

ROXONIN® 60 mg Tablets SAJA PHARMA

Loxoprofen sodium

1. NAME OF THE MEDICINAL PRODUCT

ROXONIN 60 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ROXONIN Tablet contains the following ingredients per tablet

Active Ingredient: Loxoprofen sodium hydrate (JP) 68.1 mg (60 mg as anhydride)

Excipients:

Lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

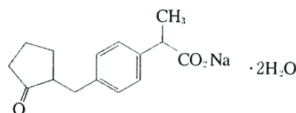
ROXONIN 60 mg is Pale red tablet, Coded by SJ 112 on one side and plain on the other side

PHYSICOCHEMICAL PROPERTIES OF THE ACTIVE INGREDIENTS

Nonproprietary name: Loxoprofen Sodium Hydrate

Chemical name: Monosodium 2-{4-[(2-oxocyclopentyl)methyl]phenyl} propanoate dehydrate

Molecular formula: C₁₅H₁₇NaO₃·2H₂O



Molecular weight: 304.31

Structural formula:

Description: Loxoprofen sodium hydrate occurs as white to off-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 (1 → 20) shows no optical rotation.

Partition Coefficient:

Organic solvent	pH of aqueous phase	Partition coefficient K
1-Octanol	JP, Medium 1 (pH 1.2)	190
	JP, Medium 2 (pH 6.8)	0.82

Chloroform	JP, Medium 1 (pH 1.2)	87
	JP, Medium 2 (pH 6.8)	0.95

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1. For relief of inflammation and pain in the following disorders and symptoms:

Rheumatoid arthritis, osteoarthritis, lower back pain, peri-arthritis of the shoulder, and shoulder-arm-neck syndrome, toothache

2. For relief of postoperative, post-traumatic or post-exodontal pain and inflammation

3. For antipyresis and relief of pain in the following disorder:

Acute upper respiratory, tract inflammation, (including acute upper. airway inflammation, accompanying acute bronchitis)

4.2 Posology and method of administration

Posology:

For indications (1 & 2) the usual adult dosage is 60 mg of loxoprofen sodium (as anhydride) orally three times a day.

For p.r.n. use, administer 60-120 mg once orally. The dosage may be adjusted according to the patient's age and symptoms.

For indication (3) the usual adult dosage is 60 mg of loxoprofen sodium (as anhydride) p.r.n. once orally.

The dosage may be adjusted according to the patient's age and symptoms. In principle, the recommended maximum daily dose of ROXONIN is twice daily administration, and the total daily dose should not exceed 180 mg/day.

Use of ROXONIN on an empty stomach should be avoided.

Use in the Elderly

In as much as adverse reactions are likely to occur in elderly patients, ROXONIN should be used with caution, e.g., starting at a low dose, while closely monitoring the patient's condition (see "Important Precautions").

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Pediatric Use

The safety of ROXONIN in low birth weight infants, newborn infants, Infants and toddlers, Children and adolescents has not been established.

Precautions Concerning Use

When ROXONIN Tablets are dispensed, patients should be instructed to remove each tablet from the PTP blister package before taking the drug. [It has been reported that accidental ingestion of the blister package can lead to esophageal mucosal injury and subsequent perforation caused by the pointed corner of the package, resulting in serious complications such as mediastinitis.]

4.3 Contraindications

(ROXONIN is contraindicated in the following patients.)

- Patients with peptic ulcers [Peptic ulcers may be aggravated due to reduced gastric blood flow resulting from inhibition of prostaglandin biosynthesis.] (See “Careful Administration”)
- Patients with severe blood disorders [Platelet dysfunction may occur and the abnormality may be worsened.]
- Patients with severe hepatic functions disorders [Hepatic function disorders have been reported with the use of ROXONIN, and the patient’s hepatic function disorder may be aggravated.]
- Patients with severe renal impairment [Adverse reactions such as acute renal failure, nephrotic syndrome, etc. have been reported with the use of ROXONIN.]
- Patients with severe cardiac function failure [Cardiac symptoms may be exacerbated because inhibition of prostaglandin biosynthesis in the kidneys may cause edema and an increase in circulating body fluid volume, with a consequent increase in cardiac work.]
- Patients with a history of hypersensitivity to any ingredients of ROXONIN.
- Patients with or with a history of aspirin-induced asthma (induction of asthmatic attack with non steroidal anti-inflammatory-analgesics, etc.) [May induce an aspirin-induced asthmatic attack.]
- Women in the late stages of pregnancy [See “Use during Pregnancy, Delivery, or Lactation”]

