LOXOPROFEN SODIUM HYDRATE PATCH

Containing Loxoprofen Sodium Hydrate (JP) 113.4mg (100mg as Anhydride)

1. NAME OF THE MEDICINAL PRODUCT

Japrolox Patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

QUALITATIVE COMPOSITION

Generic Name

Loxoprofen Sodium Hydrate (JAN) / Loxoprofen (INN)

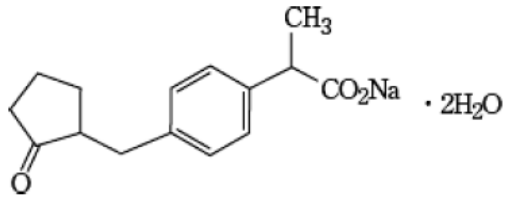
Chemical Name

Monosodium 2-{4-[(2-oxocyclopentyl)methyl]phenyl}propanoate dihydrate

Molecular Formula $C_{15}H_{17}NaO_3 2H_2O$

Molecular Weight 304.31

Structural Formula



Description

Loxoprofen sodium hydrate occurs as a white to off-white crystal 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 (1 → 20) shows no polarization rotation.

QUANTITATIVE COMPOSITION

Loxoprofen sodium water-based patch

A patch containing 113.4mg (100mg as anhydride) of loxoprofen sodium hydrate in 10g of ointment (a sheet of 140 cm^2).

3. PHARMACEUTICAL FORM

Loxoprofen sodium water-based patch

Patch preparation comprising ointment, uniformly spread over a support with the surface of the ointment covered by a liner. The ointment surface is white to pale yellow in color. The ointment has a fragrance of mentha oil.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Loxoprofen sodium patch is indicated for Anti-inflammation and pain relief in Osteoarthritis, Myalgia, Posttraumatic Swelling and Pain.

4.2 Posology and method of administration

Apply to the affected area once daily.

4.3 Contraindications

Loxoprofen sodium patch is contraindicated in the following patients.

- Patients with a history of hypersensitivity to any ingredients of Loxoprofen sodium patch.
- Patients with or with a history of aspirin-induced asthma (induction of asthmatic attack with nonsteroidal anti-inflammatory-analgesics, etc.) [May induce an aspirin- induced asthmatic attack.]

4.4 Special warnings and precautions for use

Careful Administration

Loxoprofen sodium patch should be administered with caution in the following patients: Patients with bronchial asthma (as the disease state may be exacerbated.)

Clinically Significant Adverse Reactions

Shock, anaphylaxis: Shock or anaphylaxis (decreased blood pressure, urticaria, laryngeal oedema, dyspnoea, etc.) may occur. Patients should be carefully monitored. If any abnormalities are observed, use of this drug should be discontinued immediately and appropriate measures should be taken."

Important Precautions

- It is important to note that treatment with anti-inflammatory- analgesic agents is a symptomatic treatment, not a causal treatment.

• For treatment of skin inflammation caused by infectious disease, Loxoprofen sodium patch may cause a risk of masking the signs and symptoms of the infectious disease, therefore, the appropriate antibacterial and/or antifungal drugs must be administered in combination with Loxoprofen sodium patch to the affected part of the skin, under careful observation and caution.

• Therapies other than drug treatment must also be considered in using Loxoprofen sodium patch in the management of chronic diseases (osteoarthritis and others). The patient's clinical condition should be closely monitored with caution against the development of adverse reactions.

• Avoid using this drug in people with bleeding in the stomach, intestines or ulcers. Since this drug increases the risk of developing these symptoms.

• Avoid using in people with liver disease or kidney disease or abnormal liver function or kidney function.

• This drug, if used continuously for a long time, may produce adverse reactions, such as oral medication, such as the risk of platelet abnormalities or disorders of the cardiovascular system.

Use in the Elderly

Loxoprofen sodium patch should be used with careful monitoring of dermal condition of application area, in the elderly patients.

Pediatric Use

The safety of Loxoprofen sodium patch in low birth weight infants, newborn infants, infants and toddlers, children and adolescents has not been established (because there has been little experience of its use in pediatric patients).

Precautions Concerning Use

Site of application;

• Do not apply Loxoprofen sodium patch onto area of damaged or non-intact skin or mucosal membrane.

• Do not apply Loxoprofen sodium patch onto area of eczema and rash.

4.5 Interactions with other Medicinal Products and other Forms of Interactions

Not applicable to both contraindications and precautions for coadministration.

4.6 Pregnancy and Lactation

• Loxoprofen sodium patch should be administered to women who are or are possibly pregnant only when the anticipated therapeutic benefits are considered to outweigh any potential risk. [The safety of Loxoprofen sodium patch in these populations has not been established.]

