inflammatory drugs using NDB." [2)]

The NDB study was conducted in patients with chronic diseases and did not include salicylic acid preparations, excluding aspirin, pyrazolone preparations, and alminoprofen, which is marketed only as an over-the-counter drug. The PMDA determined that it was not necessary to take safety measures for these drugs regarding myocardial infarction and cerebrovascular disorder at this point for the following reasons, with consideration given to the difficulty in concluding the risk of myocardial infarction and cerebrovascular disorder: There are no literature reports, etc. evaluating

the risk of myocardial infarction and cerebrovascular disorder; these preparations are not marketed in Europe and the United States making it impossible to refer to measures taken by the regulatory agencies in Europe and the United States.

Based on the above, the MHLW determined that it was necessary to add "myocardial infarction, cerebrovascular disorder" to the Clinically Significant Adverse Reactions section in the electronic package inserts for NSAIDs (excluding some drugs such as aspirin) for which systemic effects are expected, because an increased risk of myocardial infarction and cerebrovascular disorder was suggested. For preparations containing ibuprofen (oral dosage form), preparations containing naproxen, and preparations containing loxoprofen (oral dosage form), which are marketed as guidance-mandatory drugs and/or over-the-counter drugs, the MHLW determined that it was appropriate to add "myocardial infarction, cerebrovascular disorder" to the Consultation section in the package inserts as rare serious adverse reactions, similarly to the prescription drugs of NSAIDs.

4. Closing remark

Healthcare professionals are requested to pay sufficient attention to the onset of myocardial infarction and cerebrovascular disorder related to prescription drugs, guidance-mandatory drugs, and over-the-counter drugs of NSAIDs as well as to take appropriate measures when symptoms or signs of myocardial infarction or cerebrovascular disorder are noted during administration of NSAIDs. Especially for guidance-mandatory drugs and over-the-counter drugs of NSAIDs, pharmacists and registered salesclerks are requested to inform consumers that myocardial infarction and cerebrovascular disorder may occur and that they should discontinue the use of the drug and consult a doctor immediately if symptoms indicating adverse reactions occur.

[References]

1) JCS 2023 Guideline on the Primary Prevention of Coronary Artery Disease (edited by the Japanese Circulation Society, published on March 10, 2023)
2) Summary of Study Results Using National Database of Health Insurance Claims and Specific Health Checkup of Japan (NDB):
https://www.pmda.go.jp/files/000270714.pdf (in Japanese)
https://www.pmda.go.jp/files/000270715.pdf (in English)

[Reference information]

- Revision of PRECAUTIONS (PSB/PSD Notification No. 1008-1 dated October 8, 2024)
  https://www.pmda.go.jp/files/000271157.pdf (in Japanese)
  English translation by the PMDA (October 8, 2024)
  https://www.pmda.go.jp/english/safety/info-services/drugs/revision-of-precautions/0012.html (in English)
- Studies conducted by the PMDA
  https://www.pmda.go.jp/safety/surveillance-analysis/0045.html (only in Japanese)
- Food and Drug Administration. 2015. FDA strengthens warnings that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes.
  https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-warning-non-aspirin-nonsteroidal-anti-inflammatory
- European Medicines Agency. 2012. Assessment report for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and cardiovascular risk
  https://www.ema.europa.eu/en/documents/opinion-any-scientific-matter/assessment-report-article-53-procedure-non-steroidal-anti-inflammatory-drugs-nsaids-cardiovascular-risk_en.pdf

3

Revisions of PRECAUTIONS (No. 354)

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

1 Antipyretics, analgesics and anti-inflammatory agents

Aspirin (preparations indicated for antipyresis/analgesia/anti-inflammation)

Brand name	Aspirin "Maruishi" (Maruishi Pharmaceutical Co., Ltd.) and the others
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.5 Pregnant Women**	Pregnant women (excluding those within 12 weeks before due date) or women who may be pregnant <Indications other than Kawasaki's disease> If administration is deemed necessary, caution should be exercised such as limiting the drug to the minimum effective use and checking amniotic fluid volume and findings suggestive of constriction of the foetal ductus arteriosus with consideration given to the gestational age and duration of administration as necessary. It has been reported that constriction of the foetal ductus arteriosus occurred in pregnant women who had been administered cyclooxygenase inhibitors (preparations with expected systemic effects) in their second trimester of pregnancy.

