TOWA PHARMACEUTICAL CO., LTD.

Revised: October 2022 (25th version, section of Adverse Reactions)
Revised: February 2021 (24th version)

Japanese Pharmacopoeia
Analgesic, Anti-inflammatory and Antipyretic Agent

LOXOPROFEN SODIUM TABLETS 60mg "TOWA"

Storage:
Store at room temperature.
Expiration date:
Indicated on the package and label

Standard Commodity Classification No. of Japan 871149	
Approval No.	22500AMX00572
Date of listing in the NHI reimbursement price	June 2013
Date of initial marketing in Japan	July 1998
Date of result of reevaluation (quality)	October 1999
Date of addition of indication	December 2005

CONTRAINDICATIONS (Loxoprofen Sodium Tablets is contraindicated in the following patients.)

1) Patients with peptic ulcers [Loxoprofen inhibits prostaglandin biosynthesis and decreases gastric blood flow, which may lead to aggravated peptic ulcers. (However, there are exceptional cases. See "Careful Administration.")]
2) Patients with serious abnormalities of the blood [Platelet dysfunction may occur or worsen.]
3) Patients with a serious hepatic disorder [Hepatic disorders have been reported to have occurred as adverse reactions, which may be aggravated.]
4) Patients with a serious renal disorder [Adverse reactions such as acute renal disorder and nephrotic syndrome may occur.]
5) Patients with serious cardiac function failure [Loxoprofen inhibits renal prostaglandin biosynthesis, thereby inducing edema and increasing blood volume, which may lead to aggravated symptoms due to increased cardiac load.]
6) Patients with a history of hypersensitivity to any of the ingredients of this product
7) Patients with aspirin asthma or a history of such asthma (asthmatic attacks induced by drugs such as nonsteroidal anti-inflammatory analgesics) [Loxoprofen may induce an attack of aspirin asthma.]
8) Pregnant women in the third trimester (See "Use during Pregnancy, Delivery or Lactation.")

DESCRIPTION

Active ingredient per tablet	Loxoprofen Sodium Hydrate JP) ····· 68.1mg (60mg as an anhydrate)		
Inactive ingredient	Lactose Hydrate, Low Substituted Hydroxypropylcellulose, Red Ferric Oxide, Yellow Ferric Oxide, Light Anhydrous Silicic Acid, Magnesium Stearate		
Product description	Pale red, uncoated tablet scored on one (reverse) side		
Identification code	Tablet	Tw109	
	Package		
Appearance	Top surface	Bottom surface	Side surface
			
Diameter (mm)	9.0		
Thickness (mm)	3.2		
Weight (mg)	250		

INDICATION

1. Anti-inflammation/analgesia in the following diseases and symptoms:
   Articular rheumatism, arthrosis deformans, low back pain, scapulohumeral periarthritis, neck, shoulder and arm symptoms, toothache
2. Analgesia/anti-inflammation after operation, after trauma, or after tooth extraction
3. Pyretolysis/analgesia in the following disease:
   Acute upper respiratory tract inflammation (including acute upper respiratory tract inflammation associated with acute bronchitis)

DOSAGE AND ADMINISTRATION

For the indications listed in the above "1" and "2":
The usual adult dosage for oral use is 60 mg of loxoprofen sodium (as an anhydrate) 3 times daily. As needed for oral use is 60-120 mg at a time. The dosage may be adjusted according to the patient's age and symptoms.
It is recommended that loxoprofen sodium administration to patients under fasting conditions be avoided.
For the indications listed in the above "3:"
The usual adult dosage as needed for oral use is 60 mg of loxoprofen sodium (as an anhydrate) once. The dosage may be adjusted according to the patient's age and symptoms. However, the recommended maximum dosing frequency is twice/day if clinically appropriate and the maximum daily dosage is 180 mg/day.
It is recommended that loxoprofen sodium administration to patients under fasting conditions be avoided.

PRECAUTIONS

1. Careful Administration

(**Loxoprofen sodium tablets 60mg** should be administered with care in the following patients.)

1) Patients with a history of peptic ulcers [Ulcers may recur.]
2) Patients with peptic ulcers due to long-term nonsteroidal anti-inflammatory analgesic administration who are in need of long-term loxoprofen sodium therapy and who are receiving misoprostol therapy [Misoprostol is indicated for peptic ulcers due to nonsteroidal anti-inflammatory analgesic administration; however, peptic ulcers may occasionally be refractory to misoprostol therapy. If loxoprofen sodium is continuously administered to such patients, this product should be administered cautiously under close observation of individual patients' clinical course.]
3) Patients with abnormalities of the blood or a history of such abnormalities [Adverse reactions including

hemolytic anemia are likely to occur in such patients.]

