The empirical formula is C18H19NO4S·HCl, representing a molecular weight of 365.87. Ranitidine HCl is a white to yellowish, granular substance that is soluble in water. ZANTAC injection is a clear, colorless to yellowish, nonpyrogenic liquid. The yellow color of the liquid tends to intensify without adversely affecting potency. The pH of the injection solution is 6.7 to 7.3.

Sterile Injection for Intramuscular or Intravenous Administration: Each 1 mL of aqueous solution contains ranitidine 25 mg (as the hydrochloride); phenol 5 mg as a preservative; and 0.96 mg of monobasic potassium phosphate and 2.4 mg of dibasic sodium phosphate as buffers. Sterile, Premixed Solution for Intravenous Administration in Single-Dose, Flexible Plastic Containers: Each 50 mL contains ranitidine HCl equivalent to 50 mg of ranitidine, sodium chloride 225 mg, and citric acid 15 mg and dibasic sodium phosphate 90 mg as buffers in water for injection. It contains no preservatives. The osmolality of this solution is 180 mOsm/L (approx.) and the pH is 6.7 to 7.3.

The flexible plastic container is fabricated from a specially formulated, nonplasticized, thermoplastic co-polyester (CR3). Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of the chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

CLINICAL PHARMACOLOGY: ZANTAC is a competitive, reversible inhibitor of the action of histamine at the histamine H2-receptors, including receptors on the gastric cells. ZANTAC does not lower serum Ca++ in hypercalcemic states. ZANTAC is not an anticholinergic agent.

Pharmacokinetics: Absorption: ZANTAC is absorbed very rapidly after intramuscular (IM) administration. Absorption occurs within 15 minutes after injection following a 50-mg IM dose. Absorption from IM sites is virtually complete, with a bioavailability of 90% to 100% compared with intravenous (IV) administration. Following oral administration of ZANTAC, Table 1 shows the bioavailability of 60%.

Distribution: The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Metabolism: In humans, the N-oxide is the principal metabolite in the urine; however, this amount constitutes <4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool. Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant, alterations in ranitidine half-life, distribution, clearance, and bioavailability.

Excretion: Following IV injection, approximately 70% of the dose is recovered in the urine as unchanged drug. Renal clearance averages 530 mL/min, with a total clearance of 760 mL/min (half-life is 2.8 hours).

Four patients with clinically significant renal function impairment (creatinine clearance 25 to 35 mL/min) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 mL/min, and a volume of distribution of 1.78 L/kg. In general, these parameters appear to be altered in proportion to the degree of renal impairment.

Pediatrics: There are no significant differences in the pharmacokinetic parameter values for ranitidine in pediatric patients (from 1 month up to 16 years of age) and healthy adults when correction is made for body weight. The pharmacokinetics of ZANTAC in pediatric patients are summarized in Table 1.

Table 1: Ranitidine Pharmacokinetics in Pediatric Patients Following IV Dosing

<table>
<thead>
<tr>
<th>Population Age</th>
<th>n</th>
<th>Dose (mg/kg)</th>
<th>T1/2</th>
<th>tmax</th>
<th>Vd (L/mg/kg)</th>
<th>Clp (mL/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric ulcer disease (≤6 years)</td>
<td>6</td>
<td>1.25 or 2.5</td>
<td>2.2</td>
<td>1.29</td>
<td>11.41</td>
<td></td>
</tr>
<tr>
<td>(6-12 years)</td>
<td>6</td>
<td>1.25 or 2.5</td>
<td>2.1</td>
<td>1.14</td>
<td>8.96</td>
<td></td>
</tr>
<tr>
<td>(12 years)</td>
<td>6</td>
<td>1.25 or 2.5</td>
<td>1.7</td>
<td>0.98</td>
<td>9.89</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>6</td>
<td>2.5</td>
<td>1.9</td>
<td>0.14</td>
<td>8.77</td>
<td></td>
</tr>
<tr>
<td>Pediatric ulcer disease (3.5-16 years)</td>
<td>12</td>
<td>0.13-0.30</td>
<td>1.8</td>
<td>2.3</td>
<td>795 mL/mg/1.73 m²</td>
<td></td>
</tr>
<tr>
<td>Children in intensive care (1 day - 12 years)</td>
<td>17</td>
<td>1.0</td>
<td>2.4</td>
<td>2</td>
<td>11.7</td>
<td></td>
</tr>
<tr>
<td>Neonates receiving ECMO</td>
<td>12</td>
<td>0</td>
<td>6.6</td>
<td>1.8</td>
<td>4.3</td>
<td></td>
</tr>
</tbody>
</table>

T1/2 = Terminal half-life; Clp = Plasma clearance of ranitidine.

