Long-acting Anti-Inflammatory/Analgesic Drug
ALVO® Tablets 100 mg
ALVO® Tablets 200 mg

(Oxaprozin)

Regulatory classification: Powerful drug.

Storage: Store at room temperature in a light-resistant container

Expiration date: Indicated on the package

<table>
<thead>
<tr>
<th>FORMULATIONS</th>
<th>Tablets 100 mg</th>
<th>Tablets 200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand name</strong></td>
<td>ALVO Tablets 100 mg</td>
<td>ALVO Tablets 200 mg</td>
</tr>
<tr>
<td><strong>Active ingredient</strong></td>
<td>Oxaprozin 100 mg/tablet</td>
<td>Oxaprozin 200 mg/tablet</td>
</tr>
<tr>
<td><strong>Inactive ingredients</strong></td>
<td>Carmelllose calcium, Hypromellose, Microcrystalline cellulose, Magnesium aluminometasilicate, Magnesium stearate</td>
<td></td>
</tr>
<tr>
<td><strong>Dosage form</strong></td>
<td>White uncoated tablet</td>
<td>White uncoated tablet</td>
</tr>
<tr>
<td><strong>ID code</strong></td>
<td>T71</td>
<td>T72</td>
</tr>
<tr>
<td><strong>Appearance, size, etc.</strong></td>
<td>Diameter: ca. 7 mm Thickness: ca. 2.7 mm Weight: ca. 115 mg</td>
<td>Diameter: ca. 8 mm Thickness: ca. 4.1 mm Weight: ca. 230 mg</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS
ALVO is contraindicated in the following patients.
- Patients with active peptic ulceration (but see PRECAUTIONS, 1. Special Precautions for Use): Because the occurrence of peptic ulcer has been reported to be associated with oxaprozin, pre-existing peptic ulcer may be aggravated.
- Patients with severe hepatic impairment: Because abnormal hepatic function has been observed with oxaprozin therapy, any hepatic impairment may be worsened.
- Patients with advanced renal impairment: Oxaprozin may cause a decrease in renal blood flow, resulting in the exacerbation of pre-existing renal disorders.
- Patients with hypersensitivity to oxaprozin or any other component of the product.
- Patients with a current or past history of aspirin asthma (asthmatic attack induced by nonsteroidal anti-inflammatory drugs [NSAIDs] etc.): An asthmatic attack may be provoked.
- Women known or suspected to be pregnant. (See PRECAUTIONS, 6. Use during Pregnancy, Delivery, or Lactation)

INDICATIONS
- Relief of pain and inflammation associated with: Rheumatoid arthritis, arthrosis deformans, lumbago, spondylitis deformans, periartthritis scapuohumeralis, gouty attack, or neck, shoulder and arm syndrome.
- Treatment of pain and inflammation following: Surgery or trauma.

DOSAGE AND ADMINISTRATION
The usual adult oral dose of ALVO is 400 mg per day in a single dose or two divided doses. The dose may be increased or decreased depending on the patient’s age and condition; however, the total daily dose should not exceed 600 mg.

PRECAUTIONS
1. Special Precautions for Use
ALVO should be administered with caution in the following patients.
(1) Patients with a past history of peptic ulcer: Peptic ulcer may recur.
(2) Patients with active peptic ulceration induced by long-term administration of NSAIDs who, nevertheless, require long-term treatment with ALVO (see CONTRAINDICATIONS) and are concomitantly receiving misoprostol therapy: Although misoprostol is indicated for peptic ulcers induced by NSAIDs, some peptic ulcers are refractory to misoprostol; accordingly, caution should be exercised in long-term administration of this product, with close monitoring of the patient’s condition.
(3) Patients with a current or past history of blood disorders: Pre-existing blood disorders may be exacerbated or the blood disorders may recur.
(4) Patients with a current or past history of hepatic impairment: Any hepatic impairment may worsen or recur.
(5) Patients with a current or past history of renal impairment: Renal blood flow may be decreased and renal impairment may worsen or recur with the use of this product.
(6) Patients with a past history of hypersensitivity.
(7) Patients with bronchial asthma: An asthmatic attack may be provoked by oxaprozin.
(8) Patients with ulcerative colitis: As with other NSAIDs, their condition may worsen with the use of this product.
(9) Patients with Crohn’s disease: As with other NSAIDs, their condition may worsen with the use of this product.
(10) Elderly patients. (See 2. Important Precautions and 5. Geriatric Use)
(11) Pediatric patients. (See 2. Important Precautions and 7. Pediatric Use)

