CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 019090, S37

MEDICAL REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

MAY 21 1997

NDA: (Pediatric Labeling Supplement)	18-703/S-056 (Zantac® 150/300 Tablets) Cross reference to: NDA 19-090 (Zantac® Injection) NDA 19-593 (Zantac® Injection Premixed) NDA 19-675 (Zantac® Syrup) NDA 20-095 (Zantac® 150/300 GELdose® Capsules) NDA 20-251 (Zantac® 150 EFFERdose® Tablets and Granules)
Date Submitted:	December 13, 1996
Sponsor:	Glaxo Wellcome Inc.
Drug:	Zantac® (ranitidine hydrochloride)
Pharmacological Category:	Antisecretory. Antiulcer. (H_2-receptor antagonist)
Material Reviewed:	Data in support of proposed revisions to the "Pediatric Use" sections of the currently approved labeling for Zantac® products. These data includes published literature, clinical studies, and the Glaxo Wellcome worldwide spontaneous AE reporting system.
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D.

I. BACKGROUND/RATIONALE

Zantac® (ranitidine hydrochloride = RAN•HCl) is an H_2-receptor antagonist approved for use in the adult population since 1983. The drug is currently available in six dosage forms: oral tablet; oral syrup; soft gelatin capsule; effervescent tablets and granules; injection; and premixed injection. The data provided in this application pertain to both oral and intravenous dosage forms. RAN•HCl is indicated for the treatment of active duodenal and gastric ulcers (DU, GU); maintenance therapy for duodenal and gastric ulcers, pathological hypersecretory conditions, gastroesophageal reflux disease (GERD); and acute and maintenance therapy for erosive esophagitis.

The sponsor is submitting this Pediatric Use Labeling supplement for Zantac® in accordance with 21 CFR 201.57(f)(9)(iii) and (iv) in response to the FDA Final Rule on Pediatrics. In accordance with this notice, the sponsor has reviewed the pediatric data regarding the use of RAN•HCl. As a result of this evaluation, Glaxo Wellcome concluded that although Zantac is undoubtably prescribed by practitioners for use in children, there is little data indicating the appropriate dosage and administration in the pediatric population.

The data contained in this application are derived from a number of sources, including published literature, clinical studies, and the Glaxo Wellcome worldwide spontaneous adverse event reporting system. Where possible, the data have been analyzed by age group (birth to <1 month; 1 month to <2 years; 2 years to <12 years; 12 years to <16 years). In addition, comparisons of the pharmacokinetics of ranitidine in children versus adults have been made, where appropriate, to allow for extrapolation of a pediatric dosage recommendation based on the currently approved adult doses.

The evidence submitted by the sponsor in support of the requested labeling changes has been organized and reviewed under the following headings.

Subheadings:

A. Summary of Current Clinical Practice
(Includes evidence of disease similarity between adults and children)

B. Review of the Literature
(Includes both oral and I.V. ranitidine and efficacy as well as PK/PD studies published)

C. Summary of Clinical Studies
(Includes PK/PD and Efficacy Data for both oral and I.V. formulations)

D. Summary of Safety
(Includes results of six studies and an overview of spontaneous AEs)

II. SUMMARY OF CURRENT CLINICAL PRACTICE

The sponsor provided a summary of the current pediatric practice patterns regarding the treatment of PUD (Peptic Ulcer Disease) and GERD. It was clarified that this information was summarized from standard pediatric and pediatric G.I. textbooks. Included were discussions under headings such as definition/etiology, pathophysiology, clinical presentation, diagnosis and present treatment of PUD and GERD. The MO highlights only certain aspects of these topics, including some references when appropriate.

PUD

- Although this term includes mainly DU and GU, ulcers may also arise in the lower esophagus or in the more distal intestine adjacent to Meckel's diverticulum. A differentiation is made between primary (i.e. those DUs and GUs that have no underlying cause) and secondary ulcers. The latter are due to medications, chemicals, toxins or systemic disease. In children, secondary ulcers are associated with severe burns (Curling ulcer), intracranial lesions (Cushing ulcer), sepsis, shock, severe acute respiratory distress, collagen vascular disease, malignancies of the bone marrow and lymph nodes or immunosuppressive therapy [sponsor's Ref. 1 and 9].