ECMO = extracorporeal membrane oxygenation.

Pharmacodynamics: Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/mL. Following single IV or IM 50-mg doses, serum concentrations of ZANTAC are in this range for 6 to 8 hours.

Antiseptivity Activity: 1. Effects of Acid Secretion: ZANTAC injection inhibits basal gastric acid secretion as well as gastric acid secretion stimulated by betazole and pentagastrin, as shown in Table 2.

Table 2: Effect of Intravenous ZANTAC on Gastric Acid Secretion

<table>
<thead>
<tr>
<th>Time After Dose, h</th>
<th>Betazole</th>
<th>Pentagastrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 min</td>
<td>47</td>
<td>99</td>
</tr>
<tr>
<td>60 mg</td>
<td>49</td>
<td>99</td>
</tr>
<tr>
<td>100 mg</td>
<td>47</td>
<td>99</td>
</tr>
</tbody>
</table>

In a group of 10 known hypersecretors, ranitidine plasma levels of 71, 180, and 376 ng/mL inhibited basal acid secretion by 76%, 90%, and 95.5%, respectively. It appears that basal- and betazole-stimulated secretions are most sensitive to inhibition by ZANTAC. These findings are consistent with other studies. It is more difficult to suppress other pharmacological actions:

Pepsin: ZANTAC does not affect pepsin secretion. Total pepsin output is reduced proportionally to the dose, as determined by gastric juice volume.

Intrinsic Factor: ZANTAC has no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Serum Gastrin: ZANTAC has little or no effect on fasting or postprandial serum gastrin.

Other Pharmacological Actions:

1. Gastric bacterial flora—increase in nitrate-reducing organisms, significance not known.
2. Prolactin levels—no effect in recommended oral or intravenous (IV) dosage, but small, transient, or inconsistent changes in serum prolactin have been reported after IV bolus injections of 100 mg or more.
3. Other pituitary hormones—no effect on serum gonadotropins, TSH, or GH. Possible impairment of vasopressin release not observed.
4. No change in cortisol, aldosterone, androgen, or estrogen levels.
5. No antianodic action.
6. No effect on count, motility, or morphology of sperm.

Pediatrics: The ranitidine concentration necessary to suppress basal acid secretion by at least 90% of doses has been reported to be 40 to 80 ng/mL in pediatric patients with duodenal or gastric ulcers.

In a study of 20 critically ill pediatric patients receiving ranitidine IV at 1 mg/kg every 6 hours, 10 patients with a baseline pH of less than 4.5 maintained this baseline throughout the study. Eight of the remaining 10 patients with a baseline pH2 of 4.8 achieved pH4 throughout varying periods after dosing. It should be noted, however, that because these pharmacokinetic parameters were observed in critically ill pediatric patients, the data should be interpreted with caution when dosing recommendations are made for a less seriously ill pediatric population.

In another small study of neonatal patients (n = 5) receiving ECMO, gastric pH4 pretreatment increased to 4 after a 2 mg/kg dose and remained above 4 for at least 15 hours.

Clinical Trials: Active Duodenal Ulcer: In a multicenter, double-blind, controlled, US study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the patients treated with ZANTAC as shown in Table 3.

Table 3: Duodenal Ulcer Patient Healing Rates

<table>
<thead>
<tr>
<th>Number Entered</th>
<th>Healed/ Evaluable</th>
<th>Number Entered</th>
<th>Healed/ Evaluable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatients Week 2</td>
<td>116/192 (38%)</td>
<td>137/187 (73%)</td>
<td>31/16 (19%)</td>
</tr>
<tr>
<td>Week 4</td>
<td>31/16 (19%)</td>
<td>188</td>
<td>76/168 (45%)</td>
</tr>
</tbody>
</table>

*All patients were permitted p.r.n. antacids for relief of pain.

