**APLACE® Tablets 100 mg**

*< The Japanese Pharmacopoeia Troxipide tablets >*

**APLACE® Fine Granules 20%**

*< The Japanese Pharmacopoeia Troxipide fine granules >*

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### DESCRIPTION

#### Product description

<table>
<thead>
<tr>
<th>Tablets 100mg</th>
<th>Fine Granules 20%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active ingredient</strong></td>
<td><strong>Active ingredient</strong></td>
</tr>
<tr>
<td>JP Troxipide 100 mg (in one tablet)</td>
<td>JP Troxipide 200 mg (in 1g)</td>
</tr>
<tr>
<td><strong>Inactive ingredient</strong></td>
<td><strong>Inactive ingredient</strong></td>
</tr>
<tr>
<td>Corn starch, less substituted hydroxypropylcellulose, magnesium stearate, hypromellose, carnauba wax</td>
<td>Less substituted hydroxypropylcellulose, sodium alginate, calcium lactate hydrates, corn starch, aspartame (L-phenylalanine compound), flavor</td>
</tr>
<tr>
<td><strong>Type of tablet</strong></td>
<td><strong>Type of tablet</strong></td>
</tr>
<tr>
<td>Film-coated tablet</td>
<td>Fine granules</td>
</tr>
<tr>
<td><strong>Color</strong></td>
<td><strong>Color</strong></td>
</tr>
<tr>
<td>White</td>
<td>Faint to pale yellow</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td><strong>Size</strong></td>
</tr>
<tr>
<td>Diameter 8.1 mm</td>
<td></td>
</tr>
<tr>
<td>Thickness 4.1 mm</td>
<td></td>
</tr>
<tr>
<td>Weight About 200 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Identification code</strong></td>
<td><strong>Identification code</strong></td>
</tr>
<tr>
<td>アプレース® 100 (on tablet)</td>
<td>KP-315 (on package)</td>
</tr>
<tr>
<td>KP-296 (on package)</td>
<td></td>
</tr>
</tbody>
</table>

#### Taste

- Slightly sweet at first, then tasteless or slightly bitter

#### Odor

- Faint odor

### INDICATIONS

Gastric ulcers

Amelioration of gastric mucosal lesions (erosion, hemorrhage, redness and edema) in the following diseases: acute gastritis, acute exacerbation stage of chronic gastritis.

### DOSAGE AND ADMINISTRATION

The usual adult dosage for oral use is 100 mg of troxipide (one tablet or 0.5 g of fine granules) three times daily after meals. The dosage may be adjusted depending on the patient's age and symptoms.

### PRECAUTIONS

1. **Adverse Reactions**

   <At the end of the re-examination period>

Adverse reactions to this drug, including abnormal laboratory tests, were reported in 91 (0.75%) of 12,092 patients treated. The most frequently observed adverse reactions were gastrointestinal symptoms including constipation 23 patients (0.19%), increased AST(GOT) levels in 21 patients (0.17%) and increased ALT(GPT) levels in 30 patients (0.25%).

   1. **Clinically significant adverse reactions**

   1) **Shock, anaphylactoid symptoms**

   Shock, anaphylactoid symptoms may occur. If any of abnormal findings (such as urticaria, dyspnoea, blood pressure fell, etc.) are observed, administration should...
be discontinued and appropriate therapeutic measures must be taken.

2) Hepatic dysfunctions, jaundice

Hepatic dysfunction or jaundice with increased AST (GOT), ALT (GPT), Al-P, γ-GTP and/or LDH may occur. Patients should be carefully monitored. If any symptoms are observed, administration should be discontinued and appropriate therapeutic measures must be taken.