- Most primary PUs are duodenal, whereas secondary PUs can be duodenal or gastric. In infancy, **80% of ulcers are secondary**. After the age of 6, **70% of ulcers are primary** [sponsor's Ref. 2 and 9].

- Genetics appears to play a role in ulcer disease.

  - 20% to 70% of pediatric patients with primary PUD have a relative (usually the father) with PUD.

  - The concordance for duodenal ulcers is 50% for monozygotic twins.

  - Blood type O is also associated with PUD.

  - PUD is more common in males than females, except in very young patients, where the incidence is the same in both sexes [sponsor's REF. 1, 2, 4 and 9].

- It is pointed out that the pathogenesis of UD (ulcer disease) is multifactional. The final common pathway is a breakdown in the normal mucosal defense that permits acid peptic digestion of the mucosa. Among the causes of this breakdown are: 1) a reduced mucous protective layer (aspirin, NSAIDs, hypoxia); 2) reduced metabolic activity of the gastric mucosal cell; 3) increased gastric secretion of acid or pepsin (increased parietal cell mass, increased postprandial secretion of gastrin, increased vagal tone); 4) reflux of bile from duodenum to stomach; 5) decreased neutralizing activity in DU and 6) infection with *Helicobacter pylori (H. pylori)* in primary PUD [sponsor's references 1, 4, 5, 7 and 9].

- Results of a study in 270 pediatric patients are worth mentioning [Pediatric Clinics of No. Amer. 55:103-116 and 117-140 (1988)]:

  - H. pylori was detected in 91 pts. (38.7%)

  - Of 12 GU pts., 9 (75%) had H. pylori, whereas

  - Of 11 DU pts., 10 (90.9%) had H. pylori.

  The reviewer came across the publication by D.M. Israel et al. [J. Pediatr. 123:53-58 (1993)] who have reported initial data in children supporting a causal relationship between H. pylori and DUD (duodenal ulcer disease).

- Data were reviewed demonstrating that the clinical manifestations of PUD vary according to the age of presentation (neonatal, older infants and toddlers, preschooler (3 to 6y) and older children and adolescents).

  - In the first month of life, PUD is acute and has two major presentations-GI hemorrhage and/or perforation. Perforation most often occurs along the greater curvature of the stomach. Most ulcers in this age group are secondary to stress associated with

disorders such as sepsis, heart disease, respiratory distress syndrome, hypoglycemia, hypoxia or CNS disease. Patients may also present with vomiting, feeding difficulties, or failure to thrive [sponsor's Ref. 1, 2, 4, 5, 7, 9 and 10].

- In the older infants and toddlers age group, children present most often with vomiting (within two hours after feeding), poor appetite, failure to thrive or unexplained crying. GI bleeding may be characterized by tarry or guaiac positive stools or hematemesis [sponsor's Ref. 1, 2, 4, 5, 7 and 10].

- In preschoolers (3-6y) vomiting after eating is a major symptom. Patients may complain of periumbilical or generalized pain which may be exacerbated by eating (although some have pain which is unrelated to eating or fasting). Some patients present with GI hemorrhage or perforation [sponsor's Ref. 1, 2, 4, 5, 7 through 10].

- In older children and adolescents the clinical manifestations of PUD are similar to those in adults. Most complain of epigastric pain, described as sharp, burning, dull, crampy or aching. The majority of pediatric (and adult) patients have short, discrete episodes (lasting minutes to hours) followed by pain-free intervals. Classically the pain is relieved by food or antacids but recurs within several hours. Nocturnal pain is very common, with up to 60% of patients awakening from sleep. Patients may also present with nausea, vomiting, anemia, perforation and occult or gross bleeding. It is also noted that chronic illnesses such as chronic lung disease, Crohn's disease, cirrhosis or rheumatoid arthritis may be associated with an increased frequency of peptic disease. As in adults, ulcers in this age range are more common in males and are predominantly duodenal [sponsor's Ref. 1 through 5, 7 and 9].

