- H₂-receptor antagonist -

**ALTAT® Capsules 37.5**

**ALTAT® Capsules 75**

<**Roxatidine Acetate Hydrochloride**>

### Designated drug

### Storage

Store at room temperature.

<table>
<thead>
<tr>
<th>37.5</th>
<th>75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval No.</td>
<td>21000AMZ00283000 (61AM)No.3538</td>
</tr>
<tr>
<td>Date of listing in the NHI reimbursement price</td>
<td>July 1998</td>
</tr>
<tr>
<td>Date of initial marketing in Japan</td>
<td>July 1998</td>
</tr>
<tr>
<td>Date of latest reexamination</td>
<td>September 1994</td>
</tr>
<tr>
<td>Date of latest approval of indications (Gastritis)</td>
<td>June 1993</td>
</tr>
<tr>
<td>International birth date</td>
<td>July 1, 1986</td>
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</tbody>
</table>

### Expiration date

Do not use after the expiration date indicated on the package.

### DESCRIPTION

#### 1. Composition

**ALTAT Capsules 37.5:**
Each capsule contains 37.5 mg of roxatidine acetate hydrochloride.

**ALTAT Capsules 75:**
Each capsule contains 75 mg of roxatidine acetate hydrochloride.

Both products contain sodium lauryl sulfate as a component of capsule (inactive ingredient).

#### 2. Product description

**ALTAT Capsules 37.5:**
White capsules (size 5) containing white sustained release granules.

**ALTAT Capsules 75:**
White capsules (size 3) containing white sustained release granules.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>ALTAT Capsules 37.5</th>
<th>ALTAT Capsules 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td><img src="image1" alt="Image" /> <img src="image2" alt="Image" /></td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>Approx. 11.3 mm</td>
<td>Approx. 15.8 mm</td>
</tr>
<tr>
<td>Weight</td>
<td>82.5 mg (Content)</td>
<td>165 mg (Content)</td>
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<tr>
<td>Identification code</td>
<td>TZ351</td>
<td>TZ321</td>
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</table>

### INDICATIONS

Gastric ulcers, duodenal ulcers, stomal ulcers, Zollinger-Ellison syndrome, reflux esophagitis and preanesthetic medication.

Improvement of gastric mucosal lesions (erosion, hemorrhage, redness or edema) in the following diseases:

Acute gastritis or acute exacerbation stage of chronic gastritis.

### DOSAGE AND ADMINISTRATION

#### 1. Gastric ulcers, duodenal ulcers, stomal ulcers, reflux esophagitis
Usually for adults, administer orally 75 mg as roxatidine acetate hydrochloride twice daily after breakfast and at bedtime or after evening meals, or 150 mg once daily at bedtime. The dose may be increased or decreased according to age and symptoms.

#### 2. Zollinger-Ellison syndrome
Usually for adults, administer orally 75 mg as roxatidine acetate hydrochloride twice daily after breakfast and at bedtime or after evening meals. The dose may be increased or decreased according to age and symptoms.

#### 3. Preanesthetic medication
Usually for adults, administer orally 75 mg as roxatidine acetate hydrochloride twice daily at bedtime on the day before operation and 2 hours before anesthetization, or 150 mg at bedtime on the day before operation.

#### 4. Improvement of gastric mucosal lesions (erosion, hemorrhage, redness or edema) in the following diseases: Acute gastritis or acute exacerbation stage of chronic gastritis
Usually for adults, administer orally 75 mg as roxatidine acetate hydrochloride once daily at bedtime or after evening meals. The dose may be increased or decreased according to age and symptoms.

### <Precautions>

In patients with renal dysfunction, high plasma concentrations may persist. Therefore, dose should be reduced, or the dosage interval should be prolonged. (refer to "PHARMACOKINETICS")
PRECAUTIONS

1. Careful Administration (ALTAT Capsules should be administered with care in the following patients.)
   (1) Patients with a history of drug hypersensitivity
   (2) Patients with hepatic dysfunction
   (3) Patients with renal dysfunction
      [High plasma concentrations may persist, and dose should be reduced, or the administration interval should be prolonged: refer to "PHARMACOKINETICS"]
   (4) Elderly patients (refer to "Use in the Elderly")

2. Important Precautions
   Patients should be carefully observed during the treatment, and the minimum required doses should be used depending on the symptoms. If response does not appear, other treatment should be implemented. Careful observation should be taken for any changes in hepatic and renal functions, hematology, etc.