2. Important Precautions
(1) It is important to note that treatment with anti-inflammatory and analgesic agents is a symptomatic therapy, not a causal therapy.
(2) If ALVO is used for the treatment of chronic diseases (rheumatoid arthritis, ankylosing spondylitis, etc.), the following suggestions should be taken into consideration:
• Perform laboratory tests periodically (urinalysis, blood tests, liver function tests, etc.) when administering this product for an extended period of time. If any abnormalities are observed, take appropriate measures, such as reduction of the dosage, withdrawal of the product, and/or the like.
• Explore possible therapeutic interventions other than drug treatment.
(3) When ALVO is administered for post-surgical or post-traumatic treatment, the following recommendations should be implemented:
• Determine the proper dosage regimen, depending on the degree of inflammation or pain.
• As a general rule, avoid using this product for an extended period of time.
(4) Patients should be monitored closely for adverse reactions.
(5) Note that ALVO may mask the signs and symptoms of infection when used in patients with concomitant infectious diseases; accordingly, administer the product carefully with concurrent use of appropriate antimicrobial agents to control the infection. Keep the patient under close supervision.
(6) It is preferable to avoid co-administration of ALVO with other NSAIDs.
(7) In elderly and pediatric 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. Drug Interactions
Precautions for co-administration:
Caution should be exercised when considering the concomitant use of ALVO with the following drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Signs, symptoms, and treatment</th>
<th>Mechanism and risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulants</td>
<td>Oxaprozin may enhance the anticoagulant effect of these medications when used concomitantly; therefore, care should be taken and the dosage of the anticoagulant reduced if necessary.</td>
<td>The interaction is probably due to competition for plasma protein binding sites, resulting in an increase in the blood levels of free anticoagulant (i.e., anticoagulant not bound to plasma protein).</td>
</tr>
</tbody>
</table>

Lithium
Since concomitant use with oxaprozin may result in an increase in the blood lithium levels, potentially leading to lithium toxicity, blood lithium concentrations should be monitored. Lithium dose adjustment may be needed.
The mechanism may involve enhanced reabsorption of lithium by oxaprozin of prostaglandin synthesis in the kidney, resulting in a reduction in renal lithium clearance.

New quinolone antibiotics
In animal studies, co-administration of new quinolones and oxaprozin has been reported to cause convulsions. Patients should be monitored closely during concurrent use.
New quinolones are known to inhibit the binding of GABA (an inhibitory neurotransmitter) to its receptors: blockade of GABA-ergic neurotransmission in the CNS is presumed to be a dominant mechanism of convulsion induced by new quinolones. The drug interaction is probably due to the blockade of the GABA receptor by the new quinolones and its potentiation by oxaprozin.

4. Adverse Reactions
A total of 648 adverse reactions were encountered in 571 (1.30%) of 43,787 patients treated with ALVO. The most common adverse reactions included stomach discomfort in 117 cases, stomachache in 112 cases, rash in 62 cases, nausea in 41 cases, and edema in 31 cases. [Results of double-blind and open-label clinical trials and post-marketing clinical experience studies, submitted for reexamination]

1) Clinically significant adverse reactions
1) Shock, anaphylactoid reaction (incidence unknown): Since shock or anaphylactoid reaction may occur, patients should be closely monitored. If any abnormalities (urticaria, dyspnea, decreased blood pressure, etc.) are observed, ALVO should be discontinued and appropriate therapeutic action taken.
2) Peptic ulcer (incidence unknown): Since peptic ulcer may occur, patients should be closely monitored. If any abnormalities (stomachache, vomiting, or gastrointestinal hemorrhage with hematemesis, melena, and/or the like) are observed, appropriate measures, such as reduction of the dosage, withdrawal of ALVO, and/or the like, should be instituted.
3) Ocuolomucocutaneous syndrome (Stevens-Johnson syndrome) (incidence unknown): Since oculomucocutaneous syndrome (Stevens-Johnson syndrome) may occur, patients should be closely monitored. If any abnormalities are observed, ALVO should be discontinued and appropriate therapeutic action taken.
4) Acute renal failure (incidence unknown): Since acute renal failure may occur, patients should be closely monitored. If any abnormalities are observed, ALVO should be discontinued and appropriate therapeutic action taken.