4.4 Special warnings and precautions for use**1) Careful Administration (ROXONIN should be administered with caution in the following patients.)**

- a) Patients with a history of peptic ulcers [since the use of ROXONIN may cause recurrence of ulceration.]
- b) Patients with peptic ulcer associated with chronic use of nonsteroidal anti-inflammatory-analgesic agents whose clinical condition requires long-term administration of ROXONIN and who are currently on misoprostol therapy [ROXONIN must be administered with care while closely monitoring the clinical condition of patients receiving this drug continuously, because peptic ulcers may be refractory to treatment with misoprostol, which is indicated for nonsteroidal antiinflammatory- analgesic drug-induced peptic ulceration.]
- c) Patients with or with a history of blood disorders [since adverse reactions such as hemolytic anemia are prone to occur.]
- d) Patients with or with a history of hepatic function disorders [because exacerbation or recurrence of the hepatic function disorders have been reported with the use of ROXONIN.]
- e) Patients with or with a history of renal impairment [since adverse reactions such as edema, proteinuria, serum creatinine elevation or hyperkalemia have been reported with the use of ROXONIN.]
- f) Patients with cardiac dysfunction [See “CONTRAINDICATIONS”]
- g) Patients with a history of hypersensitivity
- h) Patients with bronchial asthma [as the disease state may be exacerbated.]
- i) Patients with colitis ulcerative [as the disease state may be exacerbated.]
- j) Patients with Crohn’s disease [as the disease state may be exacerbated.]
- k) Elderly subjects [See “Use in the Elderly”].]

2) Important Precautions

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

- b) The following should be considered when using ROXONIN in the management of chronic diseases (rheumatoid arthritis, osteoarthritis):
- i) Patients receiving long-term medication should be followed by periodic laboratory examinations (e.g., urinalysis, hematological examination, liver function tests). If any abnormality is noted, appropriate measures such as dosage reduction or withdrawal should be taken.
 - ii) Therapies other than drug treatment must also be considered.
- c) The following should be considered in using ROXONIN in the management of acute diseases:
- i) The proper dosage regimen, depending on the degree of acute inflammation, pain and fever, should be determined.
 - ii) Long-term use of the same drug(s) must be avoided in principle.
 - iii) If any causal treatment is available, should be undertaken preferentially. Aimless treatment with ROXONIN should be avoided.
- d) The patient's clinical condition should be closely monitored with caution against the development of adverse reactions. As an excessive decrease in body temperature, collapse, coldness of limbs, etc. may be manifested in patients using ROXONIN, the clinical status must be carefully monitored after administration of the drug especially in elderly patients with a high-grade fever or patients with a debilitating disease.
- e) ROXONIN may mask the signs and symptoms of infections. Therefore, an appropriate antibiotic should be used in combination to treat inflammation due to infection, and the patient should be closely monitored and ROXONIN administered with care.
- f) It is recommended to avoid the concomitant use of other anti-inflammatory- analgesic agents with ROXONIN.
- g) In elderly patients pay special attention to adverse reactions. Careful administration is necessary; for example, care should be taken to administer the individual minimum effective dose.

3) Other Precautions

- a) It has been reported that temporary sterility is observed in women receiving long-term NSAID therapy

4.5 Interaction with other medicinal products and other forms of interaction

1. Drug Interactions Precautions for co-administration (ROXONIN should be co-administered with care when administered with the following drugs.).

See Table.

4.6 Pregnancy, Delivery and lactation

Pregnancy

- ROXONIN 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 this ROXONIN in these populations has not been established.]
- ROXONIN should not be used in women in the late stages of pregnancy. [Delayed parturition has been reported in an animal study (in rats).]
- Fetal arterial vasoconstriction has been reported in a study on rats receiving the drug in the late stages of gestation.