3. Adverse Reactions
   Of the 15,745 patients investigated in the clinical trials and at post-marketing survey, 269 patients (1.71%) of adverse reactions, including abnormal laboratory values, were reported. Major findings are: 47 cases of increased ALT (GPT) (0.30%), 26 cases of constipation (0.17%), 24 cases of increased AST (GOT) (0.15%) and 16 cases of increased eosinophil (0.10%). (Collected and calculated in June 1998)
   (1) Clinically significant adverse reactions (less than 0.1%)
      1) Since shock (Initial symptoms: unwell feeling, facial pallor, hypotension, etc.) may occur, patients should be carefully observed, and in such cases, discontinue the treatment with the drug immediately and take appropriate measures.
      2) Since aplastic anemia, pancytopenia, agranulocytosis and thrombocytopenia (Initial symptoms: general malaise, weakness, subcutaneous and submucosal hemorrhage, fever, etc.) may occur, periodical blood examination should be performed, and in case of abnormalities, discontinue the treatment with the drug immediately and take appropriate measures.
      3) Since mucocutaneous-ocular syndrome (Stevens-Johnson Syndrome) and toxic epidermal necrolysis (Lyell Syndrome) may occur, in case of abnormalities, discontinue the treatment with the drug immediately and take appropriate measures.
      4) Since hepatic disorder or jaundice, such as increased AST (GOT), ALT (GPT), γ-GTP, may occur, patients should be carefully observed, and in case of abnormalities, discontinue the treatment with the drug immediately and take appropriate measures.
   (2) Clinically significant adverse reactions (by similar drugs) (incidence unknown)
      1) Since anaphylactoid symptoms in the treatment with other H₂-receptor antagonists have been reported, in case of abnormalities, discontinue the treatment with the drug immediately and take appropriate measures.
      2) Since interstitial nephritis [Initial symptoms: fever, abnormal findings in renal function test (increased BUN, increased creatinine, etc.)] in the treatment with other H₂-receptor antagonists has been reported, in case of abnormalities, discontinue the treatment with the drug immediately and take appropriate measures.
      3) Since rhabdomyolysis in the treatment with other H₂-receptor antagonists has been reported, in case of abnormalities, discontinue the treatment with the drug immediately and take appropriate measures.
      4) Since heart block, such as atrioventricular block, in the treatment with other H₂-receptor antagonists has been reported, in case of abnormalities, discontinue the treatment with the drug immediately and take appropriate measures.
      5) Since asystole in the treatment with other H₂-receptor antagonists has been reported, in case of abnormalities, discontinue the treatment with the drug immediately and take appropriate measures.

(3) Other adverse reactions

<table>
<thead>
<tr>
<th>Incidence</th>
<th>5%≥</th>
<th>&lt;0.1%</th>
<th>Occurrence</th>
</tr>
</thead>
</table>
| Hypersensitivity
t(1) | Rash, pruritus, etc. |
| Hematologic | Eosinophilia | Leukopenia(2) | Anemia |
| Gastrointestinal | Constipation, etc. | Diarrhea, nausea, feeling of enlarged abdomen, thirst, etc. |
| Hepatic | Increased AST (GOT), increased ALT (GPT), etc. | Increased Al-P, increased LDH, etc. | Abnormal hepatic function |
| Psychoneurologic(3) | Reversible confusion, hallucination, numbness, drowsiness, insomnia, dizziness, headache, etc. |
| Others | Gynecomastia, galactorrhoea, malaise, increased blood pressure, increased BUN |

[Note]
1) In such cases, the treatment with the drug should be discontinued.
2) In case of abnormalities, the treatment with the drug should be discontinued.
3) Convulsion (incidence unknown) in the treatment with other H₂-receptor antagonists has been reported.

4. Use in the Elderly
   The drug should be carefully administered, such as, by reducing dose, by prolonging administration interval, etc. [The drug is mainly excreted by the kidney. Since elderly patients may have reduced renal function, and high plasma concentrations may persist] (refer to "PHARMACOKINETICS")

5. Use during Pregnancy, Delivery or Lactation
   (1) The drug should be used in pregnant women and women who may be pregnant only if the expected
therapeutic benefits outweigh the possible risk associated with treatment.

[The safety of this drug during pregnancy has not been established. In the toxicity studies by administration during the period of organogenesis in rats and rabbits, abnormality in delivery were observed in the 400 mg/kg group in rats,1) and abortion and premature labor were observed in a small number of animals in the 400 mg/kg in rabbits.2) Also in the toxicity study by administration during the perinatal and lactation periods in rats, abnormality in delivery were observed in the 200 mg/kg group.3)]

(2) Nursing mothers should discontinue breast feeding during treatment. [Animal studies (rats) have shown that the drug is excreted in breast milk.]

6. Pediatric Use
Safety of this drug in children has not been established. (There is insufficient clinical data in pediatric patients).

7. Precautions concerning Use
At dispensing drugs
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.)

8. Other Precautions
Treatment with the drug may mask the symptoms of gastric cancer. Administration should be made after confirming the absence of malignancy.