2) Other adverse reactions
The following adverse reactions may occur. If any of these symptoms develop, appropriate measures should be instituted.

<table>
<thead>
<tr>
<th>Neuro-psychiatric</th>
<th>Incidence</th>
<th>Gastro-intestinal</th>
<th>Incidence</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1% &gt; 0.1%</td>
<td>Stomach discomfort, stomachache</td>
<td>0.1% &gt; 0.01%</td>
<td>Sleepiness, dizziness, headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea, vomiting, anorexia, constipation, diarrhea, stomatitis, glossitis, gastritis, abdominal pain, abdominal discomfort, thirst</td>
<td>&lt; 0.1%</td>
<td>Anemia, decreased WBC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anemia, decreased WBC</td>
<td></td>
</tr>
</tbody>
</table>

5. Geriatric Use
Oxaprozin is eliminated mainly through the kidney and has a high binding affinity to plasma albumin. In elderly patients, renal function is often reduced, thus leading to increased blood levels of oxaprozin; moreover, their plasma albumin levels are generally lower than those in their younger counterparts, suggesting that more free oxaprozin may be available. Caution should be exercised in the use of ALVO for this patient group, with close monitoring of the patient’s condition; for example, it is advisable to use a low starting dose.

6. Use during Pregnancy, Delivery, or Lactation
(1) ALVO is contraindicated in women known or suspected to be pregnant; animal studies on female rats in the late stages of pregnancy have shown that oxaprozin caused constriction of the fetal ductus arteriosus.
(2) Nursing mothers should discontinue breast-feeding during ALVO therapy; in rats, oxaprozin has been reported to be excreted in breast milk.

7. Pediatric Use
The safety of ALVO in pediatric patients has not been established; the available clinical data on the use of this product in pediatric patients is insufficient.

8. Precautions concerning Use
When ALVO is provided in a press-through package (PTP) sheet (a blister sheet), instruct the patient to remove each tablet from the package sheet prior to swallowing. It has been reported that, if a small part of the package is mistakenly swallowed along with a tablet, its sharp corners may penetrate and eventually perforate the esophageal mucosa, leading to serious complications (e.g., mediastinitis).

9. Other Precautions
It has been reported that reversible infertility was observed in women after long-term therapy with NSAIDs.

PHARMACOKINETICS

1. Blood levels
Following oral administration of a single dose of 400 mg to healthy adults, the pharmacokinetic parameters of oxaprozin were as follows:

<table>
<thead>
<tr>
<th></th>
<th>Cmax (µg/mL)</th>
<th>Tmax (hr)</th>
<th>T1/2 (hr)</th>
<th>AUC (µg·hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>66.9</td>
<td>3.7</td>
<td>49.5</td>
<td>4001.8</td>
</tr>
</tbody>
</table>

When oxaprozin (400 mg per day in a single dose or two divided doses) was repeatedly administered orally to healthy adults for 10 consecutive days, the blood levels reached steady state in 4 to 6 days in all cases, and their average concentrations showed a steady value (approximately 100 µg/mL).

No significant differences were found in its pharmacokinetics when administered either before or after meals.

2. Distribution
Animal studies: Rats were given [14C]oxaprozin per os, and the radioactivity levels in various organs and tissues were measured. Two hours after dosing, the highest level of radioactivity was found in the gastrointestinal tract. The rank of order of distribution was: gastrointestinal tract > kidney > liver > plasma. The concentrations found in other organs and tissues were lower than those in the blood. Radioactivity in the brain was the lowest. In the case of rabbits, at 2 hours after dosing, the highest radioactivity was found in the plasma. The levels found in the gastrointestinal tract, kidney, liver, and blood were relatively high. No long-term retention of radioactivity in any specific organ or tissue was observed in either rats or rabbits.
3. Metabolism and excretion
When a single 400-mg oral dose of oxaprozin was administered to healthy adults, approx. 32% of the dose was excreted in the urine within 5 days. The major metabolite was the ester glucuronide of oxaprozin; other detected metabolites were the oxaprozin derivatives hydroxylated on either of the phenyl rings and their glucuronides.