2 Antipyretics, analgesics and anti-inflammatory agents

[1] Acemetacin
[2] Indometacin (suppositories)
[3] Indometacin farnesil
[4] Oxaprozin
[5] Tiaramide hydrochloride
[6] Proglumetacin maleate
[7] Meloxicam

Brand name	[1] Rantudil Kowa Tablets 30 mg (Kowa Company, Ltd.) [2] Inteban Suppositories 25, 50 (Teikoku Seiyaku Co.,Ltd.), and the others [3] Infree Capsules 100 mg, Infree S Capsules 200 mg (Eisai Co., Ltd.) [4] Alvo tablets 100 mg, 200 mg (Taisho Pharmaceutical Co., Ltd.) [5] Solantal Tablets 50 mg, 100 mg (LTL Pharma Co.,Ltd.) [6] Miridacin tablets 90 mg (TAIHO Pharmaceutical Co., Ltd.) [7] Mobic Tablets 5 mg, 10 mg (Nippon Boehringer Ingelheim Co ., Ltd.) and the others
11. ADVERSE REACTIONS	Myocardial infarction, cerebrovascular disorder Cardiovascular thromboembolic events including myocardial infarction and cerebrovascular disorder may occur.

11.1 Clinically Significant Adverse Reactions (newly added)

3 Antipyretics, analgesics and anti-inflammatory agents

[1] Ampiroxicam
[2] Ibuprofen
[3] Etodolac
[4] Naproxen
[5] Piroxicam (oral dosage form)
[6] Flurbiprofen (oral dosage form)
[7] Flurbiprofen axetil
[8] Loxoprofen sodium hydrate (oral dosage form)
[9] Lornoxicam

Brand name	[1] Flucam Capsules 13.5 mg, 27 mg (Pfizer Japan Inc.) [2] Brufen Tablets 100, 200, Brufen Granule 20% (Kaken Pharmaceutical Co., Ltd.), and the others [3] Osteluc Tablets 100, 200 (Aska Pharmaceutical. Co., Ltd.), Hypen Tablets 100 mg, 200 mg (Nippon Shinyaku Co., Ltd.), and the others [4] Naixan Tablets 100 mg (Nipro ES Pharma Co., Ltd.) [5] Baxo Capsule 10, 20 (FUJIFILM Toyama Chemical Co., Ltd.) [6] Froben Tablets 40, Froben Granule 8% (Kaken Pharmaceutical Co., Ltd.) [7] Ropion Intravenous 50 mg (Kaken Pharmaceutical Co., Ltd.) [8] Loxonin Tablets 60 mg, Loxonin Fine Granules 10% (Daiichi Sankyo Co., Ltd.), and the others [9] Lorcam tab. 2 mg, 4 mg (Taisho Pharmaceutical Co., Ltd.), and the others
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.5 Pregnant Women**	Pregnant women (excluding the third trimester) or women who may be pregnant This drug should be administered only when the therapeutic benefits are considered to outweigh the risks. If administration is deemed necessary, caution should be exercised such as limiting the drug to the minimum effective use and checking amniotic fluid volume <u>and findings suggestive of constriction of the foetal ductus arteriosus with consideration given to the gestational age and duration of administration</u> as necessary. Renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women. <u>It has been reported that constriction of the foetal ductus arteriosus occurred in pregnant women who had been administered cyclooxygenase inhibitors (preparations with expected systemic effects) in their second trimester of pregnancy.</u>
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	<u>Myocardial infarction, cerebrovascular disorder</u> <u>Cardiovascular thromboembolic events including myocardial infarction and cerebrovascular disorder may occur.</u>

4 Antipyretics, analgesics and anti-inflammatory agents, Agents used for common cold

[1] Isopropylantipyrine/acetaminophen/allylisopropylacetylurea/ anhydrous caffeine
[2] Salicylamide/acetaminophen/anhydrous caffeine/ chlorpheniramine maleate
[3] Salicylamide/acetaminophen/anhydrous caffeine/ promethazine methylenedisalicylate

Brand name	[1] SG Combination Granules (Shionogi Pharma Co., Ltd.) [2] Pelex combination granule (TAIHO Pharmaceutical Co., Ltd.) [3] PL Combination Granules (Shionogi Pharma Co., Ltd.) and the others
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. If administration is deemed necessary, caution should be exercised such as limiting the drug to the minimum effective use and checking amniotic fluid volume and findings suggestive of constriction of the foetal ductus arteriosus with consideration given to the gestational age and duration of administration as necessary. Renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women. It has been reported that constriction of the foetal ductus arteriosus occurred in pregnant women who had been administered cyclooxygenase inhibitors in their second and/or third trimester of pregnancy with a higher risk known in women exposed to the drug in their third trimester.

