ALTAT® Injection 75
<Roxatidine Acetate Hydrochloride>

Powerful drug and Designated drug

**DESCRIPTION**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>ALTAT Injection 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>Each ampule contains 75 mg of roxatidine acetate hydrochloride</td>
</tr>
<tr>
<td>Product description</td>
<td>Ampule (lyophilized preparation of white lumps or amorphous powder)</td>
</tr>
<tr>
<td>Inactive ingredient</td>
<td>Each ampule contains 75 mg of aminoacetic acid</td>
</tr>
</tbody>
</table>

When one ampule is dissolved by 20 mL of physiological saline, the solution is colorless and transparent.

**PH** 3.5-4.5

**Osmotic pressure** About 1 (ratio against physiological saline)

**INDICATIONS**

Hemorrhage of upper digestive tract (caused by peptic ulcers, acute stress ulcers or hemorrhagic gastritis) and preanesthetic medication.

**DOSAGE AND ADMINISTRATION**

1. Hemorrhage of upper digestive tract (caused by peptic ulcers, acute stress ulcers or hemorrhagic gastritis)
   Usually for adults, 75 mg of roxatidine acetate hydrochloride is dissolved in 20 mL of physiological saline (The Japanese Pharmacopoeia) or glucose injection (The Japanese Pharmacopoeia) and slowly administered intravenously twice a day (every 12 hours) or infused intravenously after it is mixed with transfusion fluid. The dosage may be adjusted depending on the age of the patients and symptoms. Generally, onsets of effects are observed within 1 week, and oral doses should be substituted if the patient becomes able to take the drug orally.

2. Preanesthetic medication
   Usually for adults, 75 mg of roxatidine acetate hydrochloride is dissolved in 20 mL of physiological saline (The Japanese Pharmacopoeia) or glucose injection (The Japanese Pharmacopoeia) and slowly administered intravenously one hour before anesthetization.

**<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 Injection 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 362 patients investigated in the clinical trials, 5 patients (1.38%) developed adverse reactions. Major findings are: 2 cases of transient injection site pain (0.55%); rash, itching, epigastric discomfort at injection and nausea (1 case of each, 0.28%). The abnormal laboratory values observed are: increased AST(GOT) and ALT(GPT) (4 cases of each); leucopenia and eosinophilia (1 case of each), etc.

   (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.

5) Since convulsion (incidence unknown) 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.

(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>Category</th>
<th>5%&gt;</th>
<th>20.1%</th>
<th>Incidence unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>†1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash, pruritus, etc.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilia, leukopenia†2</td>
<td></td>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td>Constipation, diarrhea, feeling of enlarged abdomen, thirst, etc.</td>
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</tbody>
</table>

[Note]
1) In such cases, the treatment with the drug should be discontinued.
2) In the event 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 rats1) (63 mg/kg group) and rabbits2) (32 mg/kg group), and during the perinatal and lactation periods in rats3) (60 mg/kg group), deaths were observed in the small number of animals.]

(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

(1) Route of administration

This product should be used only by intravenous injection.

(2) Rate of administration

The product contained in an ampule should be diluted in 20 mL of a solvent. The solution should be administered slowly over at least 2 minutes.

(3) Cautions in administration

Transient injection site pain may occur during the intravenous injection of this product, care should be taken of the method of injection. During injection, it is also necessary to avoid extravascular leakage of the solution.
(4) Others
The product is supplied as one-point-cut ampules. The cut point of the ampule should be wiped with an alcohol swab, etc., before opening.

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
When 75 mg of the drug was intravenously administered to healthy adults, maximum plasma concentration was 773 ng/mL, and plasma half life was 3.36 hours. When the drug was administered intravenously to healthy adults for 3 consecutive days (two 75 mg doses a day), no tendency for the accumulation of the drug in plasma was noted.

(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). 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>
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<tbody>
<tr>
<td>Ccr ≥ 90</td>
<td>3.94±0.34</td>
<td>2362±160</td>
</tr>
<tr>
<td>90 &gt; Ccr ≥ 60</td>
<td>5.68±0.51</td>
<td>4101±618</td>
</tr>
<tr>
<td>60 &gt; Ccr ≥ 30</td>
<td>7.70±0.49</td>
<td>4981±477</td>
</tr>
<tr>
<td>30 &gt; Ccr</td>
<td>12.13±1.13</td>
<td>12993±1245</td>
</tr>
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</table>

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.

