



# Summary of Investigation Results

## NSAIDs for which systemic effects are expected (prescription drugs)

October 8, 2024

### **Non-proprietary name**

See attachment.

### **Brand name (marketing authorization holder)**

See attachment.

### **Japanese market launch**

See attachment.

### **Indications**

See attachment.

### **Summary of revisions**

1. The necessity of taking safety measures regarding myocardial infarction and cerebrovascular disorder was evaluated.
2. to 24. "Myocardial infarction, cerebrovascular disorder" should be added to the 11.1 Clinically Significant Adverse Reactions section in 11. ADVERSE REACTIONS.

### **Investigation results and background of the revision**

Based on the summary of the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) study on the risk of myocardial infarction and cerebrovascular disorder of non-steroidal anti-inflammatory drugs (NSAIDs) (appendix), the PMDA determined that the risk of myocardial infarction and cerebrovascular disorder for NSAIDs (excluding aspirin) for which systemic effects are expected was suggested. For



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aspirin, the possibility that it was prescribed prophylactically in patients at a high risk of cardiovascular events in the NDB study could not be ruled out. For this and other reasons, the PMDA determined that it was difficult to conclude the relationship between aspirin and the risk of myocardial infarction and cerebrovascular disorder.

As a result of consultation with expert advisors regarding the appropriateness of the above-mentioned PMDA's opinion and the necessity of taking safety measures regarding myocardial infarction and cerebrovascular disorder, the MHLW/PMDA concluded that revision of PRECAUTIONS of NSAIDs (excluding aspirin) for which systemic effects are expected was necessary.

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the "Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

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Attachment

No.	Non-proprietary name (Therapeutic category)	Brand name (marketing authorization holder)	Japanese market launch	Indications
1	Aspirin (Therapeutic category 114: Antipyretics, analgesics and anti- inflammatory agents)	Aspirin "Maruishi" (Maruishi Pharmaceutical Co., Ltd.) and the others	October 1950*	<ul style="list-style-type: none"> <li>•Rheumatoid arthritis, rheumatic fever, osteoarthritis, ankylosing spondylitis, peri-arthritis, fibrositis, post-operative pain, toothache, symptomatic neuralgia, arthralgia, lumbago, myalgia, pain caused by sprain, contusion, and gout, headache, painful menses</li> <li>•Antipyresis/analgesia in the following diseases: Acute upper respiratory tract inflammation (including acute upper respiratory tract inflammation accompanied by acute bronchitis)</li> <li>•Kawasaki disease (including cardiovascular sequelae of Kawasaki disease)</li> </ul>
2	Acemetacin (Therapeutic category 114: Antipyretics, analgesics and anti- inflammatory agents)	Rantudil Kowa Tablets 30 mg (Kowa Company, Ltd.)	July 1992	<ul style="list-style-type: none"> <li>•Anti-inflammation/analgesia in the following diseases and symptoms: Periarthritis scapulohumeralis, lumbago, neck, shoulder and arm syndrome, osteoarthritis, rheumatoid arthritis</li> <li>•Post-operative or post-traumatic anti-inflammation/analgesia</li> <li>•Antipyresis/analgesia in the following diseases: Acute upper respiratory tract inflammation (including acute upper respiratory tract inflammation accompanied by acute bronchitis)</li> </ul>
3	Ampiroxicam (Therapeutic category 114: Antipyretics,	Flucam Capsules 13.5 mg, 27 mg (Pfizer Japan Inc.)	January 1994	<p>Analgesia/anti-inflammation in the following diseases and symptoms:</p> <ul style="list-style-type: none"> <li>•Rheumatoid arthritis</li> </ul>