5 Antipyretics, analgesics and anti-inflammatory agents

[1] Ethenzamide
[2] Sulpyrine hydrate

Brand name	[1] Ethenzamide "Yoshida" (Yoshida Pharmaceutical Company Limited) [2] Sulpyrine Injection 250 mg "NP" (Nipro Corporation) and the others
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.5 Pregnant Women**	Pregnant women or women who may be pregnant This drug should be administered only when the therapeutic benefits are considered to outweigh the risks. If administration is deemed necessary, caution should be exercised such as limiting the drug to the minimum effective use and checking amniotic fluid volume and findings suggestive of constriction of the foetal ductus arteriosus with consideration given to the gestational age and duration of administration as necessary. Renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women. It has been reported that constriction of the foetal ductus arteriosus occurred in pregnant women who had been administered cyclooxygenase inhibitors in their second and/or third trimester of pregnancy with a higher risk known in women exposed to the drug in their third trimester.

6 Antipyretics, analgesics and anti-inflammatory agents

Ketoprofen (injections, suppositories)

Brand name	Capisten IM 50 mg (Kissei Pharmaceutical Co., Ltd., Ketoprofen Suppositories 50 mg "JG", Ketoprofen Suppositories 75 mg "JG" (Choseido Pharmaceutical Co.,Ltd.), and the others
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.5 Pregnant Women**	Pregnant women (excluding the third trimester) or women who may be pregnant This drug should be administered only when the therapeutic benefits are considered to outweigh the risks. If administration is deemed necessary, caution should be exercised such as limiting the drug to the minimum effective use and checking amniotic fluid volume and findings suggestive of constriction of the foetal ductus arteriosus with consideration given to the gestational age and duration of administration as necessary. It has been reported that oligohydramnios occurred in pregnant women who had been administered a dermatologic preparation of ketoprofen in their second trimester of pregnancy. In addition, renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women. It has been reported that constriction of the foetal ductus arteriosus occurred in pregnant women who had been administered cyclooxygenase inhibitors (preparations with expected systemic effects) in their second trimester of pregnancy.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions (newly added)**	Myocardial infarction, cerebrovascular disorder Cardiovascular thromboembolic events including myocardial infarction and cerebrovascular disorder may occur.

7 Antipyretics, analgesics and anti-inflammatory agents

Zaltoprofen

Brand name	Soleton Tablets 80 (Nippon Chemiphar Co., Ltd.), Peon tablets 80 (Zeria Pharmaceutical Co., Ltd.), and the others
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.5 Pregnant Women**	Pregnant women or women who may be pregnant This drug should be administered only if the potential therapeutic benefits are considered to outweigh the potential risks. If administration is deemed necessary, caution should be exercised such as limiting the drug to the minimum effective use and checking amniotic fluid volume and findings suggestive of constriction of the foetal ductus arteriosus with consideration given to the gestational age and duration of administration as necessary. Renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women. It has been reported that constriction of the foetal ductus arteriosus occurred in pregnant women who had been administered cyclooxygenase inhibitors in their second and/or third trimester of pregnancy with a higher risk known in women exposed to the drug in their third trimester.
11. ADVERSE REACTIONS **11.1 Clinically Significant Adverse Reactions**	Myocardial infarction, cerebrovascular disorder Cardiovascular thromboembolic events including myocardial infarction and cerebrovascular disorder may occur.

(newly added)

8 Antipyretics, analgesics and anti-inflammatory agents

Dibucaine hydrocholoride/sodium salicylate/calcium bromide

Brand name	Neo Vitacain Injection 2 mL, 5 mL, Neo Vitacain Injection Syringe 2 mL, 5 mL (VITACAIN PHARMACEUTICAL Co., LTD.), and the others
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.5 Pregnant Women**	<Epidural block, infiltration/conduction block (trigger point injection, etc.)> 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. If administration is deemed necessary, caution should be exercised such as limiting the drug to the minimum effective use and checking amniotic fluid volume and findings suggestive of constriction of the foetal ductus arteriosus with consideration given to the gestational age and duration of administration as necessary. Renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women. It has been reported that constriction of the foetal ductus arteriosus occurred in women who had been administered cyclooxygenase inhibitors in their second and/or third trimester of pregnancy with a higher risk known in women exposed to the drug in their third trimester.