(2) Other adverse reactions

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Gastro-intestinal</th>
<th>Hepatic</th>
<th>Hyper-sensitivity</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% &gt; ≥0.1%</td>
<td>Constipation</td>
<td>Elevation of AST (GOT), ALT (GPT)</td>
<td>Pruritus, rash, etc.</td>
<td>Headache dull, heart pounding, generalized fatigability, etc.</td>
</tr>
<tr>
<td>&lt;0.1%</td>
<td>Feeling of enlarged abdomen, heartburn, nausea, etc.</td>
<td>Elevation of ALP, γ-GTP, etc.</td>
<td>Edema</td>
<td></td>
</tr>
<tr>
<td>Incidence unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note) Incidence from voluntary reports could not be determined.

2. Use in the Elderly

In general, elderly patients often have physiological hypofunction, therefore these products should be administered carefully.

3. Use during Pregnancy, Delivery or Lactation

1) The safety of this product in pregnant women has not been established. Therefore, these drugs should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.

2) Breast-feeding must be discontinued during treatment. Troxipide is shown to be excreted in breast milk in animal studies with rats.

4. Pediatric Use

The safety of these products in children has not been established. (insufficient clinical data)

5. Precautions concerning Use

Precautions regarding dispensing

For drugs that are dispensed in a press-through package (PTP), 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, resulting in severe complications such as mediastinitis.]

6. Other Precautions

1) Urinary occult blood which might be caused by inflammation and haemorrhage in the urinary bladder were observed more frequently than in the control group at an oral dose of 1,000 mg/kg/day in rat repeated dose toxicity study, which is 170 times or more higher dose than recommended human clinical dose. 5)

2) Oestrous cycle disorder which might be caused by the abnormal parasecretion of prolactin was reported in animal experiments 2). Therefore, patients must therefore be carefully monitored for abnormal menstruation and lactation. If abnormal findings are observed, appropriate measures, such as reducing the dose, should be taken. If any abnormalities are observed, the appropriate measures such as suspension or discontinuance of the dose should be taken.

PHARMACOKINETICS

1) Blood concentrations

Blood concentrations and pharmacokinetic parameters of troxipide after a single oral dose of 100 mg to the healthy adults are shown below.

2) Metabolism

Following a single oral administration of 100 mg troxipide to the healthy adults, more than 96% of the metabolites excreted in urine were unchanged compound, and only one metabolite was observed.

3) Excretion

When a single oral dose of 100 mg troxipide to the healthy adults, about 61% of dose was excreted up to 24 hours and about 67% of dose was excreted up to 48 hours in urine.

CLINICAL STUDIES

1. Effect on gastritis

The overall amelioration rate of these products in acute gastritis or acute gastric mucosal lesions of chronic gastritis in clinical studies performed in 310 cases, which included double blind clinical trial, was 82.9% (257/310). The clinical usefulness of these products in acute gastritis or
acute gastric mucosal lesions of chronic gastritis was proved by double blind clinical trial.

2. Effect on gastric ulcer
   The amelioration rate of these products in gastric ulcer in clinical studies performed in 514 cases, which included double blind clinical trial, was 79.4% (408/514). The clinical usefulness of these products in gastric ulcer was proved by double blind clinical trial.

PHARMACOLOGY

1. Therapeutic and preventive effects on experimental gastritis
   Troxipide was shown to have therapeutic and preventive effects on experimental chronic gastritis (atrophic) caused by sodium taurocholate in rats. 7)

2. Preventive effect on acute gastric mucosal lesions
   Troxipide was shown to have a preventive effect on gastric mucosal lesions caused by aspirin, 0.6N HCl, ethanol (99.5) or under water-immersion stress in rats. 8)9)10)

3. Tissue repair-accelerating effect
   Troxipide was shown to give a well balanced reconstruction of gastric mucosa and growth of collagenous fibers on the basal portion of ulcer in histological studies on an clamping cortisone ulcer, acetic acid-induced ulcer and clamping ulcer in rats, and to accelerate the healing of chronic ulcers. 11)12)

4. Preventive activity on various experimental ulcers
   Troxipide was shown to prevent the formation of ulcers by under water-immersion stress, stress-reserpine, indomethacin, demethylazation-aspirin, hydrocortisone and pylorus-ligated, and to have a protective effect on mucosa in rats. 10)14)

5. Gastrumucosal blood flow increasing effect
   Troxipide was observed to increase the gastromucosal blood flow in the studies using thermoelectrical method (at 25ºC) and enantiomer.

