Famotidine Tablets USP

DESCRIPTION
The active ingredient in famotidine is a histamine H2-receptor antagonist. Famotidine is N-[2-amino-sulfonyl]-3-[2-[di(2-methylamino)ethyl]amino]-4-[[trans]-thiazolyl]methyl]thio)propansulfonamide. The empirical formula of famotidine is C29H39N7O3S6 and its molecular weight is 337.45. Its structural formula is:

H₃N
\[ \text{C}_8\text{H}_{15}\text{N}_7\text{O}_2\text{S}_3 \]

Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Each tablet for oral administration contains either 20 mg or 40 mg of famotidine and the following inactive ingredients: hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, modified corn starch (pregelatinized starch), talc, inulin, titanium dioxide.

CLINICAL PHARMACOLOGY IN ADULTS
GI Effects
Famotidine is a competitive inhibitor of histamine H2-receptors. The pharmacologic activity of famotidine is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by famotidine, while changes in pepsin secretion are proportional to volume output.

Gastroesophageal Reflux Disease (GERD)
Orally administered famotidine was compared to placebo in a U.S. study of patients with symptoms of GERD and without endoscopic evidence of erosion or ulceration of the esophagus. Famotidine 20 mg p.o. b.i.d. was statistically significantly superior to 40 mg h.s. and to placebo in providing a successful symptomatic outcome, defined as moderate or excellent improvement of symptoms (Table 3).

Pharmacodynamics
Pharmacodynamics of famotidine were evaluated in 5 pediatric patients 2-13 years of age using the sigmoid Emax model. These data suggest that the relationship between serum concentration of famotidine and gastric acid suppression is similar to that observed in one study of adults (Table 7).

Table 7
Pharmacodynamics of famotidine using the sigmoid Emax model

<table>
<thead>
<tr>
<th>Age (N=patients)</th>
<th>Area Under the Curve (AUC) (ng*h/mL)</th>
<th>Total Clearance (CL) (L/h)</th>
<th>Volume of Distribution (Vd) (L)</th>
<th>Elimination Half-life (T1/2) (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-11 years (N=20)</td>
<td>1089 ± 83</td>
<td>0.04 ± 0.34</td>
<td>2.07 ± 1.49</td>
<td>3.8 ± 2.00</td>
</tr>
<tr>
<td>11-15 years (N=6)</td>
<td>1140 ± 32</td>
<td>0.48 ± 0.14</td>
<td>1.54 ± 0.4</td>
<td>2.3 ± 0.4</td>
</tr>
</tbody>
</table>

*Values are presented as means ± SD unless indicated otherwise.

<Mean value only.

†Single center study.

‡‡ p ≤ 0.001 vs Ranitidine 150 mg b.i.d.

‡‡‡ p ≤ 0.001 vs Placebo h.s.

Data from one study

Clinical Studies
Duodenal Ulcers
In a U.S. multicenter, double-blind study in outpatients with endoscopically confirmed duodenal ulcer, orally administered famotidine was compared to placebo. As shown in Table 1, 70% of patients treated with Famotidine 40 mg h.s. were healed by week 4.

Table 1
Patients with Endoscopically Confirmed Healed Duodenal Ulcers

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo (N=73)</th>
<th>Famotidine 20 mg h.s. (N=149)</th>
<th>Famotidine 40 mg h.s. (N=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>39%</td>
<td>45%</td>
<td>65%</td>
</tr>
<tr>
<td>Week 6</td>
<td>65%</td>
<td>64%</td>
<td>80%</td>
</tr>
<tr>
<td>Week 8</td>
<td>78%</td>
<td>78%</td>
<td>78%</td>
</tr>
</tbody>
</table>

*Statistically significantly different than placebo (p ≤ 0.05).

Values of p ≤ 0.05 vs Famotidine 20 mg h.s.

††† p ≤ 0.001 vs Placebo 20 mg h.s.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas)
In studies of patients with pathological hypersecretory conditions such as Zollinger-Ellison Syndrome or with multiple endocrine adenomas, famotidine significantly inhibited gastric acid secretion and controlled acid secretion in all patients. Orally administered doses of 20 to 160 mg q.d. or b.i.d. maintained basal acid secretion below 10 mEq/hr; initial doses were increased to achieve a >2 pH unit increase within 6-8 hours. There was no cumulative effect with repeated doses. The mean pH and acid suppression in all subjects; mean nocturnal gastric acid secretion was within 6-8 hours. There was no cumulative effect with repeated doses. The mean pH was 6.8 ± 1.1 hours (17.3, 21.8) c

Five published studies (Table 8) examined the effect of famotidine on gastric pH and duration of acid suppression in pediatric patients. While each study had a different design, acid suppression data over time are summarized as follows:

Table 8
Dosing Route Effect * Number of Patients (age range)

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Route</th>
<th>Effect</th>
<th>Number of Patients (age range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg/kg</td>
<td>I.V.</td>
<td>gastric pH &gt;4</td>
<td>11 (5-19 years)</td>
</tr>
<tr>
<td>0.3 mg/kg</td>
<td>I.V.</td>
<td>gastric pH &gt;3.5</td>
<td>6 (2-7 years)</td>
</tr>
<tr>
<td>0.4-0.8 mg/kg</td>
<td>I.V.</td>
<td>gastric pH &gt;4</td>
<td>18 (2-6 months)</td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>I.V.</td>
<td>gastric pH &gt;3.5</td>
<td>9 (2-13 years)</td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>oral</td>
<td>gastric pH &gt;4</td>
<td>4 (6-15 years)</td>
</tr>
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<td>oral</td>
<td>gastric pH &gt;4</td>
<td>4 (11-15 years)</td>
</tr>
</tbody>
</table>

*Values reported in published literature.