- For diagnosis of PUD, a complete history and physical, including a family history, should be performed. In addition, some authors recommend a fasting serum gastrin level [sponsor's Ref. 2, 9, 10]. An upper GI series or endoscopy are the procedures utilized to diagnose PUD. Many gastroenterologists start with an UGI series, progressing to endoscopy when X-ray findings are questionable or absent in symptomatic patients or when symptoms are persistent. UGI series is not as accurate as endoscopy to diagnose PU. Indeed, in patients with acute GI hemorrhage, endoscopy is the procedure of choice. In addition, endoscopy also permits gastric biopsy to identify H. pylori [sponsor's Ref. 1 through 4, 7]. In children, endoscopy will locate 90-95% of lesions. In contrast, an UGI series will identify 25-50% of GUs and 50% of DUs in children [sponsor's Ref. 5].

  - The differential diagnosis of PUD includes: esophagitis, GERD, Meckel's diverticulum, Zollinger-Ellison syndrome, pancreatitis, inflammatory bowel disease, cholelithiasis, appendicitis,

recurrent mid-gut volvulus, giardiasis, pneumonia and non-specific or functional abdominal pain [sponsor's Ref. 2, 3, 7, 9 and 10].

- The treatment of PUD may include any or all of the following:

  - avoidance of irritants: adolescents should avoid alcohol and cigarettes; all children and adolescents should avoid foods that cause pain, aspirin, and NSAIDs [sponsor's Ref. 1, 2 and 4].

  - acid neutralization: magnesium or aluminum hydroxide antacids are given one and three hours after meals and at bedtime, in doses of 0.5 to 2 ml/Kg/dose. According to most references, it is difficult for most children to adhere to an effective antacid regimen [sponsor's Ref. 1 through 5, 7 through 10].

  - H_2-receptor antagonists: these substances inhibit gastric acid output, gastric volume and pH in response to stimulants of acid secretion, including food. The two major H_2-receptor antagonists used in pediatric patients are cimetidine (given in doses of 20 to 40 mg/Kg/day, q.i.d., before meals and at bedtime) and ranitidine (given in doses ranging from 4 to 6 mg/Kg/day, b.i.d.; t.i.d. in infants). Both ranitidine and cimetidine cause healing in 75 to 95% of DUs in 6 to 8 weeks, and 80 to 90% of GUs in 8 to 12 weeks. A single daily dose at night is effective in preventing recurrence. In critically ill patients being prophylaxed with H_2-receptor antagonists, the goal of therapy is to keep gastric pH>4.0 [sponsor's Ref. 1 through 5 and 7 through 10].

  - proton pump inhibitors: experience with these compounds in children is limited and dosing is not established [sponsor's Ref. 1, 2, 7 and 9].

  - mucosal protectors: these included drugs such as sucralfate (given in a dose of 1 g q.i.d.), which are sometimes used in the treatment of ulcers.

  - combination of drugs to treat H. pylori infection, such as oral bismuth for 4 to 6 weeks and amoxicillin or metronidazole for 2 to 4 weeks [sponsor's Ref. 4, 7through 9]. As mentioned above, as in adults, intensive investigations of the role of H. pylori in primary DUs are ongoing.

  - surgery: which is reserved for children with perforation, hemorrhage, obstruction, and rarely, irritable pain. Most surgeons perform ulcer plication, pyloroplasty and vagotomy [sponsor's Ref. 1, 2, 7, 8 and 10].

- In the pediatric population, recurrence rates in long-term follow-up ulcer studies vary from 13 to 69%. A pediatric patient with an ulcer may continue to have difficulty into adulthood but statistics on these matters are not available.