9 Antipyretics, analgesics and anti-inflammatory agents

Celecoxib

Brand name	Celecox Tablets 100 mg, 200 mg (Viatris Pharmaceuticals Japan Inc.), and the others
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS **9.5 Pregnant Women**	Pregnant women (excluding the third trimester) or women who may be pregnant This drug should be administered only when the therapeutic benefits are considered to outweigh the risks. If administration is deemed necessary, caution should be exercised such as limiting the drug to the minimum effective use and checking amniotic fluid volume and findings suggestive of constriction of the foetal ductus arteriosus with consideration given to the gestational age and duration of administration as necessary. Renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women. It has been reported that constriction of the foetal ductus arteriosus occurred in pregnant women who had been administered cyclooxygenase inhibitors (preparations with expected systemic effects) in their second trimester of pregnancy.

10 Antipyretics, analgesics and anti-inflammatory agents

[1] Nabumetone
[2] Bucolome
[3] Mefenamic acid

Brand name	[1] Relifen Tab. 400 mg (Sanwa Kagaku Kenkyusho Co., Ltd) [2] Paramidin Capsules 300 mg (Aska Pharmaceutical. Co., Ltd.) [3] Pontal Capsules 250 mg, Pontal Powder 50%, Pontal Fine

	Granules 98.5%, Pontal Syrup 3.25% (Pfizer Japan Inc.)
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.5 Pregnant Women	Pregnant women (excluding the third trimester) or women who may be pregnant This drug should be administered only when the therapeutic benefits are considered to outweigh the risks. If administration is deemed necessary, caution should be exercised such as limiting the drug to the minimum effective use and checking amniotic fluid volume and findings suggestive of constriction of the foetal ductus arteriosus with consideration given to the gestational age and duration of administration as necessary. Renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women. It has been reported that constriction of the foetal ductus arteriosus occurred in pregnant women who had been administered cyclooxygenase inhibitors (preparations with expected systemic effects) in their second trimester of pregnancy.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Myocardial infarction, cerebrovascular disorder Cardiovascular thromboembolic events including myocardial infarction and cerebrovascular disorder may occur.

11 Antipyretics, analgesics and anti-inflammatory agents

Flufenamate aluminum

Brand name	Opyrin tab. 125 mg, 250 mg (Taisho Pharmaceutical Co., Ltd.)
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. If administration is deemed necessary, caution should be exercised such as limiting the drug to the minimum effective use and checking amniotic fluid volume and findings suggestive of constriction of the foetal ductus arteriosus with consideration given to the gestational age and duration of administration as necessary. Renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women. It has been reported that constriction of the foetal ductus arteriosus occurred in pregnant women who had been administered cyclooxygenase inhibitors in their second and/or third trimester of pregnancy with a higher risk known in women exposed to the drug in their third trimester.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Myocardial infarction, cerebrovascular disorder Cardiovascular thromboembolic events including myocardial infarction and cerebrovascular disorder may occur.

12 Analgesics, anti-itchings, astrigents and anti-inflammatory agents

[1] Ibuprofen piconol
[2] Indometacin (patches)
[3] Diclofenac sodium (dermatologic preparation)

[4] Piroxicam (dermatologic preparation)
[5] Flurbiprofen (dermatologic preparation)
[6] Loxoprofen sodium hydrate (dermatologic preparation)