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No.	Non-proprietary name (Therapeutic category)	Brand name (marketing authorization holder)	Japanese market launch	Indications
	analgesics and anti-inflammatory agents)			<ul style="list-style-type: none"> <li>•Osteoarthritis</li> <li>•Lumbago</li> <li>•Periarthritis scapulohumeralis</li> <li>•Neck, shoulder and arm syndrome</li> </ul>
4	Ibuprofen (Therapeutic category 114: Antipyretics, analgesics and anti-inflammatory agents)	Brufen Tablets 100, 200, Brufen Granule 20% (Kaken Pharmaceutical Co., Ltd.), and the others	Tablets 100, Granule: November 1971 Tablets 200: April 1978	<ul style="list-style-type: none"> <li>•Anti-inflammation/analgesia in the following diseases and symptoms: Rheumatoid arthritis, arthralgia and arthritis, neuralgia and neuritis, back and low back pain, cervicobrachial syndrome, adnexitis, dysmenorrhea, erythema (erythema nodosum, erythema multiforme exudativum, erythema annulare centrifugum)</li> <li>•Post-operative or post-traumatic anti-inflammation/analgesia</li> <li>•Antipyresis/analgesia in the following diseases: Acute upper respiratory tract inflammation (including acute upper respiratory tract inflammation accompanied by acute bronchitis)</li> </ul>
5	Indometacin (Therapeutic category 114: Antipyretics, analgesics and anti-inflammatory agents)	Inteban Suppositories 25, 50 (Teikoku Seiyaku Co.,Ltd.), and the others	Suppositories 25 April 1978 Suppositories 50 September 1968	<ul style="list-style-type: none"> <li>•Anti-inflammation/analgesia in the following diseases: Rheumatoid arthritis, osteoarthritis</li> <li>•Post-operative relief of inflammation and swelling</li> </ul>
6	Indometacin farnesil (Therapeutic category 114: Antipyretics,	Infree Capsules 100 mg, Infree S Capsules 200 mg (Eisai Co., Ltd.)	Capsules 100 mg May 1991 S Capsules 200 mg December 1994	<ul style="list-style-type: none"> <li>Anti-inflammation/analgesia in the following diseases and symptoms: Rheumatoid arthritis, osteoarthritis, lumbago, periarthritis scapulohumeralis, neck, shoulder and arm</li> </ul>

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	analgesics and anti-inflammatory agents)			syndrome
7	Esflurbiprofen/mentha oil (Therapeutic category 264: Analgesics, anti-itchings, astrigents and anti-inflammatory agents)	Loqoa tape (Taisho Pharmaceutical Co., Ltd.)	January 2016	Analgesia/anti-inflammation in osteoarthritis
8	Etodolac (Therapeutic category 114: Antipyretics, analgesics and anti-inflammatory agents)	a. Osteluc Tablets 100, 200 (Aska Pharmaceutical Co., Ltd.) b. Hypen Tablets 100 mg, 200 mg (Nippon Shinyaku Co., Ltd.) and the others	a., b. September 1994	<ul style="list-style-type: none"> <li>•Anti-inflammation/analgesia in the following diseases and symptoms: Rheumatoid arthritis, osteoarthritis, lumbago, peri-arthritis scapulohumeralis, cervicobrachial syndrome, tenosynovitis</li> <li>•Post-operative or post-traumatic anti-inflammation/analgesia</li> </ul>
9	Oxaprozin (Therapeutic category 114: Antipyretics, analgesics and anti-inflammatory agents)	Alvo tablets 100 mg, 200 mg (Taisho Pharmaceutical Co., Ltd.)	December 1985	<ul style="list-style-type: none"> <li>•Anti-inflammation/analgesia in the following diseases and symptoms: Rheumatoid arthritis, osteoarthritis, lumbago, neck, shoulder and arm syndrome, peri-arthritis scapulohumeralis, gout attack</li> <li>•Post-traumatic or post-operative anti-inflammation/analgesia</li> </ul>
10	Ketoprofen (Therapeutic category 114: Antipyretics, analgesics and anti-inflammatory agents)	a. Capisten IM 50 mg (Kissei Pharmaceutical Co., Ltd.) b. Ketoprofen Suppositories 50 mg "JG", Ketoprofen	a. January 1989 b. July 1994*	<ul style="list-style-type: none"> <li>a.</li> <li>•Analgesia/anti-inflammation in the following diseases and conditions: Post-surgery, traumatic injury, various types of cancer, gout attack, symptomatic neuralgia</li> </ul>