GERD

- The etiology of GERD in infants and children is felt to be multifactorial. Possible etiologies for GERD include: 1) decreased LES (lower esophageal sphincter) tone; 2) transient LES relaxation; 3) delayed gastric emptying; 4) increased intra-abdominal pressure and 5) large hiatus hernia.

- Silverberg and Daum and other investigators [sponsor's Ref. 1] feel that the LES zone of high pressure may be reduced in early infancy secondary to decreased muscle mass. In addition, certain foods, drugs, or hormones may alter the LES pressure. Others have noted, however, that although decreased LES occurs in some patients with reflux, many patients with GERD have normal resting LES pressures [Werlin et al., Pediatr. Clinics No. Amer. 35:103-116 and 117-140 (1988)]. It is pointed out that the LES undergoes spontaneous, transient relaxations. During such relaxations, the sphincter relaxes completely and remains atonic for 5 to 35 seconds [belches or partial swallows may result from such relaxations].

- The sponsor summarized results of a trial by Werlin et al. [(locus cited) (1988)]. These authors studied pediatric patients with reflux, monitoring distal esophageal pH, upper and LES pressure, intragastric pressure, and intra-esophageal pressure. In these patients, only 12% of reflux episodes occurred while there was a decrease in LES pressure. The majority of episodes (54%) occurred when there was a transient rise in intra-abdominal pressure above the level of the resting LES (due to such activities as crying, coughing, moving around and defecating). The remaining episodes (34%) occurred during transient, spontaneous relaxations of the LES. In normal patients, reflux episodes occurred 94% of the time during such transient relaxations. It was theorized that reflux patients have more frequent episodes of transient LES relaxation and have more frequent increases in intra-abdominal pressure. In addition, patients with GERD frequently have a delay in gastric emptying of a liquid meal. Distension of the stomach with a meal or air tends to increase the frequency of transient spontaneous LES relaxation. In reflux patients a delay in gastric emptying may be one factor that increases the likelihood of GERD by increasing the number of spontaneous relaxations and increasing the time during which there is significant gastric content to reflux [Werlin et al., locus cited (1988)].

- Evidence is mentioned [sponsor's Ref. 1] that the clinical presentation of GERD in infancy differs from that in older children and adults. Infants generally present with effortless postprandial regurgitation, often accompanied by chronic irritability or colic. They may exhibit acute weight loss or failure to thrive. Hemetemesis, occult GI bleeding, and pulmonary disorders such as aspiration pneumonia, bronchiectasis and asthma are less common. Other clinical manifestations include esophagitis, esophageal stricture, Sandifer's syndrome (abnormal posturing of the head and neck), and laryngospasm

leading to apnea. The latter may be responsible for cases of sudden infant death syndrome. A typical history of laryngospasm is a recently fed supine or seated infant with a prior history of regurgitation becoming rigid, apneic, staring and plethoric, then cyanotic or pale. There may be no coughing, choking or gagging. Stridor may also be a presenting symptom. This represents incomplete laryngeal obstruction [sponsor's Ref. 7]. In older children and adults, presenting symptoms may include dysphagia (a sensation of food "sticking"), heartburn, persistent vomiting, asthma, recurrent pneumonia or nocturnal cough. Painful swallowing, esophageal strictures and bleeding are less frequent [sponsor's Ref. 1 and 7].

- There is evidence that complications of GERD are also similar in adults and in children. For example, **Barrett's esophagus**, which was found in 13% of patients in one study undergoing endoscopy for esophagitis symptoms [sponsor's Ref. 7], may be associated with esophageal ulcers, strictures and adenocarcinoma. Peptic strictures may present with dysphagia and may result in malnutrition, hematemesis, severe iron-deficiency anemia and chest pain. GERD may prolong the course of bronchopulmonary dysplasia. In patients with cystic fibrosis, hyperinflation of the lungs along with the chronic cough may predispose to reflux.