In these studies, patients treated with oral ZANTAC reported a reduction in both daytime and nocturnal pain, and they were also consumed less antacids than the placebo-treated patients.

Table 4: Mean Daily Doses of Antacid

<table>
<thead>
<tr>
<th>Oral ZANTAC</th>
<th>Oral Placebo *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer Healed</td>
<td>Ulcer Not Healed</td>
</tr>
<tr>
<td>Oral ZANTAC</td>
<td>0.06</td>
</tr>
<tr>
<td>Oral placebo</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): ZANTAC inhibits basal acid secretion and decreases acid output.

INDICATIONS AND USAGE: ZANTAC injection and ZANTAC Injection Premixed are indicated in some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication.

CONTRAINDICATIONS: ZANTAC injection and ZANTAC Injection Premixed are contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:

General: 1. Systemic response to therapy with ZANTAC does not preclude the presence of gastric malignancy.

2. Since ZANTAC is excrated primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

3. In controlled studies in normal volunteers, elevations in SGPT have been observed when H2-antagonists are administered intravenously at greater than recommended dosages for 5 days or longer. Therefore, it seems prudent in patients receiving IV ranitidine at doses >100 mg i.q. for periods of 5 days or longer to monitor SGPT daily (from day 5) for the remainder of IV therapy.

4. Bradycardia in association with rapid administration of ZANTAC injection has been reported rarely, usually in patients with factors predisposing to cardiac rhythm disturbances. Recommended rates of administration should not be exceeded (see DOSAGE AND ADMINISTRATION).

5. Rare reports suggest that ZANTAC may precipitate acute porphyrin attacks in patients with acute porphyria. ZANTAC should therefore be avoided in patients with a history of acute porphyria.

Laboratory Tests: False positive tests for urine protein with MULISTIX may occur during therapy with ZANTAC, and therefore testing with sulfosalicylic acid is recommended.
ZANTAC® (ranitidine hydrochloride) injection

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P450-450-linked oxidase enzymes in the liver. However, there have been isolated reports of drug interactions with ZANTAC. Drug interactions may occur with certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution).

In general, it should be decided whether to discontinue treatment with a particular drug or whether to adjust the dosages of both drugs. Some of these interactions have been reported during concurrent use of ranitidine and warfarin. In human, in pharmacokinetic studies with doses of ranitidine hydrochloride and oral warfarin, 40 mg of ranitidine given alone and in combination with oral warfarin caused a 34% decrease in oral warfarin peak plasma concentrations and a 19% decrease in trough plasma concentrations of warfarin. In healthy male volunteers, a single 150 mg dose of ranitidine hydrochloride given with a single 5 mg dose of warfarin caused a 20% decrease in oral warfarin peak plasma concentrations and a 13% decrease in trough plasma concentrations of warfarin. In healthy volunteers, treatment with ZANTAC caused a decrease in the oral bioavailability of warfarin of 17%. These results are consistent with the decreases in warfarin plasma concentrations reported in patients who have been treated with ZANTAC concurrently. Therefore, ZANTAC should be used with caution in patients on warfarin. In controlled studies, plasma warfarin concentration monitoring is usually not required in patients who are taking warfarin and concomitantly receiving ranitidine hydrochloride, although the patient’s international normalized ratio should be monitored more closely.

Concomitant Use: The risk of bleeding associated with warfarin therapy is greater when it is used with ZANTAC, and gastric ulceration is a significant complication in patients receiving ZANTAC,Warfarin, and aspirin together. Careful monitoring of the patient’s coagulation status is recommended when ZANTAC is used with warfarin.

ZANTAC® (ranitidine hydrochloride) Injection Premixed

b. Intermittent infusion: 50 mg (2 ml) every 6 to 8 hours. Dilute ZANTAC Injection, 50 mg in 5% dextrose injection or other compatible IV solution (see Stability) to a concentration no greater than 0.5 mg/ml (100 ml). Infuse at a rate no greater than 0.2 mg/min (15 to 20 minutes).