Brand name	[1] Vesicum Ointment 5%, Vesicum Cream 5% (Hisamitsu Pharmaceutical Co., Inc.), Staderm Ointment 5%, Staderm Cream 5% (Torii Pharmaceutical Co., Ltd.) [2] Idomethine Kowa Gel 1%, Idomethine Kowa Sol 1%, Idomethine Kowa Cream 1%, Idomethine Kowa Pap (Kowa Company, Ltd.), Inteban Ointment 1%, Inteban Solution for Cutaneous Application, Inteban Cream 1% (Teikoku Seiyaku Co., Ltd.), Inside Pap 70 mg (Hisamitsu Pharmaceutical Co., Inc.), Catlep Pap 70 mg, Catlep Tape 35 mg, 70 mg (Teikoku Seiyaku Co., Ltd.), Intenurse Pap 70 mg (Toko Pharmaceutical industries Co., Ltd.), Aconip PAP 70 mg (Teika Pharmaceutical Co., Ltd.), Hapstar - ID 70 mg (Oishi Koseido Co., Ltd.), Laction Pap 70 mg (Teika Pharmaceutical Co., Ltd.), and the others [3] Voltaren Gel 1%, Voltaren Tape 15 mg, 30 mg, Voltaren Lotion 1% (DOJIN IYAKU-KAKO CO., LTD.), Naboal Gel 1%, Naboal Tape 15 mg, Naboal Tape L 30 mg, Naboal Pap 70 mg, 140 mg (Hisamitsu Pharmaceutical Co., Inc.), and the others [4] Baxo Ointment 0.5% (FUJIFILM Toyama Chemical Co., Ltd.), Feldene Ointment 0.5% (Pfizer Japan Inc.) [5] Zepolas Pap 40 mg, 80 mg, Zepolas Tape 20 mg, 40 mg (Mikasa Seiyaku co., ltd), Adofeed Pap 40 mg (LEAD CHEMICAL Co., Ltd.), Fulruban Pap 40 mg (Taikyo pharmaceutical co., ltd.), Yakuban tape 20 mg, 40 mg, 60 mg (TOKUHON Corporation), and the others [6] Loxonin Pap 100 mg, Loxonin Tape 50 mg, 100mg (LEAD CHEMICAL Co., Ltd.), Loxonin Gel 1% (Daiichi Sankyo Co., Ltd.), and the others
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. It has been reported that constriction of the foetal ductus arteriosus occurred in pregnant women who had used cyclooxygenase inhibitors in their second and/or third trimester of pregnancy. In addition, renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women.

13 Analgesics, anti-itchings, astrigents and anti-inflammatory agents

Indometacin (topical preparations excluding patches)

Brand name	Idomethine Kowa Gel 1%, Idomethine Kowa Sol 1%, Idomethine Kowa Cream 1%, Idomethine Kowa Pap (Kowa Company, Ltd), Inteban Ointment 1%, Inteban Solution for Cutaneous Application, Inteban Cream 1% (Teikoku Seiyaku Co., Ltd.), Inside Pap 70 mg (Hisamitsu Pharmaceutical Co., Inc.), Catlep Pap 70 mg, Catlep Tape 35 mg, 70 mg (Teikoku Seiyaku Co., Ltd.), Intenurse Pap 70 mg (Toko Pharmaceutical industries Co., Ltd.), Aconip PAP 70 mg (Teika Pharmaceutical Co., Ltd.), Hapstar - ID 70 mg (Oishi Koseido Co., Ltd.), Laction Pap 70 mg (Teika Pharmaceutical Co., Ltd.), and the others
9. PRECAUTIONS CONCERNING	Pregnant women or women who may be pregnant should be administered this drug only if the potential therapeutic benefits are

PATIENTS WITH SPECIFIC BACKGROUNDS 9.5 Pregnant Women	considered to outweigh the potential risks. Long-term treatment at a high dose or with extensive administration should be avoided. It has been reported that constriction of the foetal ductus arteriosus occurred in pregnant women who had used cyclooxygenase inhibitors in their second and/or third trimester of pregnancy. In addition, renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women.

14 Analgesics, anti-itchings, astrigents and anti-inflammatory agents

Esflurbiprofen/mentha oil

Brand name	Loqoa tape (Taisho Pharmaceutical Co., Ltd.)
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.5 Pregnant Women	Pregnant women (excluding the third trimester) or women who may be pregnant This drug should be administered only when the therapeutic benefits are considered to outweigh the risks. If administration is deemed necessary, caution should be exercised such as limiting the drug to the minimum effective use and checking amniotic fluid volume and findings suggestive of constriction of the foetal ductus arteriosus with consideration given to the gestational age and duration of administration as necessary. The safety of this drug administered during pregnancy has not been established. Renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women. It has been reported that constriction of the foetal ductus arteriosus occurred in women who had been administered cyclooxygenase inhibitors (preparations with expected systemic effects) in their second trimester of pregnancy.
11. ADVERSE REACTIONS 11.1 Clinically Significant Adverse Reactions (newly added)	Myocardial infarction, cerebrovascular disorder Cardiovascular thromboembolic events including myocardial infarction and cerebrovascular disorder may occur.