- It has been reported that constriction of the fetal ductus arteriosus is observed when woman in the late stage of pregnancy received other nonsteroidal anti-inflammatory analgesic drugs for external use.

4.7 Effects on Ability to Drive and Use Machines

There is no data available on effects on ability to drive and use machines.

4.8. Undesirable Effects

	0.5% to <3%	<0.5%	Incidence unknown
Hypersensitivity	Pruritus, erythema, contact dermatitis, rash	Haemorrhage subcutaneous, skin irritation, pigment precipitation	Blister, swelling
Gastrointestinal		Stomach discomfort, upper abdominal pain, diarrhea, loose stools	
Hepatic		Increased AST(GOT), increased ALT(GPT), increased $\gamma - GTP$	
Other		Edema	

4.9. Overdose

There is no data available on overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of Action

After being absorbed transdermally, loxoprofen sodium hydrate is biotransformed into an active metabolite trans-OH form (SRS coordination) to exert its excellent anti-inflammatory and analgesic effects in acute inflammations, chronic inflammations and pain.

Anti-inflammatory effects

Loxoprofen sodium water-based patch has been demonstrated significant anti-inflammatory effects on both acute inflammations such as carrageenan-induced edema (rat) and chronic inflammations such as adjuvant arthritis (rat).

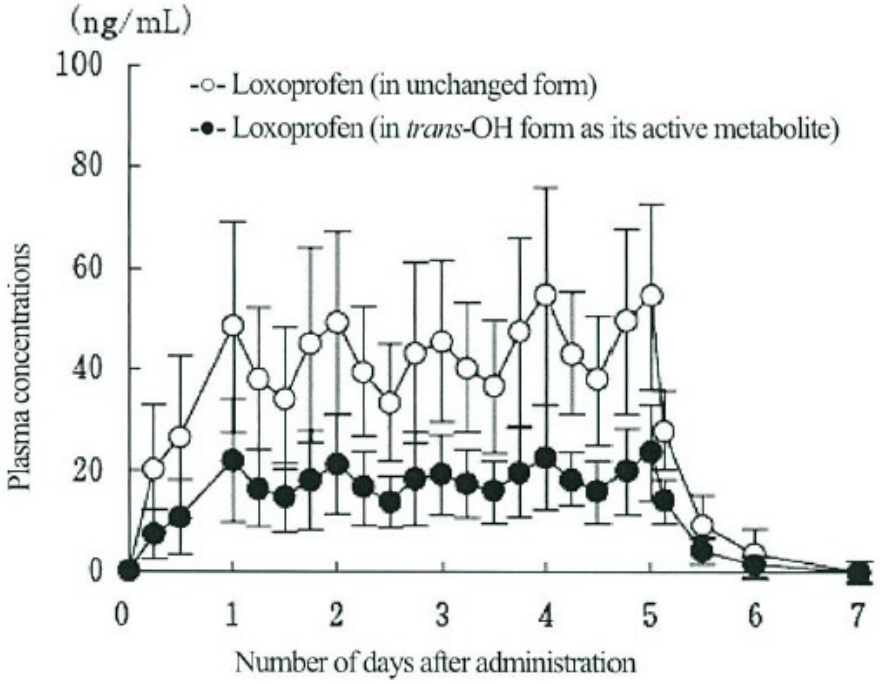
Analgesic effects

Loxoprofen sodium water-based patch has been demonstrated to show the analgesic effect in the Randoll-Selitto test (inflamed paw pressuring method: rat), and in the chronic adjuvant arthritis pain test (rat).

5.2 Pharmacokinetic properties

Plasma Concentration

Each of 14 Japanese healthy male adult volunteers was subjected to repeated administration of two Loxoprofen sodium water-based patches on the back once a day for five days, showing detection of loxoprofen and its trans-OH form (active metabolite) in the plasma immediately after the start of the administration with their plasma concentrations gradually increasing over the period of the administration before reaching steady state in four or five days after the administration at low levels compared to those achieved by the equivalent oral dose of the same drug until, upon the discontinuation of the administration, they rapidly disappeared from the plasma to concentrations below the limit of quantitative determination (LQD).



Data are expressed as mean ± SD (n=14).

Plasma concentrations of loxoprofen and its *trans*-OH active metabolite after five-day repetitive administration of LOXONIN® PAP 100mg (2 patches)

	Css (ng/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	MRT (hr)
Loxoprofen (in unchanged form)	54.9 ±19.3	5,281 ±1,704	72.2 ±4.8
Loxoprofen (in *trans*-OH form as its active metabolite)	23.5 ±9.5	2,278 ±863	73.1 ±4.9

Data are expressed as mean ± SD (n=14).