6. Metabolism accelerating effect in gastric mucosa
   Troxipide was observed to activate the energy metabolism of gastric mucosa as a consequence of increased oxygen consumption and ATP contents in gastric mucosa. These effects were particularly remarkable in the marginal gastric mucosa in which the blood flow was reduced due to the ulcers. 19)20)

7. Effects on mucosal components
   Troxipide was shown to increase the mucopolysaccharide contents in gastric mucosa and prevent the decrement of mucopolysaccharide due to anti-inflammatory agents or stress in rats.
   Thus, troxipide was shown to strengthen the barrier on gastric mucosa. 21)22)

8. Effect on mucosal prostaglandin level
   Troxipide was shown to increase the levels of prostaglandins which exhibited the cytoprotective effect in gastric mucosa in rats. 23)

PHYSICOCHEMISTRY

Nonproprietary name: Troxipide (JAN)
Chemical name: 3,4,5-Trimethoxy-N-[(3RS)-piperidin-3-yl]benzamide
Molecular formula: C15H22N2O4
Molecular weight: 294.35
Structural formula:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{N} & \quad \text{H}
\end{align*}
\]

and enantiomer

Description:
Troxipide occurs as a white crystalline powder. Freely soluble in acetic acid (100), soluble in methanol, sparingly soluble in ethanol (99.5), slightly soluble in water. Troxipide is soluble in hydrochloric acid solution (0.1mol/L).The hydrochloric acid (1mol/L) solution of troxipide (1 in 5) shows no optical rotation.

Melting point: 177-181ºC

Partition coefficient:

<table>
<thead>
<tr>
<th>Organic phase</th>
<th>Aqueous phase</th>
<th>Partition coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Octanol</td>
<td>Phosphate buffer</td>
<td>17.9</td>
</tr>
<tr>
<td>Chloroform</td>
<td>Phosphate buffer</td>
<td>159</td>
</tr>
</tbody>
</table>

(at 25ºC)

PACKAGING

APLACE Tablets 100 mg:
Boxes of 100 tablets (10 tablets x 10), 500 tablets (10 tablets x 50), 1,000 tablets (10 tablets x 100) and 1,050 tablets (21 tablets x 50) in press-through packages, and bottles of 500 tablets

APLACE Fine Granules 20%:
Boxes of 0.5g x 600 packets (3 packets x 200) and bottles of 100g and 500g

REFERENCES
1) Imai S et al.: Subacute toxicity study of troxipide in rats (In-house data)
2) Murayama J et al.: Effects of troxipide on blood prolactin and estrous cycle (In-house data)
3) Kamijo S et al.: Bioequivalence study of troxipide tablets (In-house data)
4) Kusajima H et al.: Bioequivalence study of troxipide fine granules (In-house data)
5) Irikura T et al.: Oyo Yakuri, 18, 619, 1979
6) Kawahara T et al.: The Clinical Report, 18, 2859, 1984
10) Kuwayama H et al.: Oyo Yakuri, 40, 63, 1990
12) Momo K: "Experimental ulcer, disease-model and its pathogenesis" Nippon Medical Center, pp 197, 1976
14) Irikura T et al.: Oyo Yakuri, 17, 371, 1979
21) Abe Y et al.: Oyo Yakuri, 27, 521, 1984

REQUEST FOR LITERATURE SHOULD BE MADE TO:
A request for in-house data mentioned in the References can also be made to the following.
Kyorin Pharmaceutical Co., Ltd. Drug Information Center
6, Kanda surugadai 4-chome, Chiyoda-ku, Tokyo 101-8311, Japan
Tel. 0120-409-341 (Toll-free)
9:00 to 17:30 (weekday, exclusive of Saturday and national holidays)

Manufactured and marketed by:
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