ZANTAC Injection Premixed solution, 50 mg in 0.45% sodium chloride, 50 ml requires no dilution and should be infused over 15 to 20 minutes. This is necessary, the increases should be made by more frequent administration of the dose, but generally should not exceed 400 mg/day. Continuous Intravenous Infusion: Add ZANTAC Injection to 5% dextrose injection or other compatible IV solution (see Stability). Deliver at a rate of 6.25 mg/hr (i.e., 150 mg [6 ml] of ZANTAC Injection in 250 ml of 5% dextrose injection at 19.7 ml/hr).

For Zollinger-Ellison patients, dilute ZANTAC Injection in 5% dextrose injection or other compatible IV solution (see Stability) to a concentration no greater than 2.5 mg/ml (100 ml). Start the infusion at a rate of 2.5 mg/hr. After 4 hours either measure gastric acid output $>$ 10 mEq/hr or the patient becomes symptomatic, the dose should be adjusted upward incrementally in 0.5 mg/ml increments, and the acid output should be reassessed. Dosages up to 2.5 mg/hr per hour and infusion rates as high as 220 mg/hr have been used.

ZANTAC Injection Premixed in Flexible Plastic Containers: Instructions for Use: To Open: Tear outer wrapper at notch and remove solution container. Check for minute air leaks by squeezing container. Discard unit if any air leak is present.

Preparation for Administration: Use aseptic technique.
1. Close flow control clamp of administration set.
2. Remove cover from outlet port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton.
4. Suspend container from drip stand.
5. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion of ZANTAC Injection Premixed.
6. Open flow control clamp to expel air from set. Close clamp.
7. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
8. Perfuse with venous return.
9. Regulate rate of administration with flow control clamp.

Storage: ZANTAC Injection Premixed in flexible plastic containers is to be administered by slow IV drip infusion only. Additives should not be introduced into this solution.

Dosage Adjustment for Patients With Impaired Renal Function: The administration of ranitidine as a continuous infusion has not been evaluated in patients with impaired renal function. On the basis of experience with a group of subjects with severely impaired renal function (creatinine clearance less than 20 ml/min) and a few cases of renal failure, recommended dosage in patients with a creatinine clearance $<$ 50 ml/min is 50 mg every 12 to 18 hours. Should the patient’s condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the patient’s hemodialysis.

Stability: Undiluted, ZANTAC Injection tends to exhibit a yellow color that may intensify over time without adversely affecting potency. ZANTAC Injection is stable for 48 hours at room temperature when exposed to light or for diluted with most commonly used IV solutions, e.g., 0.9% sodium chloride injection, 5% dextrose injection, lactated Ringer’s solution, and 5% dextrose and 0.5% sodium bicarbonate injection.

ZANTAC Injection Premixed in flexible plastic containers is sterile through the expiration date on the label when stored under recommended conditions.

How Supplied: ZANTAC Injection, 25 mg/ml, containing phenol 0.5% as preservative, is available as follows:
NDC 0173-0382-38-2 ml single-dose vials (Tray of 10)
NDC 0173-0382-38-5 ml single-dose vials (25 trays)
Store between 4°C and 30°C (39° and 86°F). Protect from light.
ZANTAC Injection Premixed, 50 mg/50 ml, in 0.45% sodium chloride, is available as a sterile, preservative-free solution compatible with most IV administration sets, flexible plastic containers (NDC 0173-0441-00) (case of 24). It contains no preservatives.
Store between 2°C and 25°C (36° and 77°F). Protect from light.
ZANTAC Injection Premixed in flexible plastic containers is sterilized with glutaraldehyde for use in cases where the product is used for patients receiving detoxification therapy or who have had recent surgery.

GastroWelcome

Glaxo Welcome
Research Triangle Park, NC 27709

ZANTAC® Injection: Glaxo Welcome Inc.
Pharmaceutical Division
Research Triangle Park, NC 27709

ZANTAC® Injection Premixed: Manufactured for Glaxo Welcome Inc.
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US Patent No. 4,585,790
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