4) Patients with a hepatic disorder or a history of such disorders [Hepatic disorders may worsen or recur.]
5) Patients with a renal disorder or a history of such disorders [Adverse reactions such as edema, proteinuria, increased serum creatinine, and hyperkalemia may occur.]
6) Patients with abnormal cardiac function (See "CONTRAINDICATIONS.")
7) Patients with a history of hypersensitivity
8) Patients with bronchial asthma [Disease status may be aggravated.]
9) Patients with ulcerative colitis [Disease status may be aggravated.]
10) Patients with Crohn's disease [Disease status may be aggravated.]
11) Elderly patients [See “Use in the Elderly”.]

2. Important Precautions

1) It should be noted that anti-inflammatory analgesic therapy is symptomatic therapy, not causal therapy.
2) For chronic diseases (rheumatoid arthritis, osteoarthritis), loxoprofen sodium should be administered with attention paid to the following aspects:
   (1) If long-term loxoprofen sodium therapy is administered, periodic laboratory tests (e.g., urine analysis, blood tests, and liver function tests) should be performed. If any abnormalities are noted, appropriate measures should be taken, including dosage reduction and/or suspension of this product.
   (2) Therapies other than drug therapy should be considered.
3) For acute diseases, loxoprofen sodium should be administered with attention paid to the following aspects:
   (1) Loxoprofen sodium should be administered in consideration of the severity of acute inflammation, pain and pyrexia.
   (2) Long-term treatment with the same drug should be avoided if possible.
   (3) Loxoprofen sodium therapy should not take the place of causal therapy nor be administered unthoughtfully.
4) Patients' clinical conditions should be closely monitored, and precautions should be taken for the onset of adverse reactions. Excessively decreased body temperature, collapse, cold extremities and such symptoms may develop. Particularly for elderly patients with such symptoms associated with hyperthermia or patients with such symptoms complicated by wasting disease, careful attention should be paid to patients' clinical conditions after loxoprofen sodium administration.
5) Infections may become latent due to loxoprofen sodium administration. For inflammation due to an infection, this product should be administered cautiously in combination with appropriate antibacterial agents as needed, along with close monitoring.
6) It is recommended that coadministration of loxoprofen sodium with other anti-inflammatory analgesic drugs be avoided.
7) When loxoprofen sodium is administered to elderly patients, special precautions (e.g., loxoprofen sodium administration at the minimum required dosage) should be taken for the onset of adverse reactions.

3. Drug Interactions

Precaution for coadministration (**Loxoprofen sodium tablets 60mg** should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms and Treatment	Mechanism and Risk Factors
Coumarin anticoagulant Warfarin	Coadministration of loxoprofen sodium with warfarin may lead to its increased anticoagulant effect; thus, caution should be exercised. Dosage reduction should be performed if necessary.	Loxoprofen inhibits prostaglandin biosynthesis, thereby inhibiting platelet aggregation, which leads to decreased blood coagulation capacity; this is considered to additively contribute to the anticoagulant effect of warfarin.
Factor Xa inhibitors	Coadministration of loxoprofen sodium with these inhibitors may lead to increased risk of hemorrhage.	Coadministration of loxoprofen sodium with these inhibitors is considered to lead to increased antithrombotic effects of such inhibitors.
Sulphonylurea antihyperglycemic drugs Tolbutamide, etc.	Coadministration of loxoprofen sodium with these antihyperglycemic drugs may lead to their increased antihyperglycemic effects; thus, caution should be exercised. Dosage reduction should be performed if necessary.	Regarding the protein binding of loxoprofen in humans, loxoprofen and its *trans*-OH metabolite are 97.0% and 92.8%, respectively, bound to blood proteins (both are highly protein bound). Thus, coadministration of this product with drugs that are highly protein bound is considered to increase blood levels of coadministered drugs that are active and to increase the effects of coadministered drugs.
New quinolone antibacterial agents Levofloxacin hydrate, etc.	Coadministration of loxoprofen sodium with these antibacterial agents may lead to their increased effects of inducing convulsions.	New quinolone antibacterial agents inhibits binding of the neurotransmitter gamma-aminobutyric acid (GABA), the inhibitory compound in the central nervous system, to the GABA receptors, thereby inducing convulsions. Coadministration of loxoprofen sodium with these antibacterial agents is considered to lead to increased inhibition of GABA receptor binding.
Methotrexate	Coadministration of loxoprofen sodium with methotrexate may lead to increased blood methotrexate concentrations, resulting in its increased effects. Thus, dosage reduction should be performed if necessary.	The mechanism is unknown; however, when loxoprofen sodium is coadministered with methotrexate or lithium carbonate, the inhibitory action of loxoprofen on prostaglandin biosynthesis in the kidneys is considered to lead to decreased renal excretion of these drugs, thereby increasing blood concentrations of the drugs.
Lithium preparations Lithium carbonate	Coadministration of loxoprofen sodium with lithium carbonate may lead to increased blood lithium concentrations, resulting in lithium poisoning; thus, attention should be paid to blood lithium concentrations. Dosage reduction should be performed if necessary.	