PHARMACOKINETICS
1. Plasma concentration
(1) Healthy adults
In healthy adults given an oral 75 mg and 150 mg dose, the plasma concentration of the drug reached a peak about 3-4 hours after administration, and the half-life in plasma was about 4-5 hours.4,5) Analysis of the data from healthy adults to whom the drug was orally administered for 56 consecutive days (50 mg twice daily) did not indicate accumulation of the drug in the body.4)

(2) Patients with renal dysfunction
The absorption of roxatidine acetate hydrochloride following a 75 mg oral dose did not differ between patients with renal dysfunction and healthy adults, but the time required for the drug to disappear from plasma after reaching the maximum plasma concentration was prolonged with the decrease in renal function (Table 1).6) It is therefore necessary to appropriately adjust the dose and dosing interval when the drug is administered to the patients with renal dysfunction.

Table 1 Renal function and T1/2 and AUC

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>T1/2 (hr)</th>
<th>AUC (ng•hr/mL)</th>
</tr>
</thead>
</table>

| 30 > Cer | 12.13±1.13 | 12993±1245 |
| 60 > Cer ≥ 30 | 7.70±0.49 | 4981±477 |
| 90 > Cer ≥ 60 | 5.68±0.51 | 4101±618 |
| Cer ≥ 90 | 3.94±0.34 | 2362±160 |

2. Metabolism
Roxatidine (desacetylated metabolite of roxatidine acetate) is a main metabolite detected in urine after a 75 mg oral administration to healthy adults. Carboxylic acid derivative accounted for the second highest percentage.7)

3. Excretion
About 70% of 75 mg of the drug orally administered to healthy adults was excreted into urine within 24 hours, about 80% of which was roxatidine.5)

4. Transfer to fetus
To the pregnant women planned for caesarean section, two oral doses of 75 mg of the drug were administered before surgery, and the concentration in umbilical plasma was about 60% of that in maternal venous plasma. The amount transferred into amniotic fluid was 0.3% or less of the administered amount.8)

CLINICAL STUDIES

<Gastric ulcer (at 8th week)>

<table>
<thead>
<tr>
<th>75 mg, twice daily administration</th>
<th>Open labeled clinical trials</th>
<th>Healing rate assessed by endoscopy</th>
<th>Improvement rate of subjective and objective symptoms (“improved” or better)</th>
<th>Overall improvement rate (“improved” or better)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trials including double blind clinical trials</td>
<td>-</td>
<td>-</td>
<td>94.7% (699/738)</td>
<td></td>
</tr>
</tbody>
</table>

The usefulness of the drug was confirmed by double blind clinical trials.

<table>
<thead>
<tr>
<th>150 mg, once daily administration</th>
<th>Open labeled clinical trials</th>
<th>Healing rate assessed by endoscopy</th>
<th>Improvement rate of subjective and objective symptoms (“improved” or better)</th>
<th>Overall improvement rate (“improved” or better)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trials including double blind clinical trial</td>
<td>-</td>
<td>-</td>
<td>94.4% (185/196)</td>
<td></td>
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</tbody>
</table>

No significant differences were observed in clinical effects between the doses of 150 mg once daily and 75 mg twice daily by double blind clinical trials.

<Duodenal ulcer (at 6th week)>

<table>
<thead>
<tr>
<th>75 mg, twice daily administration</th>
<th>Open labeled clinical trials</th>
<th>Healing rate assessed by endoscopy</th>
<th>Improvement rate of subjective and objective symptoms (“improved” or better)</th>
<th>Overall improvement rate (“improved” or better)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trials including double blind clinical trial</td>
<td>-</td>
<td>-</td>
<td>96.6% (588/609)</td>
<td></td>
</tr>
</tbody>
</table>
Acute gastritis or acute exacerbation stage of chronic hemorrhage, redness or edema) in the following diseases:

- Improvement of gastric mucosal lesions (erosion, hemorrhage, redness or edema)
- Refflux esophagitis (at 8th week)
- Zollinger-Ellison syndrome
- Stomal ulcer (at 8th week)

The usefulness of the drug was confirmed by double blind clinical trials.