  - Certain drugs may cause or worsen reflux. Theophylline and caffeine, used to treat asthma and the apnea of prematurity, may exacerbate reflux by relaxing the LES and stimulating gastric acid secretion. Isoproterenol, metaproterenol and terbutaline have also been implicated as causing LES hypotonia. Cigarette smoking has caused LES relaxation and increased frequency of reflux, mediated by nicotine or adrenergic stimulation or both.

  - Finally, several medical procedures may impact reflux. The placement of an NG tube may cause reflux severe enough to cause peptic strictures. Gastrostomy tube placement decreases LES pressure and increases reflux. Mechanical ventilation may increase reflux due to intubation effects, positioning effects and removal of the contribution of the diaphragm to GE (gastric esophageal) competence. In sponsor's Ref. 7, it is mentioned that, in some children, chest PT may induce reflux through positioning, as well as forced expiration and coughing.

- Regarding diagnosis of GERD, the sponsor mentions the clinical assessment, history and a number of available tests. Although a barium swallow is often the first examination done, this test has a high incidence of false positives (i.e. 31% in one study) and false negatives (i.e. 14%). An esophageal scintiscan can also diagnose reflux as well as measure gastric emptying time. Although esophageal manometry is a useful adjuvant in evaluating patients for GERD and may reveal that the resting LES pressure is reduced, this procedure cannot confirm the diagnosis. Esophagoscopy, especially if accompanied by biopsy, can

confirm the presence of esophagitis resulting from reflux. Although the results are subject to wide variation, the best method for the diagnosis of GERD is continuous monitoring of the pH in the distal esophagus.[1]

- Regarding treatment of GERD, the three mainstays in infants and children are: alteration of feedings,[2] pharmacologic management and surgery.

  - ranitidine (2 mg/Kg/dose t.i.d.) and cimetidine (5 to 10 mg/Kg/dose q.i.d. ac and hs) are the two H_{2s} most often recommended.

  - bethanecol (0.1 to 0.3 mg/Kg/dose t.i.d. or q.i.d., 30 to 60 min. ac and hs increases the resting tone of the LES.

  - Metoclopramide (0.1 to 0.15 mg/Kg/dose q.i.d.) and domperidone (0.2 to 0.6 mg/Kg/dose t.i.d. or q.i.d.) increase LES pressure and also enhance gastric emptying by increasing antral contractions.

    Neither is recommended for use in infants <6 mo of age due to CNS side effects [sponsor's Ref. 1, 2, 5 through 8, 11].

  - Cisapride (0.2 to 0.3 mg/Kg/dose t.i.d. or q.i.d.) is recommended by some authors [sponsor's Ref. 2, 7, 11].

  - Sucralfate is used by some physicians [sponsor's Ref. 1 and 7].

  - For those who fail medical management, surgery is recommended.[3]

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[1] A pH probe is inserted into the nares until the tip rests 5 cm above the LES (in adults) or at a point 13% of the nares to LES distance above the LES in children. A reference electrode is attached to the skin and recordings are made continuously for 24h. The number of episodes detected and their duration are affected by the position of the patient, frequency of feeds, acidity and physical characteristics of the feedings, gastric acidity, medications, exact position of the probe, total duration of monitoring, and the proportion of time spent in sleep.

A shortened version of the test may be performed. The Tuttle test involves placing a standard volume of acid clear fluid in the distal esophagus 87% of the distance from the nares to the LES. In a quiet sleeping child, if the pH of the esophagus falls below 4 once in a period of 10 min., GERD is most likely present.

[2] Infants with GERD should receive small, frequent feedings, and be burped often. In addition, their feedings should be thickened with rice cereal. Most authors recommend maintaining the infant in an upright, 30° prone position during postprandial periods and sleep. Older children should avoid large means, obesity, tight clothing and food or medications that decrease LES tone.

[3] The most common procedure is a Nissen fundoplication. The stomach is wrapped and sutured 360° around the distal esophagus. As the stomach distends, fundal pressure compresses the distal esophagus, creating a valve-like mechanism. Complications of the procedure include gas-bloat and dumping syndromes, as patients are unable to belch [sponsor's Ref. 1, 5 through 8, 11].