Thiazide diuretics Hydrochloro-thiazide, etc.	Coadministration of loxoprofen sodium with these diuretics may lead to their decreased diuretic and antihypertensive effects.	Loxoprofen inhibits prostaglandin biosynthesis in the kidneys, thereby decreasing the excretion of water and sodium.
Antihypertensive drugs Angiotensin-converting-enzyme (ACE) inhibitors Angiotensin II receptor antagonists, etc.	Coadministration of loxoprofen sodium with these antihypertensive drugs may lead to their decreased antihypertensive effects.	Loxoprofen inhibits prostaglandin biosynthesis, which may lead to decreased antihypertensive effects of these drugs.
	Coadministration of loxoprofen sodium with these antihypertensive drugs may lead to aggravated renal function.	Loxoprofen inhibits prostaglandin biosynthesis, thereby decreasing renal blood flow.

4. Adverse Reactions

No investigation such as a drug use investigation clearly showing the incidence of adverse reactions has been conducted.

1) Clinically significant adverse reactions (incidence unknown)

(1) **Shock and anaphylaxis**: Shock and anaphylaxis (decreased blood pressure, urticaria, laryngeal edema, dyspnea, etc.) may occur. Patients should be carefully monitored, and if any abnormalities are observed, loxoprofen sodium administration must immediately be discontinued and appropriate measures should be taken.

(2) **Agranulocytosis, hemolytic anemia, leukopenia, decreased platelets**: Agranulocytosis, hemolytic anemia, leukopenia or decreased platelets may occur; thus, close monitoring (e.g., blood tests) should be performed. If any such abnormalities are noted, loxoprofen sodium administration should immediately be discontinued and appropriate treatment should be given.

(3) **Toxic Epidermal Necrolysis: TEN, Mucocutaneo-ocular syndrome (Stevens-Johnson syndrome), Erythema multiforme, acute generalised exanthematous pustulosis**: toxic epidermal necrolysis, mucocutaneo-ocular syndrome (Stevens-Johnson syndrome), erythema multiforme or acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored, and if such symptoms occur, loxoprofen sodium administration should be immediately discontinued and appropriate measures should be taken.

(4) **Acute renal disorder, nephrotic syndrome, interstitial nephritis**: Acute renal disorder, nephrotic syndrome, or interstitial nephritis may occur; thus, close monitoring should be performed. If any such abnormalities are noted, loxoprofen sodium administration should be immediately discontinued and appropriate treatment should be given. Furthermore, hyperkalemia associated with acute renal disorder may occur; special caution should be exercised.

(5) **Congestive cardiac failure**: Congestive cardiac failure may occur; thus, close monitoring should be performed. If any such abnormalities are noted, loxoprofen sodium administration should be immediately discontinued and appropriate treatment should be given.

(6) **Interstitial pneumonia**: Interstitial pneumonia associated with pyrexia, cough, dyspnea, chest X-ray abnormalities, eosinophilia and such may occur. If any such symptoms develop, loxoprofen sodium administration must immediately be discontinued and appropriate treatment should be given, including corticosteroid therapy.

(7) **Gastrointestinal hemorrhages**: Gastrointestinal hemorrhages including hematemesis, melena, and bloody stools due to serious peptic ulcers or due to hemorrhages from the small or large intestine may occur followed by shock; thus, close monitoring should be performed. If any such symptoms develop, loxoprofen sodium administration must immediately be discontinued and appropriate treatment should be given.

(8) **Gastrointestinal perforation:** Gastrointestinal perforation may occur. If any such symptoms as epigastric pain and abdominal pain are noted, loxoprofen sodium administration must immediately be discontinued and appropriate treatment should be given.

(9) **Small/large intestinal stenosis and obstruction**: Small or large intestinal stenosis or obstruction associated with small or large intestine ulcers may occur; thus, close monitoring should be performed. If any such symptoms as nausea/vomiting, abdominal pain, and abdominal distension are noted, loxoprofen sodium administration must immediately be discontinued and appropriate treatment should be given.