15 Analgesics, anti-itchings, astrigents and anti-inflammatory agents

Ketoprofen (dermatologic preparation)

Brand name	Sector Gel 3%, Sector Lotion 3%, Sector Cream 3% (Hisamitsu Pharmaceutical Co., Inc.), Mohrus Pap 30 mg, 60 mg, Mohrus Tape 20 mg, Mohrus Tape L 40 mg, Mohrus Paps XR 120 mg, 240 mg (Hisamitsu Pharmaceutical Co., Inc.), Miltax Pap 30 mg (Nipro Pharma Corporation), and the others
9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS 9.5 Pregnant Women	Pregnant women (excluding the third trimester) or women who may be pregnant This drug should be administered only when the therapeutic benefits are considered to outweigh the risks. Caution should be exercised such as limiting the drug to the minimum effective use. It has been reported that oligohydramnios occurred in pregnant women who had used a dermatologic preparation of ketoprofen in their second trimester of pregnancy. In addition, renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios

	have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women. It has been reported that constriction of the foetal ductus arteriosus occurred in pregnant women who had used cyclooxygenase inhibitors (preparations with expected systemic effects) in their second trimester of pregnancy.

16 Analgesics, anti-itchings, astrigents and anti-inflammatory agents, anti-dermoinfectives, emollients (including caustics)

[1] Glycol salicylate/l-menthol
[2] Methyl salicylate
[3] Methyl salicylate/dl-camphor/capsicum extract
[4] Methyl salicylate/dl-camphor/l-menthol
[5] Methyl salicylate/l-menthol/dl-camphor/glycyrrhetinic acid
[6] Felbinac
[7] Heparinoid/adrenal extract/salicylic acid
[8] Salicylic acid

Brand name	[1] GS PLASTER C “YUTOKU” (YUTOKU PHARMACEUTICAL IND. Co., LTD.) [2] Methyl Salicylate ”Toho” (Toho Pharmaceutical Co., Ltd.) [3] MS onshippu “TAIHO” (OKAYAMA TAIHO Pharmaceutical Co., Ltd.) and the others [4] MS reishippu “TAIHO” (OKAYAMA TAIHO Pharmaceutical Co., Ltd.) and the others [5] Stickzenol A (Mikasa Seiyaku co., ltd) [6] Napageln Ointment 3%, Napageln Lotion 3%, Napageln Cream 3% (Teikoku Seiyaku Co., Ltd.), Seltouch Pap 70, 140, Seltouch Tape 70 (Teikoku Seiyaku Co., Ltd.), and the others [7] Zestak Cream (Mikasa Seiyaku co., ltd) [8] 5% Salicylic Acid Ointment Toho, 10% Salicylic Acid Ointment Toho (Toho Pharmaceutical Co., Ltd.), and the others
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. Renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women. It has been reported that constriction of the foetal ductus arteriosus occurred in pregnant women who had been administered cyclooxygenase inhibitors in their second and/or third trimester of pregnancy.

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

Diclofenac etalhyaluronate sodium

Brand name	Joyclu 30 mg Intra-articular Injection (Seikagaku Corporation)
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. Renal impairment and decreased urine output in foetuses as well as accompanying oligohydramnios have been reported following use of cyclooxygenase inhibitors (oral dosage form or suppository) in pregnant women. It has been reported that constriction of the foetal ductus arteriosus occurred

in pregnant women who had been administered cyclooxygenase inhibitors in their second and/or third trimester of pregnancy.

18 Cold medicines, Antipyretics and analgesics

[1] Preparations containing ibuprofen (OTC drugs)
[2] Preparations containing naproxen (guidance-mandatory drugs)
[3] Preparations containing loxoprofen sodium hydrate (oral dosage form) (OTC drugs, guidance-mandatory drugs)

Brand name

[1] Eve-A Tablets (SSP Co., Ltd.) and other OTC drugs, Pabron Ace Pro-X Granules (Taisho Pharmaceutical Co., Ltd.) and other OTC drugs
[2] Motrin NX (JNTL Consumer Health K.K.)
[3] Loxonin S (Daiichi Sankyo Healthcare Co., Ltd.) and other OTC drugs, Loxonin Common cold medicine (Daiichi Sankyo Healthcare Co., Ltd.) and other guidance-mandatory drugs

Consultation (newly added)

If the following symptoms are observed after taking this drug, these may be adverse reactions. In such cases, the use of this drug should be immediately discontinued, and a physician, dentist[1)], pharmacist or registered salesclerk[2)] should be consulted, presenting them with this document.