Tissue Penetration

Administration of 3.5cm^2 of the Loxoprofen sodium water-based patch (containing ^{14}C-loxoprofen) to the rat dorsal skin for a time period of 24 hours showed that the concentration of radioactivity in the skeletal muscle immediately under the patch administered area of the skin was 3.6- to 24-fold higher than that in the skeletal muscle under the patch non-administered area of the skin, confirming the formation of the trans-OH form of ^{14}C-loxoprofen as its active metabolite.

Metabolism

An in vitro test of loxoprofen sodium hydrate for metabolism inhibition using human hepatic microsome showed that the drug did not inhibit the metabolism of substrates for cytochrome P450 enzymes (CYP1A1/2, 2A6, 2B6, 2C8/9, 2C19, 2D6, 2E1 and 3A4) even at a concentration of 200µM equivalent to 1,000 times or more than the maximum plasma concentration observed by administration of Loxoprofen sodium water-based patch in a dose of one patch a day.

Urinary Excretion

Each of 14 Japanese healthy male adult volunteers was subjected to repeated administration of two Loxoprofen sodium water-based patches on the back once a day for five days, showing that the daily urinary excretion of loxoprofen, its trans-OH form (active metabolite) and *cis*-OH form remained almost constant after the elapse of 24 hours following the administration with the total cumulative excretion rate of 2.67% from the start of the administration until 48 hours after the discontinuation of the administration.

5.3 Preclinical safety data

Toxicity test
Single dose toxicity test

0, 2 and 4% (0, 28.6 and 57.1 mg/body as anhydride respectively) of Loxoprofen sodium water-based patch (4 x 5 cm) was percutaneously administered to the trimmed and shaved dorsal skin of Wistar-Imamichi rats (5 males and 5 females per group) for 24 hours (occluded exposure). In each group, no fatal cases were found and no effects were observed on general conditions, body weight and autopsy findings.

Repeated dose toxicity test
Rat

0, 0.5, 1 and 2% of Loxoprofen sodium water-based patch was percutaneously administered to Wistar-Imamichi rats (10 males and 10 females per group) once a day for 3 months. The amount of exposure to loxoprofen sodium hydrate was 0, 10, 20 and 40 mg/kg as anhydride respectively. In the control group, 0, 5, 10 and 20 mg/kg of loxoprofen sodium hydrate as anhydride was orally administered once a day for 3 months. In the male, degeneration in renal papillary interstitium was observed in 1 case among the 1% administered group. In the female, it was observed in 2 cases among both the 0.5% and 1% administered groups and 3 cases among the 2% administered group. The degeneration in kidney was mild, and in the other organs, no apparent toxicity findings were observed even at the highest dose. No-observed-adverse-effect level of Loxoprofen sodium water-based patch was estimated to be

0.5% (equivalent to 10 mg/kg) for male and less than 0.5% (equivalent to 10 mg/kg) for female.

Monkey

0, 1, 2 and 4% of Loxoprofen sodium water-based patch was percutaneously administered to cynomolgus monkeys (3 males and 3 females per group) once a day (21 to 26 hours) for 3 months (13 weeks) (occluded exposure). No changes were observed in general conditions, body weight, food consumption, and haematology, blood chemical and pathology tests. No-observed-adverse-effect level of Loxoprofen sodium water-based patch was estimated to be equal to or higher than 4% in both male and female.

Other specific toxicity

Local irritation, skin sensitization, skin photosensitization and phototoxicity tests were performed using the base of Loxoprofen sodium water-based patch and 1, 2 and 4% of Loxoprofen sodium water-based patch. No toxicity findings were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Loxoprofen sodium water-based patch

Mentha oil, polysorbate 80, titanium oxide, tartaric acid, disodium edetate hydrate, concentrated glycerin, carmellose sodium, talc, dried aluminum hydroxide gel, crotamiton, partially neutralized polyacrylate, Starch Grafted Acrylate 300 and Emulsion of Methyl Acrylate and 2-Ethylhexyl Acrylate Copolymer.

6.2 Incompatibilities data

No applicable data is available.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Japrolox Patch must be stored in light-proof tightly-sealed container. Do not store above 30°C.

6.5 Nature and contents of container

A light-protective/moisture-proof.

6.6 Instructions for use/handling

Expiration date for use

Loxoprofen sodium patch must be used before the expiration date indicated on the package or label.

Instructions for use/handling

After removing the patch from the pouch for use, be sure to close it securely by gently pressing both sides of its zip-lock portion against each other.

7. MANUFACTURER

Lead Chemical Co., Ltd.

Hisagane Plant

327 Hisagane Kamiichi-machi Nakaniikawa-gun, Toyama, Japan

8. MARKETING AUTHORISATION NUMBERS

Refer to outer box and immediate label.

9. IMPORTER AND MARKETING AUTHORIZATION HOLDER

ZUELLIG PHARMA LTD., Bangkok, Thailand

10. DATE OF REVISION OF THE TEXT

OCT 2, 2019