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No.	Non-proprietary name (Therapeutic category)	Brand name (marketing authorization holder)	Japanese market launch	Indications
		Suppositories 75 mg "JG" (Choseido Pharmaceutical Co., Ltd.) and the others		<ul style="list-style-type: none"> <li>• When emergency antipyresis is required</li> <li>b.</li> <li>• Analgesia/anti-inflammation/antipyresis in the following diseases and symptoms: Rheumatoid arthritis, osteoarthritis, lumbago, neck, shoulder and arm syndrome, symptomatic neuralgia</li> <li>• Post-traumatic or post-operative analgesia/anti-inflammation</li> </ul>
11	Zaltoprofen (Therapeutic category 114: Antipyretics, analgesics and anti-inflammatory agents)	a. Soleton Tablets 80 (Nippon Chemipharm Co., Ltd.) b. Peon tablets 80 (Zeria Pharmaceutical Co., Ltd.) and the others	a., b. September 1993	<ul style="list-style-type: none"> <li>• Anti-inflammation/analgesia in the following diseases and symptoms: Rheumatoid arthritis, osteoarthritis, lumbago, peri-arthritis scapulohumeralis, neck, shoulder and arm syndrome</li> <li>• Post-operative, post-traumatic, or post-tooth extraction anti-inflammation/analgesia</li> </ul>
12	Tiaramide hydrochloride	Solantal Tablets 50 mg, 100 mg (LTL Pharma Co., Ltd.)	January 1975	<ul style="list-style-type: none"> <li>• Post-operative or post-traumatic analgesia/anti-inflammation in various medical fields</li> <li>• Analgesia/anti-inflammation in the following diseases: Arthritis, lumbago, neck, shoulder and arm syndrome, pelvic inflammation, soft birth canal injury, breast engorgement, herpes zoster, erythema multiforme exudativum, cystitis, epididymitis, anterior eye inflammation, pericoronitis of the wisdom tooth</li> <li>• Post-tooth extraction analgesia/anti-inflammation</li> <li>• Analgesia in the following disease: Acute upper respiratory tract inflammation</li> </ul>

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No.	Non-proprietary name (Therapeutic category)	Brand name (marketing authorization holder)	Japanese market launch	Indications
13	Nabumetone (Therapeutic category 114: Antipyretics, analgesics and anti- inflammatory agents)	Relifen Tab. 400 mg (Sanwa Kagaku Kenkyusho Co., Ltd)	October 1990	Anti-inflammation/analgesia in the following diseases and symptoms: Rheumatoid arthritis, osteoarthritis, lumbago, neck, shoulder and arm syndrome, peri-arthritis scapulohumeralis
14	Naproxen (Therapeutic category 114: Antipyretics, analgesics and anti- inflammatory agents)	Naixan Tablets 100 mg (Nipro ES Pharma Co., Ltd.)	March 1978	<ul style="list-style-type: none"> <li>•Anti-inflammation, analgesia, and antipyresis in the following diseases: Rheumatoid arthritis, osteoarthritis, gout attack, ankylosing spondylitis, lumbago, peri-arthritis scapulohumeralis, neck, shoulder and arm syndrome, tendonitis/tenosynovitis, dysmenorrhea, herpes zoster</li> <li>•Post-operative or post-traumatic anti-inflammation, analgesia</li> <li>•Post-tooth extraction or post-minor operative anti- inflammation, analgesia in the dental/oral surgery fields</li> </ul>
15	Piroxicam (Therapeutic category 114: Antipyretics, analgesics and anti- inflammatory agents)	Baxo Capsule 10, 20 (FUJIFILM Toyama Chemical Co., Ltd.)	August 1982	Anti-inflammation, analgesia in the following diseases and symptoms: Rheumatoid arthritis Osteoarthritis Lumbago Peri-arthritis scapulohumeralis Neck, shoulder and arm syndrome
16	Bucolome (Therapeutic category 114: Antipyretics,	Paramidin Capsules 300 mg (Aska Pharmaceutical. Co., Ltd.)	January 1989	<ul style="list-style-type: none"> <li>•Post-operative or post-traumatic relief of inflammation and swelling</li> <li>•Anti-inflammation/analgesia/antipyresis in the following diseases:</li> </ul>

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	analgesics and anti-inflammatory agents)			Rheumatoid arthritis, osteoarthritis, Cystitis Erythema multiforme exudativum Acute sinusitis, acute otitis media Adnexitis •Management of hyperuricaemia of gout
17	Flufenamate aluminum (Therapeutic category 114: Antipyretics, analgesics and anti-inflammatory agents)	Opyrin tab. 125 mg, 250 mg (Taisho Pharmaceutical Co., Ltd.)	125 mg: August 1967 250 mg: June 1984	•Anti-inflammation, analgesia, antipyresis in the following diseases: Rheumatoid arthritis, osteoarthritis, spinal osteoarthritis, lumbago, scapula periartthritis, arthritis, symptomatic neuralgia •Anti-inflammation, analgesia in the following diseases: Post-tooth extraction, dental pulpitis, pericementitis •Anti-inflammation in the following inflammatory diseases: Cystitis, prostatitis, herpes zoster, eczema/dermatitis, erythema, post-operative or post-traumatic inflammatory reactions in various medical fields •Antipyresis/analgesia in the following diseases: Acute upper respiratory tract inflammation (including acute upper respiratory tract inflammation accompanied by acute bronchitis)
18	Flurbiprofen (Therapeutic category 114: Antipyretics,	Froben Tablets 40, Froben Granule 8% (Kaken Pharmaceutical Co., Ltd.)	Tablets: April 1979 Granule: September 1981	•Analgesia/anti-inflammation in the following diseases and symptoms: Rheumatoid arthritis, osteoarthritis, lumbago, dental pulpitis, pericementitis