(10) **Hepatic function disorder, jaundice**: Hepatic function disorder (e.g., jaundice, increased AST (GOT), increased ALT (GPT), increased γ-GTP) or fulminant hepatitis may occur; thus, close monitoring should be performed. If any such abnormalities are noted, appropriate measures should be taken, including discontinuation of loxoprofen sodium administration.

(11) **Asthmatic attacks**: Acute respiratory disorder such as asthmatic attacks may occur; thus, close monitoring should be performed. If any such abnormalities are noted, loxoprofen sodium administration must immediately be discontinued and appropriate treatment should be given.

(12) **Aseptic meningitis**: Aseptic meningitis (pyrexia, headache, nausea/vomiting, nuchal rigidity, clouding of consciousness and such symptoms) may occur; thus, close monitoring should be performed. If any such abnormalities are noted, loxoprofen sodium administration must immediately be discontinued and appropriate treatment should be given. (Aseptic meningitis is likely to occur particularly in patients with systemic lupus erythematosus (SLE) or mixed connective tissue disease (MCTD).)

(13) **Rhabdomyolysis**: Rhabdomyolysis may occur; thus, close monitoring should be performed. If any such symptoms as myalgia, feelings of weakness, increased CK (CPK), and increased blood/urine myoglobin develop, loxoprofen sodium administration should be discontinued and appropriate treatment should be given. Furthermore, precautions should be taken for the onset of acute renal disorder due to rhabdomyolysis.

2) Clinically significant adverse reactions (similar drugs)

Aplastic anemia: Occurrences of aplastic anemia due to administration of other nonsteroidal anti-inflammatory analgesics have been reported.

3) Other adverse reactions

	Incidence unknown
Hypersensitivity*)	Rash, itching, urticaria, pyrexia
Gastrointestinal	Abdominal pain, stomach discomfort, anorexia, nausea/vomiting, diarrhea, peptic ulcer*), constipation, heartburn, stomatitis, dyspepsia, thirst abdominal distension, ulcer of small/large intestines
Cardiovascular	Palpitations, increased blood pressure
Psychoneurologic	Sleepiness, headache, numbness, dizziness
Hematologic	Anemia, leukopenia, eosinophilia, thrombocytopenia
Hepatic	Increased AST(GOT), increased ALT(GPT), increased A1-P
Urinary organ	Hematuria, proteinuria, dysuria, decreased urine volume
Others	Edema, hot flush, chest pain, malaise, diaphoresis

*): Administration of this product should be discontinued.

5. Use in the Elderly

Adverse reactions are likely to occur in the elderly; thus, loxoprofen sodium should be cautiously administered under close monitoring of elderly patients' clinical conditions (e.g., initiation of administration at a low dose) (See "Important Precautions.")

6. Use during Pregnancy, Delivery or Lactation

1) This product should be used in pregnant women (except at the end of pregnancy) or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. Loxoprofen sodium should be cautiously administered at the minimum required dosage by checking the amniotic fluid volume as appropriate. [The safety of this product in pregnant women has not been established. It has been reported that cyclooxygenase inhibitors (oral and suppository) were administered to pregnant women, resulting in renal dysfunction and decreased urine output in the fetus, and associated Oligohydramnios.]
2) Loxoprofen sodium should not be administered to pregnant women in the third trimester. [In animal studies (in rats), delayed delivery has been reported.]
3) In animal studies, it has been reported that, following loxoprofen sodium administration in rats in late pregnancy, vasoconstriction of arteries was observed in fetuses.
4) Loxoprofen sodium administration to nursing women should be avoided; if it is considered essential, breast-feeding must be suspended. [In animal studies (in rats), loxoprofen has been reported to be excreted in breast milk.]

7. Pediatric Use

The safety of this product in low birth weight infants, neonates, nursing infants, infants and children has not been established.

8. Precautions Concerning Use

Precautions regarding dispensing:

For drugs that are dispensed in a PTP (press-through package) sheet, instruct the patient to remove the drug from the package prior to use [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, causing perforation and resulting in severe complications such as mediastinitis.]