The following serious symptoms may occur rarely. In such cases, medical attention should be sought immediately.

Name of symptoms	Symptoms
Myocardial infarction	Tight chest pain, difficulty breathing, and cold sweat may occur.
Cerebrovascular disorder	Some symptoms such as decrease in consciousness/loss of consciousness, difficulty in moving unilateral extremities, headache, vomiting, dizziness, difficulty speaking, and speech apraxia may occur suddenly.

1) “Dentist” should be listed only for antipyretics and analgesics.
2) ”Registered salesclerk” should be listed only for preparations containing ibuprofen.

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

	Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiation
◎	Coronavirus (SARS-CoV-2) RNA Vaccine[*1] Kostaive intramuscular injection	Meiji Seika Pharma Co., Ltd.	September 30, 2024
◎	Brexpiprazole[*2] Rexulti tablets 1 mg, 2 mg, Rexulti OD tablets 0.5 mg, 1 mg, 2 mg	Otsuka Pharmaceutical Co., Ltd.	September 24, 2024
◎	Treprostinil[*3] Treprost Inhalation Solution 1.74 mg	Mochida Pharmaceutical Co., Ltd.	September 24, 2024
◎	Inactivated tissue culture tick-borne encephalitis vaccine Ticovac suspension liquid for intramuscular injection 0.5 mL, Ticovac Junior suspension liquid for intramuscular injection 0.25 mL	Pfizer Japan Inc.	September 13, 2024
◎	Freeze-dried human protein C concentrate Ceprotin for Intravenous Injection 1000 IU	Takeda Pharmaceutical Company Limited	September 6, 2024
	Pneumococcal 20-valent conjugate vaccine adsorbed (mutated diphtheria CRM_{197} conjugate)[*4] Prevenar 20 Suspension Liquid for Injection	Pfizer Japan Inc.	August 30, 2024
	Brivaracetam Briviact Tablets 25 mg, 50 mg, Briviact for I.V. injection 25 mg	UCB Japan Co. Ltd.	August 30, 2024
	Mepolizumab (genetical recombination)[*5] Nucala solution for s.c. injection 100 mg	GlaxoSmithKline K.K.	August 28, 2024
	Maribavir Livtencity tablets 200 mg	Takeda Pharmaceutical Company Limited	August 28, 2024
	Vilanterol trifenatate/fluticasone furoate Relvar 50 Ellipta 14 doses for Pediatric, Relvar 50 Ellipta 30 doses for Pediatric	GlaxoSmithKline K.K.	August 23, 2024
	Pirtobrutinib Jaypirca Tablets 50 mg, 100 mg	Eli Lilly Japan K.K.	August 21, 2024

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiation
Zinc histidine hydrate Zintus Tablets 50 mg	Nobelpharma Co., Ltd.	August 20, 2024
Momelotinib hydrochloride hydrate Omjjara Tablets 100 mg, 150 mg, 200 mg	GlaxoSmithKline K.K.	August 15, 2024
Iptacopan hydrochloride hydrate Fabhalta capsules 200 mg	Novartis Pharma K.K.	August 15, 2024
Favipiravir[*6] Avigan Tablets 200 mg	FUJIFILM Toyama Chemical Co., Ltd.	August 15, 2024
Sargramostim (genetical recombination) Sargmalin for inhalation 250 μg	Nobelpharma Co., Ltd.	July 29, 2024
Fluciclovine (^{18}F) Injection Axumin Injection	Nihon Medi-Physics Co., Ltd.	July 2, 2024
Concizumab (genetical recombination)[*7] Alhemo Subcutaneous Injection 15 mg, 60 mg, 150 mg, 300 mg	Novo Nordisk Pharma Ltd.	June 24, 2024
Vilanterol trifenatate/fluticasone furoate Relvar 100 Ellipta 14 doses, 30 doses	GlaxoSmithKline K.K.	June 24, 2024
Zolbetuximab (genetical recombination) Vyloy for I.V. infusion 100 mg	Astellas Pharma Inc.	June 12, 2024
Nemolizumab (genetical recombination)[*8] Mitchga Vials 30 mg	Maruho Co., Ltd.	June 11, 2024
Susoctocog alfa (genetical recombination) Obizur Intravenous Injection 500	Takeda Pharmaceutical Company Limited	June 10, 2024
Recombinant respiratory syncytial virus vaccine[*9] Abrysvo intramuscular injection	Pfizer Japan Inc.	May 31, 2024
Lebrikizumab (genetical recombination) Ebglyss Subcutaneous Injection Syringes 250 mg, Ebglyss Subcutaneous Injection Autoinjectors 250 mg	Eli Lilly Japan K.K.	May 31, 2024
Apadamtase alfa (genetical recombination)/ cinaxadamtase alfa (genetical recombination) Adzynma Intravenous 1500	Takeda Pharmaceutical Company Limited	May 30, 2024
Cysteamine hydrochloride Cystadrops Ophthalmic Solution 0.38%	Viatris Pharmaceuticals Japan Inc.	May 30, 2024
Lonafarnib Zokinvy capsules 50 mg, 75 mg	AnGes, Inc.	May 27, 2024
Elranatamab (genetical recombination) Elrexfio S.C. Injection 44 mg, 76 mg	Pfizer Japan Inc.	May 22, 2024
Capivasertib Truqap tablets 160 mg, 200 mg	AstraZeneca K.K.	May 22, 2024
Nirsevimab (genetical recombination) Beyfortus 50 mg solution for intramuscular injection in syringe, Beyfortus 100 mg solution for intramuscular injection in syringe	AstraZeneca K.K.	May 22, 2024