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	analgesics and anti-inflammatory agents)			•Post-tooth extraction or post-minor surgery analgesia/anti-inflammation in the field of dentistry
19	Flurbiprofen axetil (Therapeutic category 114: Antipyretics, analgesics and anti-inflammatory agents)	Ropion Intravenous 50 mg (Kaken Pharmaceutical Co., Ltd.)	July 1992	Analgesia in the following diseases and conditions: Post-surgery, various types of cancer
20	Proglumetacin maleate (Therapeutic category 114: Antipyretics, analgesics and anti-inflammatory agents)	Miridacin tablets 90 mg (TAIHO Pharmaceutical Co., Ltd.)	June 1994	Anti-inflammation/analgesia in the following diseases: Rheumatoid arthritis, osteoarthritis, lumbago, neck, shoulder and arm syndrome, peri-arthritis scapulohumeralis
21	Mefenamic acid (Therapeutic category 114: Antipyretics, analgesics and anti-inflammatory agents)	Pontal Capsules 250 mg, Pontal Powder 50%, Pontal Fine Granules 98.5%, Pontal Syrup 3.25% (Pfizer Japan Inc.)	Capsules 250 mg: July 1966 Powder 50%: April 1970 Fine Granules 98.5%: September 1981 Syrup 3.25%: June 1978	•Post-surgery or post-traumatic relief of inflammation and swelling •Analgesia, anti-inflammation, antipyresis in the following diseases and symptoms: Osteoarthritis, lumbago, symptomatic neuralgia, headache (when other agents are ineffective), sinusitis, painful menses, postpartum pain, toothache (capsules, powder, and fine granule only) •Antipyresis/analgesia in the following diseases: Acute upper respiratory tract inflammation (including acute upper respiratory tract inflammation accompanied by acute bronchitis)
22	Meloxicam	Mobic Tablets 5 mg, 10 mg (Nippon Boehringer	January 2005	Anti-inflammation/analgesia in the following diseases and symptoms:

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	(Therapeutic category 114: Antipyretics, analgesics and anti-inflammatory agents)	Ingelheim Co., Ltd.) and the others		Rheumatoid arthritis, osteoarthritis, lumbago, periarthritis scapulohumeralis, neck, shoulder and arm syndrome
23	Loxoprofen sodium hydrate (Therapeutic category 114: Antipyretics, analgesics and anti-inflammatory agents)	Loxonin Tablets 60 mg, Loxonin Fine Granules 10% (Daiichi Sankyo Co., Ltd.), and the others	July 1986	<ul style="list-style-type: none"> <li>•Anti-inflammation/analgesia in the following diseases and symptoms: Rheumatoid arthritis, osteoarthritis, lumbago, periarthritis scapulohumeralis, neck, shoulder and arm syndrome, toothache</li> <li>•Post-operative, post-traumatic, or post-tooth extraction anti-inflammation/analgesia</li> <li>•Antipyresis/analgesia in the following diseases Acute upper respiratory tract inflammation: (including acute upper respiratory tract inflammation accompanied by acute bronchitis)</li> </ul>
24	Lornoxicam (Therapeutic category 114: Antipyretics, analgesics and anti-inflammatory agents)	Lorcam tab. 2 mg, 4 mg (Taisho Pharmaceutical Co., Ltd.), and the others	February 2001	<ul style="list-style-type: none"> <li>•Anti-inflammation/analgesia in the following diseases and symptoms: Rheumatoid arthritis, osteoarthritis, lumbago, neck, shoulder and arm syndrome, periarthritis scapulohumeralis</li> <li>•Post-operative, post-traumatic, or post-tooth extraction anti-inflammation/analgesia</li> </ul>

\* For active ingredients for which the brand name product is not marketed, if a product which has an older date of Japanese market launch than that of the product described in the "Brand name" column is confirmed in package inserts, etc., such a date is described.