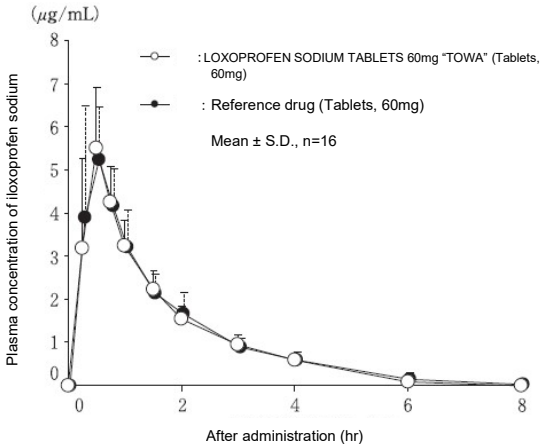
9. Other precautions

It has been reported that transient infertility was observed in women receiving nonsteroidal anti-inflammatory analgesic drugs over the long term.

PHARMACOKINETICS

1. Bioequivalence test

One tablet each of LOXOPROFEN SODIUM TABLETS 60mg "TOWA" and a reference drug (as 60 mg of loxoprofen sodium as an anhydrous) were administered orally as a single dose to healthy adult men under fasting conditions (n=16) in a crossover design to measure each unchanged drug concentration in plasma. Obtained pharmacokinetic parameters (AUC and Cmax) were statistically analyzed. The analysis results confirmed the bioequivalence of these drugs (based on PAB/PCD Notification No. 718, May 30, 1980)[1].



	Determined parameter		Reference parameter	
	AUC_8 (μg·hr/mL)	Cmax (μg/mL)	Tmax (hr)	$T_{1/2}$ (hr)
LOXOPROFEN SODIUM TABLETS 60mg "TOWA" (Tablets, 60mg)	8.74±1.38	5.85±1.39	0.48±0.14	1.45±0.20
Reference drug (Tablets, 60mg)	8.90±1.86	5.91±1.61	0.44±0.14	1.53±0.35

(Mean ± S.D., n=16)

Plasma concentration and parameters such as AUC and Cmax may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

2. Dissolution profile

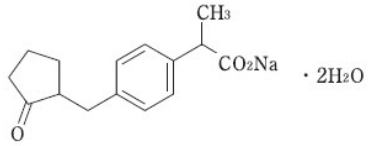
LOXOPROFEN SODIUM TABLETS 60mg "TOWA" have been confirmed to conform to the corresponding dissolution standards of Loxoprofen Sodium Tablets defined in the monograph of the Japanese Pharmacopoeia [2].

PHARMACOLOGY

Loxoprofen is a prodrug and its active trans-alcohol form (trans-OH) metabolite acts as an acidic nonsteroidal anti-inflammatory drug; i.e., this metabolite inhibits the production of prostaglandins by inhibiting cyclooxygenase (COX), a rate-limiting enzyme responsible for prostaglandin biosynthesis, thereby exerting anti-inflammatory, antipyretic, and analgesic effects. Loxoprofen is not selective for a constitutive form COX (COX-1) or inducible form COX (COX-2).[3]

PHYSICOCHEMISTRY

Structural formula:



Nonproprietary name:
Loxoprofen Sodium Hydrate
Commonly used name:
Loxoprofen Sodium
Chemical name:
Monosodium 2-{4-[(2-oxocyclopentyl)methyl] phenyl} propanoate dihydrate
Molecular formula:
$C_{15}H_{17}NaO_3 \cdot 2H_2O$
Molecular weight:
304.31
Description:
Loxoprofen Sodium Hydrate occurs as white to yellowish white, crystals or crystalline powder. It is very soluble in water and in methanol, freely soluble in ethanol (95), and practically insoluble in diethyl ether.
A solution of Loxoprofen Sodium Hydrate (1 in 20) does not show optical rotation. The pH of a solution of 1.0 g of Loxoprofen Sodium Hydrate in 20 mL of freshly boiled and cooled water is between 6.5 and 8.5.

PRECAUTIONS FOR HANDLING

1. Precautions

Red spots may appear on the surface of LOXOPROFEN SODIUM TABLETS 60mg "TOWA". These are due to the inactive ingredients used as colorants.

2. Stability test

In a long-term test using final packaging products (at 25°C and 60% relative humidity for 4 years), LOXOPROFEN SODIUM TABLETS 60mg "TOWA" were confirmed to be stable for 4 years under normal distribution conditions in the market [4)].

PACKAGING

LOXOPROFEN SODIUM TABLETS 60 mg "TOWA":
Boxes of 100 tablets, 1,000 tablets (PTP)
Polyethylene containers of 1,000 tablets

REFERENCES

1) Internal data of Towa Pharmaceutical Co., Ltd.: Bioequivalence test
2) Internal data of Towa Pharmaceutical Co., Ltd.: Dissolution test
3) The 16th revision Japanese Pharmacopoeia explanatory, C-5359, 2011
4) Internal data of Towa Pharmaceutical Co., Ltd.: Stability test

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