3. Excretion
When 75 mg of the drug was administered intravenously to healthy adults, about 67.5% of the administered drug was excreted into urine as roxatidine within 24 hours.

4. Transfer to fetus
When pregnant women planned for caesarean section was administered two oral doses of 75 mg before surgery, 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 drug.

CLINICAL STUDIES

<Hemorrhage of upper digestive tract>

<table>
<thead>
<tr>
<th>Dose-finding clinical trial(1)</th>
<th>Double blind clinical trial(2)</th>
<th>Open labeled clinical trials(10-12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemostasis rate within 3 days</td>
<td>96.8% (30/31)</td>
<td>87.8% (72/82)</td>
</tr>
<tr>
<td>Hemostasis rate within 36 hours</td>
<td>62.4% (103/165)</td>
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</tbody>
</table>

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

<Preanesthetic medication(13,14)>
When the overall efficacy on gastric fluid (volume and pH) and the usefulness were assessed based on the results of clinical trials (including a double blind clinical trial) in which the drug was used to prevent anesthesia-associated aspiration pneumonia, both effectiveness rate and usefulness rate of the drug were 96.8% (90/93).

PHARMACOLOGY
1. Effects on humans
(1) Suppression of gastric acid secretion
1) Basal secretion
An intravenous administration of 75 mg to healthy adults resulted in 92.6% suppression of total gastric acid secretion for 3 hours after the administration, respectively.

2) Pentagastrin-induced gastric acid secretion
In healthy adults, an intravenous administration of 75 mg resulted in the suppression of gastric acid secretion for 90 minutes after an intramuscular administration of pentagastrin (6 µg/kg) by 90.0%.

3) 24-hour gastric acid secretion
When patients with peptic ulcers received twice daily administrations of 75 mg at an interval of 12 hours, the gastric pH was markedly elevated. The average gastric pH for 24 hours was 4.39, which was significantly higher than that of placebo (2.66).

(2) Suppression of pepsin secretion
An intravenous administration of 75 mg to healthy adults resulted in 85.5% suppression of total pepsin secretion during 3 hours after the administration.

When healthy adults were administered a 75 mg intravenously, the total pepsin secreted during 90 minutes after an intramuscular administration of pentagastrin (6 µg/kg) was suppressed by 65.4%.

(3) Effects on serum gastrin
When patients with upper gastrointestinal hemorrhage received a daily 150 mg intravenous administration for 7 days, their serum gastrin levels showed no significant changes after dosing, when compared with their predosing levels. In the phase I study in which healthy adults received a daily 150 mg intravenous administration for 3 days, the serum gastrin level 15 and 30 minutes after administration increased up to about 400 pg/mL in one subject.
(4) Effects on serum prolactin level and other hormone levels
When patients with upper gastrointestinal hemorrhage received a daily 150 mg intravenous administration for 7 days, no clinically significant changes were noted in serum prolactin, LH, FSH, testosterone, estradiol, DHEA-S or cortisol levels.10)

(5) Effects on gastric fluid hexosamine
An intravenous administration of 75 mg to healthy adults resulted in significant elevation of gastric fluid hexosamine concentration, but the amount of hexosamine secretion did not change significantly.15)

2. Effects on animals
(1) Effects on experimental acute gastric hemorrhage
The drug suppressed the amount of gastric hemorrhage dose-dependently in experimental acute gastric hemorrhage in rats.18)

(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.19)

(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.20)

(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.21)

(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.22)

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 Injection 75:
Boxes of 10 ampules
Boxes of 50 ampules

REFERENCES
1) Baeder, C., et al.: Internal data, Hoechst AG.
2) Baeder, C., et al.: Internal data, Hoechst AG.

REQUEST FOR LITERATURE SHOULD BE MADE TO:
Medical Service Department
Teikoku Hormone Mfg. Co., Ltd.
BRAND NAMES IN OTHER COUNTRIES
ROXAN (Korea)