Lactation

- Administration of this drug to nursing mothers should be avoided. If administration of this drug is judged to be essential, nursing should be discontinued. [Preclinical studies have showed that loxoprofen is excreted into milk in rats.]

4.7 Effects on ability to drive and use machines

Some undesirable effects (e.g. dizziness or sleepiness), have been reported.

To be safe, should be careful when driving and using machine.

4.8 Undesirable effects

(Including reports on adverse reactions the incidence of which cannot be calculated)

Adverse reactions to this drug were reported in 409 (3.03%) of 13,486 patients treated. The major adverse reactions reported were gastrointestinal symptoms (Stomach discomfort, abdominal pain,

Drugs	
Signs, Symptoms, and Treatment	Mechanism and Risk factors
Coumarin Anticoagulants (e.g., Warfarin)	
The anticoagulant effect of these drugs may be enhanced. Therefore, caution should be exercised and the dosage reduced as necessary.	The inhibitory effect of this drug on prostaglandin biosynthesis may lead to inhibition of platelet aggregation and to hypo-coagulation, thereby adding to the anticoagulant effects of these drugs.
Sulfonylurea hypoglycemic agents (e.g., Tolbutamide)	
The hypo glycemc effect of these drugs may be enhanced. Therefore, caution should be exercised and the dosage reduced as necessary.	It is generally considered that co-administration of this drug, the protein-binding rate of which is as high as 97.0% as loxoprofen or 92.8% as its trans-OH form, results in increased plasma levels of active form of the concurrently administered hypoglycemic agent with a high protein-binding rate, to enhance the effect of the latter drug.
New quinolone antimicrobial agents (e.g., Enoxacin hydrate)	
The convulsant effect of these drugs may be enhanced.	New quinolone antimicrobials inhibit receptor binding of GABA, an inhibitory neuro transmitter in the central nervous system, and hence may produce a convulsant effect. Co-administration with these drugs is thus considered to enhance their inhibitory effects.
Methotrexate	
Plasma methotrexate concentration may be increased, leading to enhancement of the effects of methotrexate.	
Therefore, the dose should be reduced whenever deemed necessary.	
Although the exact mechanism is not known, it is generally thought that excretion of the drug from the kidneys is reduced with a consequent elevation in its plasma concentration due to the drug's inhibition of prostaglandin biosynthesis in the kidneys.	
Lithium preps. (e.g., Lithium carbonate)	
Plasma lithium concentration may be increased, giving rise to lithium poisoning. Therefore, plasma lithium concentration should be carefully monitored and the dosage reduced as necessary.	
Thiazide diuretics (e.g., Hydroflumethiazide, hydrochlorothiazide)	
Diuretic-anti hypertensive effects of these drugs may be reduced.	It is generally considered that the inhibitory effect of this drug on prostaglandin biosynthesis in the kidneys leads to reduction in water and sodium excretion.

nausea and/or vomiting, anorexia, etc.: 2.25%); edema (0.59%); rash, urticaria, etc. (0.21%); and sleepiness (0.10%). [At the end of reexamination period¹) and at the latest approval of indications 2-7]]

(1) **Clinically significant adverse reactions** (incidence unknown)

i) **Shock and anaphylactoid symptoms:** Shock and anaphylactoid symptoms (decreased blood pressure, urticaria, edema of the larynx, dyspnea, etc.) have been reported with the use of ROXONIN. Patients should be carefully monitored during treatment. If any abnormal symptoms occur in a patient being treated with ROXONIN, ROXONIN should be discontinued and appropriate therapies should be initiated immediately.

ii) **Hemolytic anemia, leukopenia, and thrombocytopenia:** Hemolytic anemia, leukopenia, and thrombocytopenia have been reported with the use of ROXONIN. Patients should be carefully followed by hematological examination, etc. during treatment. If any abnormal symptoms occur in a patient being treated with ROXONIN, ROXONIN should be discontinued and appropriate therapies should be initiated immediately.

iii) **Oculomucocutaneous syndrome and toxic epidermal necrolysis:** Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell syndrome) have been reported with the use of ROXONIN. Patients should be carefully monitored during treatment. If any abnormal symptoms occur in a patient being treated with ROXONIN, ROXONIN should be discon-

tinued and appropriate therapies should be initiated immediately.