### 1. Effects on humans

#### (1) Suppression of gastric acid secretion

1. **Basal secretion**
   - An oral administration of 25, 50 and 80 mg to patients with peptic ulcers resulted in 80.7%, 94.8% and 97.9% suppression of total gastric acid secretion for 150-180 minutes after the administration, respectively. 41
2. **Betazole-, pentagastrin- and insulin-induced gastric acid secretion**
   - In patients with peptic ulcers and healthy adults, an oral administration of 75 mg resulted in the suppression of total acid secretion for 2 hours after stimulation with betazole (1 mg/kg, i.m.), pentagastrin (6 µg/kg, i.m.) and insulin (0.2 U/kg, i.v.) by 97.7%, 83.7% and 64.4%, respectively. 42,43
3. **Food-stimulated secretion**
   - In healthy adults, an oral administration of 75 mg suppressed total acid secretion for 2 hours after stimulation with food by 78.2%. 46
4. **Nocturnal secretion**
   - In patients with peptic ulcers and healthy adults, an oral administration of 75 mg suppressed nocturnal 7-hour total acid secretion by 95.5%. 45
5. **24-hour gastric acid secretion**
   - In patients with peptic ulcers, two 75 mg administration (after breakfast and at bedtime) and one 150 mg administration (at bedtime) resulted in the elevation of gastric pH, which was more remarkable at night. The sum of the period of time in which pH was 3 or over after the administration of the drug was significantly longer than that of placebo. 46

#### (2) Suppression of pepsin secretion

In patients with peptic ulcers and healthy adults, an oral administration of 75 mg suppressed total pepsin secretion for 2 hours after stimulation with betazole (1 mg/kg, i.m.), pentagastrin (6 µg/kg, i.m.) and insulin (0.2 U/kg, i.v.) by 89.8%, 60.8% and 22.6%, respectively. 42,43 In addition, nocturnal 7-hour pepsin secretion was suppressed by 89.4%. 45

#### (3) Effects on serum gastrin

The use of the drug was confirmed by double blind clinical trial.
In patients with peptic ulcers, an oral administration (150 mg/day) for 8 weeks resulted in no significant change in serum gastrin level compared with the pre-dosing level.9)

(4) Effects on serum prolactin level and other hormone levels
In patients with peptic ulcers, an oral administration (150 mg/day) for 6 to 8 weeks resulted in no significant change in serum prolactin, LH, FSH, testosterone, estradiol, DHEA-S and cortisol levels compared with their pre-dosing levels.47)

2. Effects on animals
(1) Effects on gastric fluid hexosamine
An oral administration of 300 mg/kg to rats did not affect the gastric mucosal hexosamine level. The reduction of gastric mucosal hexosamine in rats caused by oral aspirin treatment and immobilization in water was significantly suppressed by an oral administration of 32 and 90 mg/kg.48)

(2) Effects on gastric mucosal potential difference
An intravenous administration of 25 mg/kg to rats significantly suppressed the reduction in gastric mucosal potential difference induced by an intragastric administration of aspirin, while no influence on the basal gastric mucosal potential difference was observed.48)

(3) Effects on gastric mucosal blood volume and oxygen saturation of hemoglobin in the mucosa
An intravenous administration of 10 mg/kg to rats did not affect basal mucosal blood volume and oxygen saturation of hemoglobin in the mucosa. However, the reduction in these parameters due to hemorrhagic shock was suppressed significantly by the administration of the drug.49)

(4) Effects on gastric mucosal prostaglandin production
An oral administration of 200 mg/kg to rats did not reduce the production of prostaglandin E₂ and prostaglandin I₂ in the gastric mucosa.50)

(5) Suppression of the gastric mucosal lesion
An intraperitoneal administration of 30 mg/kg to rats resulted in the significant suppression of gastric mucosal lesions induced by anhydrated ethanol, 0.6N HCl and 0.2N NaOH.51)

(6) Effects on experimental acute gastric hemorrhage
In experimental acute gastric hemorrhage in rats, the drug suppressed the amount of hemorrhage in a dose-dependent manner.52)

PHYSICOCHEMISTRY
Nonproprietary name:
Roxatidine acetate hydrochloride (JAN)
Roxatidine (INN)

Chemical name:
2-acetoxy-N-[3-[m-(1-piperidinylmethyl)phenoxy]propyl] acetamide hydrochloride

Molecular formula:
C₁₉H₂₈N₂O₄ • HCl

Structural formula:

Molecular weight:
384.90

Melting point:
147-151°C

Description:
Roxatidine acetate hydrochloride occurs as a white crystals or crystalline powder. It is odorless and has a bitter taste. It is very soluble in water, freely soluble in acetic acid (100) and chloroform, sparingly soluble in ethanol (99.5), slightly soluble in dehydrated acetic acid and practically insoluble in diethyl ether.

PACKAGING
ALTAT Capsules 37.5:
Boxes of 100 capsules (10 cap. × 10)
Boxes of 500 capsules (10 cap. × 50)
Bottles of 500 capsules
Boxes of 1,000 capsules (10 cap. × 100)
Boxes of 1,400 capsules (14 cap. × 100)

ALTAT Capsules 75:
Boxes of 100 capsules (10 cap. × 10)
Boxes of 500 capsules (10 cap. × 50)
Bottles of 500 capsules
Boxes of 1,000 capsules (10 cap. × 100)
Boxes of 1,400 capsules (14 cap. × 100)

REFERENCES