CLINICAL STUDIES
The results of double-blind and open-label clinical trials and post-marketing clinical experience studies are as follows:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total efficacy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>52.1% (894/1715)</td>
</tr>
<tr>
<td>Arthritis deformans</td>
<td>67.8% (2172/3203)</td>
</tr>
<tr>
<td>Lumbago</td>
<td>84.6% (11065/13076)</td>
</tr>
<tr>
<td>Spondylitis deformans</td>
<td>67.9% (2153/3170)</td>
</tr>
<tr>
<td>Periarthritis scapulohumeralis</td>
<td>77.0% (2100/2727)</td>
</tr>
<tr>
<td>Gouty attack</td>
<td>86.3% (176/204)</td>
</tr>
<tr>
<td>Neck, shoulder and arm syndrome</td>
<td>80.5% (2712/3369)</td>
</tr>
<tr>
<td>Postoperative or post-traumatic</td>
<td>84.0% (1549/1844)</td>
</tr>
</tbody>
</table>

PHARMACOLOGY

1. Anti-inflammatory effect
(1) The anti-inflammatory potency of oxaprozin was close to that of aspirin in acute and chronic inflammation such as carrageenin-induced paw edema, cotton pellet granuloma, and adjuvant arthritis in rats.
(2) Oxaprozin was more potent than ibuprofen, fenbufen, or sulindac in the acute carrageenin-induced paw edema test in mice.
(3) Oxaprozin demonstrated more potent inhibitory effects than did phenylbutazone, aspirin, or ibuprofen in the acetic acid-induced vascular permeability test in mice.

2. Analgesic effect
(1) The analgesic effect of oxaprozin was slightly greater than that of aspirin in acute and chronic inflammatory pain in yeast-induced paw edema (the Randall-Selitto assay), silver nitrate-induced arthritis, and adjuvant-induced arthritis in rats.
(2) Oxaprozin was much more potent than phenylbutazone or aspirin in terms of analgesic activity in the acetic acid-induced writhing test, the phenylquinone-induced writhing test and the acetylsalicylic acid-induced writhing test as well as the yeast-inflamed tail-pressure threshold test in mice.
(3) Analgesic effects of oxaprozin on urate-induced synovitis persisted for approx. 20 hours in dogs.

3. Mechanism of action
Oxaprozin has been shown in vitro (bovine seminal vesicle microsomes) to inhibit the production of prostaglandins by inhibiting the action of cyclooxygenase, which regulates the conversion of arachidonic acid to prostaglandins. As with other NSAIDs, the inhibition of cyclooxygenase is thought to be primarily responsible for the anti-inflammatory and analgesic effects of oxaprozin.

DESCRIPTION
Generic name: Oxaprozin
Chemical name: 3-(4,5-Diphenyloxazol-2-yl)propanoic acid
Structural formula:

![Structural formula](image)

Molecular formula: C_{14}H_{13}NO_3
Molecular weight: 293.32
Physicochemical properties:
Oxaprozin is a white to yellowish-white crystalline powder. It is sparingly soluble in methanol and 95% ethanol, slightly soluble in diethyl ether, and practically insoluble in water.
It is gradually degraded by exposure to light.
Melting point: 161–165 °C

PACKAGING

<table>
<thead>
<tr>
<th>ALVO Tablets</th>
<th>Pack with 100 tablets (PTP/blister pack)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALVO Tablets</th>
<th>Pack with 100 or 1000 tablets (PTP/ blister pack)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg</td>
<td></td>
</tr>
</tbody>
</table>

REFERENCES
4) Murota K et al.: Kiso to Rinshou, 18(3), 1037 (1984)
8) Inomata Y: Kiso to Rinshou, 18(4), 1297 (1987)

For Medical Information (including requests for literature):
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