- iv) **Acute renal failure, nephrotic syndrome and interstitial nephritis:** Acute renal failure, nephrotic syndrome and interstitial nephritis have been reported with the use of ROXONIN. Patients should be carefully monitored during treatment. If any abnormal symptoms occur in a patient being treated with ROXONIN, ROXONIN should be discontinued and appropriate therapies should be initiated immediately. ROXONIN should be used with special caution in such patients because hyperkalemia may appear in association with acute renal failure.
- v) **Cardiac failure congestive:** Cardiac failure congestive has been reported with the use of ROXONIN. Patients should be carefully monitored during treatment. If any abnormal symptoms occur in a patient being treated with ROXONIN, ROXONIN should be discontinued and appropriate therapies should be initiated immediately.
- vi) **Interstitial pneumonia:** Interstitial pneumonia with manifestations of fever, cough, dyspnea, chest X-ray abnormalities, and eosinophilia have been reported with the use of ROXONIN. If these signs/findings are observed in a patient being treated with ROXONIN, ROXONIN should be discontinued and appropriate therapies such as corticosteroid medication, should be initiated immediately.
- vii) **Gastrointestinal bleeding:** Serious peptic ulceration or gastrointestinal bleeding from the small intestine and/or large intestine, e.g., hematemesis, melena and hematochezia, and consequent shock has been reported with the use of ROXONIN. Patients should be carefully monitored during treatment. If any abnormal symptoms occur in a patient being treated with ROXONIN, ROXONIN should be discontinued and appropriate therapies should be initiated immediately.
- viii) **Gastrointestinal perforation:** Gastrointestinal perforation has been reported with the use of ROXONIN. If epigastric pain, abdominal pain,

etc. are noted in a patient being treated with ROXONIN, ROXONIN should be discontinued and appropriate therapies should be initiated immediately.

- ix) **Hepatic function disorders, and jaundice:** Hepatic function disorders including jaundice, increased serum levels of AST (GOT), ALT (GPT) and γ -GTP, or fulminant hepatitis have been reported with the use of ROXONIN. Patients should be carefully monitored during treatment. If any abnormal symptoms occur in a patient being treated with ROXONIN, ROXONIN should be discontinued and appropriate therapies should be initiated.
 - x) **Asthmatic attack:** Acute respiratory disorders such as asthmatic attack have been reported with the use of ROXONIN. Patients should be carefully monitored during treatment. If any abnormal symptoms occur in a patient being treated with ROXONIN, ROXONIN should be discontinued and appropriate therapies should be initiated immediately.
 - xi) **Aseptic meningitis:** Aseptic meningitis including fever, headache, nausea and vomiting, nuchal rigidity, clouding of consciousness, etc. has been reported with the use of ROXONIN. Patients should be carefully monitored during treatment. If any abnormal symptoms occur in a patient being treated with ROXONIN, ROXONIN should be discontinued and appropriate therapies should be initiated immediately. (in particular, the adverse event is likely to occur in the patients with systemic lupus erythematosus or mixed connective tissue disease).
- (2) Clinically significant adverse reactions reported in association with the use of other non steroidal anti-inflammatory-analgesic drugs**
- i) **Aplastic anemia:** Aplastic anemia has been reported in association with the use of other non-steroidal anti-inflammatory-analgesic drugs.

(3) Other adverse reactions

Adverse Reactions			
Frequency of Adverse Reactions			
0.1 to <1.0%	0.05to <0.1%	<0.05%	Incidence unknown
Hypersensitivity ^{Note}			
Rash	Pruritus	Urticaria	Fever
Gastrointestinal			
Abdominal pain Stomach discomfort Anorexia, Nausea and/or vomiting, Diarrhea	Peptic ulcer ^{Note} Constipation Heartburn Stomatitis	Dyspepsia	Thirst Abdominal Distension
Cardiovascular			
		Palpitations	Blood pressure increased
Psychone-urologic			
Sleepiness		Headache	Numbness
Hematologic			
		Anemia, Leukopenia Eosinophilia	Thrombocytopenia
Hepatic			
Increased AST (GOT), increased ALT (GPT)		Increased ALP	
Urinary			
			Hematuria Proteinuria
Others			
Edema		Facial- warmth	Chest pain Malaise
(Note) Discontinue administration.			