Nonproprietary name Brand name	Name of the MAH	Date of EPPV initiation
Belumosudil mesilate Rezurock Tablets 200 mg	Meiji Seika Pharma Co., Ltd.	May 22, 2024
Crovalimab (genetical recombination) Piasky for Injection 340 mg	Chugai Pharmaceutical Co., Ltd.	May 22, 2024
Sacubitril valsartan sodium hydrate*10 Entresto Granules for Pediatric 12.5 mg, 31.25 mg	Novartis Pharma K.K.	May 22, 2024
Luspatercept (genetical recombination) Reblozyl for S.C. injection 25 mg, 75 mg	Bristol-Myers Squibb K.K.	May 20, 2024
Letermovir*11 Prevymis Tablets 240 mg, Prevymis Intravenous Infusion 240 mg	MSD K.K.	May 17, 2024
Talazoparib tosilate Talzenna capsules 0.1 mg, 0.25 mg, 1 mg	Pfizer Japan Inc.	April 23, 2024
Evinacumab (genetical recombination) Evkeeza for Intravenous Infusion 345 mg	Ultragenyx Japan K.K.	April 17, 2024
Danicopan Voydeya tablets 50 mg	Alexion Pharma Godo Kaisha	April 17, 2024
Aflibercept (genetical recombination) Eylea 8 mg solution for IVT inj. 114.3 mg/mL	Bayer Yakuhin, Ltd.	April 17, 2024
Efgartigimod alfa (genetical recombination)/ vorhyaluronidase alfa (genetical recombination) Vyvdura Combination Subcutaneous Injection	argenx Japan K.K.	April 17, 2024
Perampanel hydrate Fycompa for intravenous infusion 2 mg	Eisai Co., Ltd.	April 17, 2024

*1 Prevention of disease caused by SARS-CoV-2 infection (COVID-19)

*2 Excessive motor activity or physically/verbally aggressive behavior due to rapid changes in mood, irritability, and/or outbursts associated with dementia due to Alzheimer's disease

*3 Pulmonary hypertension associated with interstitial lung disease

*4 Prophylaxis of pneumococcal disease (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V,10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F) in the elderly and individuals who are considered to be at high risk of pneumococcal disease

*5 Chronic sinusitis with nasal polyps (for use only in patients who have not sufficiently responded to conventional treatments)

*6 Severe fever with thrombocytopenia syndrome virus infection

*7 Prevention of bleeding tendency in patients with congenital haemophilia who don't have inhibitors against blood coagulation factor VIII or IX

*8 Addition of a pediatric dosage indicated for the following diseases in patients who have not responded sufficiently to conventional treatments
Pruritus associated with atopic dermatitis
Prurigo nodularis

*9 Prevention of infections caused by RS virus in individuals aged 60 years and older

*10 Addition of a pediatric dosage indicated for chronic heart failure

*11 Prophylaxis of cytomegalovirus infections in organ transplant recipients