Mean of pH is C±SD (range)

Mean (95% confidence interval).

The duration of effect of famotidine I.V. 0.5 mg/kg on gastric pH and acid suppression was shown in one study to be longer in pediatric patients <1 month of age than in older pediatric patients. This longer duration of gastric acid suppression is consistent with the decreased clearance in pediatric patients <3 months of age (see Table 6).

INDICATIONS AND USAGE
Famotidine is indicated in:

1. Short term treatment of active duodenal ulcer. Most adult patients heal within 4 weeks; there is rarely reason to use famotidine at full dosage for longer than 6 to 8 weeks. Studies have not assessed the safety of famotidine in uncomplicated active duodenal ulcer for periods of more than eight weeks.

2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer. Controlled studies in adults have not extended beyond one year.

3. Short term treatment of active benign gastric ulcer. Most adult patients heal within 6 weeks. Studies have not assessed the safety or efficacy of famotidine in uncomplicated active benign gastric ulcer for periods of more than 8 weeks.

4. Short term treatment of gastroesophageal reflux disease (GERD). Famotidine is indicated for short term treatment of patients with symptoms of GERD (see CLINICAL PHARMACOLOGY IN ADULTS, Clinical Studies).
Famotidine is also indicated for the short term treatment of erosive and ulcerative conditions of the lower esophagus and the cardia of the stomach (esophagitis and erosive gastritis), where healing is desired prior to endoscopy. Published uncontrolled clinical studies in patients 1-16 years of age have employed doses of up to 1 mg/kg per day for famotidine and 2 mg/kg per day for Gerd in patients with or without esophagitis including erosions and ulcerations.

CONTRAINDICATIONS
Symptomatic response to therapy with famotidine does not preclude the presence of gastric malignancy.

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Pediatric Patients <1 year of age
Use of famotidine in pediatric patients <1 year of age is supported by evidence from adequate and well-controlled studies in adults and, by the following studies in pediatric patients <1 year of age.

Two pharmacokinetic studies in pediatric patients <1 year of age (N=48) demonstrated that clearance of famotidine in patients >3 months was similar to that seen in older pediatric patients (1-15 years of age) and adults. In contrast, pediatric patients 0-3 months of age had famotidine clearance values that were 2-4 fold less than that observed in older pediatric patients, consistent with the longer famotidine half-life in pediatric patients 0-3 months of age. (See CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS, Pharmacokinetics and Pharmacodynamics.)

In a double-blind, randomized, treatment-withdrawal study, 35 pediatric patients <1 year of age who were diagnosed as having gastroesophageal reflux disease were treated for up to 4 weeks with oral suspension (0.5 mg/kg/dose or 1 mg/kg/dose). Although an intravenous famotidine formulation was available, no patients were treated with famotidine in this study. Also, caregivers were instructed to provide conservative treatment including thickened feedings. Enrolled patients were diagnosed primarily by history of vomiting (spitting up) and irritability (fussiness). The famotidine dosing regimen was once daily for patients >3 months and twice daily for patients <3 months. After 4 weeks of treatment, patients were randomly withdrawn from the treatment and followed an additional 4 weeks for adverse events and symptomatology. Patients were evaluated for vomiting (spitting up), irritability (fussiness) and global assessments of improvement. The study patients ranged in age at entry from 1.3 to 10.5 months (2.9 months), 57% were female, 91% were white and 6% were black. Most patients (27/35) continued into the treatment-withdrawal phase of the study. Two patients discontinued famotidine due to adverse events. Most patients improved during the initial treatment phase of the study. Results of the treatment-withdrawal phase were difficult to interpret because of small numbers of patients. Of the 35 patients enrolling in the study, initial attenuation of symptomatology was observed in 5 patients on famotidine that resolved when the medication was discontinued. (see ADVERSE REACTIONS, Pediatric Patients).

OVERDOSAGE
The adverse reactions in overdose cases are similar to the adverse reactions encountered in normal clinical experience (see ADVERSE REACTIONS).

DOSAGE AND ADMINISTRATION
Pediatric Ultracon
The recommended adult oral dosage for active duodenal ulcer is 40 mg once a day at bedtime. Most patients heal within 4 weeks; there is rarely reason to use famotidine at fully tolerated doses for longer than 8 weeks. A regimen of 20 mg b.i.d. is also effective.

Maintenance Therapy: The recommended adult oral dosage is 20 mg once a day at bedtime.

Gastroesophageal Reflex Disease
The recommended oral dosage for treatment of adult patients with symptoms of GERD is 20 mg b.i.d. for up to 6 weeks. The recommended oral dosage for the treatment of adult patients with erosive esophagitis and ulcerations, erosions and ulcerations and accompanying symptoms due to GERD is 20-40 mg b.i.d. for up to 12 weeks (see CLINICAL PHARMACOLOGY IN ADULTS, Chronic). (Revised: 06/12)

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