4.9 Overdose

Although there is no experience of acute overdose with loxoprofen sodium hydrate, it may be expected that the signs and symptoms mentioned under Adverse Reactions would be more pronounced.

There exists no specific antidote for loxoprofen sodium hydrate, overdose should be countered by conventional measures to reduce absorption (eg gastro-lavage and charcoal) and speed up elimination.

In the case of an actual or suspected overdose, patients should be observed and appropriate hydration maintained. Symptomatic and supportive treatments should be used.

5. PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties****General properties**

Loxoprofen sodium hydrate has excellent analgesic, anti-inflammatory and antipyretic properties, with particularly potent pain-relieving activity. This drug is a prodrug which, after being absorbed from the gut, is biotransformed into an active metabolite to exert its actions.

1. Analgesic effect

- i) Loxoprofen sodium hydrate has been demonstrated to show an ED₅₀ value of 0.13 mg/kg in the Randall-Selitto test (inflamed paw pressuring method: rat, p.o.), the analgesic effect being 10 to 20 times as potent as the reference drugs ketoprofen, naproxen and indomethacin.
- ii) As assessed using the rat thermal inflammatory pain test (rat, p.o.), loxoprofen sodium hydrate showed an ID₅₀ value of 0.76 mg/kg and proved to be as potent as naproxen and 3 to >5 times more potent than ketoprofen and indomethacin.
- iii) In the chronic arthritis pain test (rat, p.o.), loxoprofen sodium hydrate produced the most profound analgesic effect (ED₅₀: 0.53 mg/kg), 4 to 6 times more potent as compared with indomethacin, ketoprofen and naproxen.
- iv) The analgesic action of this drug is peripheral.

2. Anti-inflammatory effect

Loxoprofen sodium hydrate produces an anti-inflammatory effect essentially comparable with the effects of ketoprofen and naproxen on acute and chronic inflammations such as carrageenin-induced edema (rat) and adjuvant arthritis (rat).

3. Antipyretic effect

Loxoprofen sodium hydrate was demonstrated to exert an antipyretic effect, essentially comparable with the effects of ketoprofen and naproxen and about three times more potent than the effect of indomethacin on yeast-induced fever (rat).

4. Mechanism of action

Inhibition of prostaglandin biosynthesis constitutes the mechanism of action of this drug, the site of action being cyclo-oxygenase. When administered orally, loxoprofen sodium hydrate

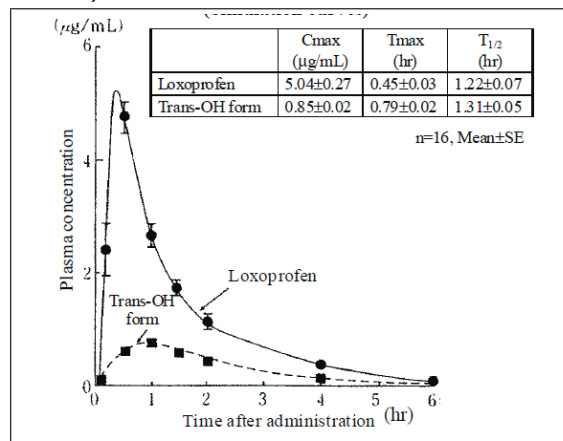
is absorbed from the gastrointestinal tract as an unchanged compound with only a modest gastric-mucosal irritation. It is then rapidly biotransformed into the active metabolite trans-OH form (SRS coordination) with a potent inhibitory effect on prostaglandin biosynthesis to exert its pharmacologic effects.

5.2 Pharmacokinetic properties

Absorption and Metabolism

In sixteen healthy adult volunteers, ROXONIN tablets was absorbed rapidly following a single 60-mg oral dose, and loxoprofen (unchanged drug) and its trans-OH form (active metabolite) were demonstrated in blood. The time to peak plasma concentration was about 30 minutes for loxoprofen and about 50 minutes for the trans-OH form, with an approximate half-life of 1 hour and 15 minutes for both compounds.

