CONTRAINDICATIONS (RIZABEN Eye Drops is contraindicated in the following patients.)
(1) Patients with a history of hypersensitivity to any of the ingredients of this product.

DESCRIPTION
1. Composition

<table>
<thead>
<tr>
<th>Active ingredient/Contents</th>
<th>Tranilast 5 mg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive ingredients</td>
<td>Boric acid, Borax, Polyvinylpyrrolidone, Polysorbate 80, Benzalkonium chloride, Sodium edetate hydrate</td>
</tr>
</tbody>
</table>

2. Product description

<table>
<thead>
<tr>
<th>Color/Dosage form</th>
<th>Pale yellowish transparent aseptic aqueous eye drops</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.0-8.0</td>
</tr>
<tr>
<td>Osmotic ratio</td>
<td>0.9-1.1 (Ratio to 0.9% physiological saline)</td>
</tr>
</tbody>
</table>

INDICATION
Allergic conjunctivitis

DOSAGE AND ADMINISTRATION
Usually, 1 to 2 drops/time are instilled into each eye, 4 times daily (morning, noon, evening and before bed-time).

PRECAUTIONS
1. Important Precautions
In patient with severe allergic conjunctivitis, adequate efficacy cannot be expected from this drug alone. Therefore, RIZABEN should be switched to other appropriate treatment or be used concurrently with them, and the prolonged single use of RIZABEN should be avoided.

2. Adverse Reactions
In 72 (1.21%) of 5,951 patients receiving tranilast eye drops, 88 adverse reactions were reported. Major adverse reactions were irritation/smarting in 22 (0.37%) patients, blepharitis in 12 (0.20%) patients, eye itching in 12 (0.20%) patients, blepharodermatitis in 8 (0.13%) patients, etc. (At the end of the reexamination)

<table>
<thead>
<tr>
<th></th>
<th>Frequency Unknown</th>
<th>0.1 - &lt;5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity[^1]</td>
<td>Contact dermatitis (periorcular)</td>
<td>Blepharodermatitis, blepharitis</td>
</tr>
<tr>
<td>Eyes</td>
<td>Conjunctival hyperemia, swelling of eyelid</td>
<td>Irritation, itching</td>
</tr>
</tbody>
</table>

Note): Appropriate measures such as discontinuation of administration should be taken if such symptoms are observed.

3. Use during Pregnancy, Delivery or Lactation
The safety of RIZABEN in pregnant women has not been established. Therefore, RIZABEN should not be administered to pregnant women (especially those in the first trimester) or women who are possibly pregnant. [RIZABEN is confirmed to be increase in incidence of skeletal anomalies in the high doses mice study.]

4. Pediatric use
The safety of RIZABEN in low birth weight infants, neonates, and nursing infants has not been established. [no clinical experience]

5. Precautions concerning Use
(1) Administration route: RIZABEN should be used for eye drops only.
(2) At instillation: The tip of the container should never be in touch direct with the eyes. The solution which flowed out around the eyes should be wiped out.
PHARMACOKINETICS

(1) When RIZABEN Eye Drops 0.5% was administered once to 6 healthy male adults (2 drops each to both eyes), unchanged drug concentration in plasma peaked about 1 hour later (mean 17.8 ng/mL). The maximum blood concentration after repeated administration to the eyes (4 times daily for 8 days) was 25.0 ng/mL. The half-life of the blood concentration was 3.6 hours after single administration and 3.9 hours after repeated administration.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Single administration (once)</th>
<th>Repeated administration (for 8 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T&lt;sub&gt;max&lt;/sub&gt; (hr)</strong></td>
<td>1.2 ± 0.4</td>
<td>0.8 ± 0.3</td>
</tr>
<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</strong></td>
<td>17.8 ± 7.1</td>
<td>25.0 ± 12.2</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;0-4hr&lt;/sub&gt; (ng·hr/mL)</strong></td>
<td>50.8 ± 17.6</td>
<td>75.6 ± 31.3</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;1/2&lt;/sub&gt; (hr)</strong></td>
<td>3.6 ± 1.3</td>
<td>3.9 ± 1.2</td>
</tr>
</tbody>
</table>

(2) An in vitro study using human liver microsomes and microsomes expressing P450 showed that the oxidative metabolic reactions to tranilast were observed in CYP2C9, CYP2C18, CYP2C8, CYP1A2, CYP3A4 and CYP2D6, and mainly CYP2C9 was involved in the metabolism1,2).

CLINICAL STUDIES

Double-blind comparative clinical studies and general clinical studies3-8):

The efficacy rate (inclusive of “moderately improved” and higher) was 70.9% (175/247) in clinical studies including double-blind comparative studies of this product for treatment of allergic conjunctivitis conducted in Japan.

PHARMACOLOGY

(1) Suppressive action on experimental allergic conjunctivitis9,10)

When tranilast was administrated to the eyes of animal conjunctivitis models, it suppressed dose-dependently acceleration of vascular permeability (rats and guinea pigs) and infiltration of inflammatory cells to conjunctival tissue (guinea pigs).

(2) Mechanism of action11-19)

Tranilast showed antiallergic action by suppressing the release of chemical mediators (histamine, leukotriene, etc.) from mast cells and various inflammatory cells on antigen stimulation (in vitro).

PHYSICOCHEMISTRY

Nonproprietary name: Tranilast (JAN,INN)
Chemical name: N-(3,4-dimethoxycinnamoyl)-anthranilic acid
Molecular formula: C<sub>18</sub>H<sub>17</sub>NO<sub>5</sub>
Molecular weight: 327.33
Structural formula:

![Structural formula of tranilast](image)

Description:

Tranilast occurs as light yellow crystals or a crystalline powder. It is odorless and tasteless. It is freely soluble in N,N-dimethylformamide, soluble in 1,4-dioxane, slightly soluble in ethanol (99.5), very slightly soluble in diethyl ether, and practically insoluble in water.

Melting point: 207-210°C

PRECAUTIONS FOR HANDLING

RIZABEN should not be stored in a refrigerator, etc., since crystals may precipitate.

PACKAGING

RIZABEN Eye Drops 0.5%:
- 5 mL × 5 plastic dispensers
- 5 mL × 10 plastic dispensers
- 5 mL × 50 plastic dispensers

REFERENCES

1) KISSEI PHARMACEUTICAL CO., LTD.
2) GlaxoSmithKline
10) Ito F. et al.: Nihon Yakurigaku Zasshi (Folia Pharmacologica Japonica), 101(1), 27, 1993
17) Tsutsumi N. et al.: Ouyo Yakuri (Pharmacometrics), 25(6), 973, 1983

REQUEST FOR LITERATURE SHOULD BE MADE TO:
Consumer Service Center
KISSEI PHARMACEUTICAL Co., Ltd.
8-9, Nihonbashi-Muromachi 1-chome, Chuo-ku, Tokyo
BRAND NAMES IN OTHER COUNTRIES
KRIX eye drop (Republic of Korea)