Plasma concentrations following a single 60-mg dose of ROXONIN tablets (Simulation curves)



Drug-Metabolizing Enzymes

Loxoprofen sodium hydrate did not affect the metabolism of the various drugs that serve as the substrates for cytochrome P450 isoforms (CYP1A1/2, 2A6, 2B6, 2C8/9, 2C19, 2D6, 2E1, and 3A4), even at concentrations approximately 10 times as high as its peak plasma concentration (200 μ M) in a metabolic inhibition study with human liver microsomes *in vitro*.

Pharmacokinetics Parameters (single dose)

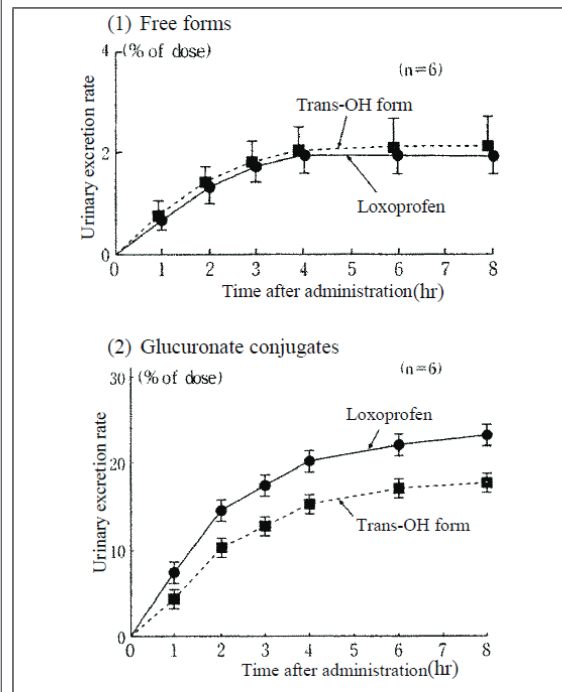
	Absorption rate constant (hr ⁻¹)	Elimination rate constant (hr ⁻¹)
Loxoprofen	11.21±1.82	$\lambda_1 = 4.04 \pm 0.93$ $\lambda_2 = 0.59 \pm 0.04$
Trans-OH form	3.56±0.21	$\lambda_1 = 4.99 \pm 0.07$ $\lambda_2 = 0.54 \pm 0.02$
n=16. Mean±SE		

- (1) Absorption rate constant and elimination rate constant
- (2) Plasma protein binding rate the plasma protein binding rate, as determined in humans (5 subjects at 1 hour after dosing of 60-mg ROXONIN tablets) was 97.0% and 92.8% for loxoprofen and the trans-OH compound, respectively.
- (3) AUC₀₋₈ (n=16, Mean±SE)
Loxoprofen: 6.70 ±0.26 μ g.hr/mL
Trans-OH form: 2.02 ±0.05 μ g.hr/mL

Excretion

ROXONIN is rapidly excreted in urine; it is excreted largely as glucuronate conjugates of loxoprofen and the trans-OH compound.

Excretion in urine after a single 60-mg dose of ROXONIN tablets



Excretion in urine over 8 hours after dose (% of dose)

	Free forms	Glucuronate conjugates
Loxoprofen	2.07±0.29	21.0±0.4
Trans-OH form	2.21±0.47	16.0±0.6

n=6, Mean±SE

Absorption and Excretion Following Multiple Doses

Absorption and excretion of ROXONIN after oral administration at 80 mg t.i.d. for 5 days in five healthy adult volunteers did not noticeably differ from those after a single oral dose; hence no evidence of accumulation.

5.3 Preclinical safety data

No safety information

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Low Substituted Hydroxypropylcellulose, Red Ferric Oxide, Lactose hydrate, Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Stored below 30°C.

6.5 Nature and contents of container

How supplied

Forming Aluminium / Aluminium blister pack.

Packs of 20 tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorisation Holder

SAJA Pharmaceuticals

Saudi Arabian Japanese pharmaceutical company limited

Jeddah – Saudi Arabia

Under license from

Daiichi Sankyo Co. Ltd.

Tokyo-Japan

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8. MARKETING AUTHORIZATION NUMBER

15/370/05

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/02/1426

10. DATE OF REVISION OF THE TEXT

June 2012