An alternative procedure is the Thal operation. In this procedure the distal esophagus is wrapped with a 270° fundal wrap. It has not been as successful in preventing reflux as the Nissen fundoplication [sponsor's Ref. 8].

III. REVIEW OF THE LITERATURE (ORAL RAN)

- >30 publications satisfying the sponsor's literature search criteria were identified. Of these,
  - ~10 were studies reporting data on the use of oral ranitidine for acute treatment and/or maintenance therapy of PUD.
- 14 studies evaluated the use of oral RAN for acute or maintenance of GERD or esophagitis.
- Other publications included Case Reports of oral RAN in children with complicated DU, GERD with severe or unusual symptoms, and hypersecretory conditions.
- 3 publications provide data from studies evaluating the PK or PD effects of RAN orally in infants.
- The remainder include studies for conditions not noted in current labeling that provide specific safety information as well as four published reports of AEs in association with RAN treatment in children.
- The results of studies evaluating acute or maintenance therapy in DU and/or GU patients are summarized in Table 1.
- The results of studies evaluating acute or maintenance therapy in GERD patients are summarized in Table 2.

In addition to the cases listed in Tables 1 and 2, the sponsor included the following case reports:

- G. Cordone et al. [Pediatr. Med. Chir. 8:85-88 (1986)] described the use of oral RAN in a girl aged 9y and 5 mo. with a bleeding DU. Following three days of treatment with RAN 50 mg t.i.d. intravenously, she received 50 mg b.i.d. (oral) for two months as acute treatment followed by 8 mo. of maintenance therapy with 150 mg daily. Her ulcer healed without relapse during this period.
- Three case reports mention oral RAN use for control of GERD. The case report by G. Taylor et al. [ASDC I. Dent. Child. 59:182-185 (1992)] describes the use of RAN 4 mg/Kg/day with MCP to prevent ongoing damage to dentition in an 8-y-old girl with severe dental erosion due to asymptomatic GER. T.H. Baron et al. [Amer. J. Gastroenterol. 88:289-292 (1993)] reports the use of RAN elixir at a dose of 75 mg b.i.d. up to 150 mg q.i.d. in a 14-y-old boy with cervical dysphagia and an unusual presentation of GERD. In the third report, RAN 150 mg/day (17 mg/Kg/day in four doses) for 12 weeks produced no endoscopic or clinical improvements in a 2-y old with bleeding esophageal ulcers (Savary Grade 3) [H. Sarda et al. Arch. Fr. Pediatr. 50:83 (1993)].

TABLE 1
NDA 18-703/S-056

Summary of Efficacy and Safety Data from Literature Reports for Oral Ranitidine in Children: PUD

Author (Reference)	Oral Treatment (unless stated otherwise)	Healing Rate Weeks of Treatment			Effects on Symptoms	Side Effects/ Adverse Events
		4	6	8		
1. Oderda et al DU= 29 GU= 9 4 to 15y	5 to 10 mg/Kg/day for 8 weeks, then 2.5 to 5 mg/Kg hs for 4 weeks. Relapse was treated with another course of RAN; then maintenance.			(36/38) 95%		None reported
9. Murphy et al. DU=34 Age unknown	RAN 150 mg b.i.d. or CIM 25 mg/Kg/day for 8 weeks			(30/34) 88%		None
10. Tam & Saing DU=29 GU= 3	RAN 3 mg/Kg/day b.i.d. or CIM 20 mg/Kg/day in three divided doses for 6 weeks		DU=89.7% GU=100%		All patients had symptomatic relief. The healed DU patients had complete relief.	No drug-related side effects were noted.
2. Socha et al. DU=18 GU= 4 Unspec.=4 8 to 18y	50 to 150 mg b.i.d. orally for 4+ weeks	(11/14) 79%			32/34 (94%) of patients with various peptic diseases had symptomatic relief at 4 weeks	3 patients reported transient AEs [headache, epistaxis and bradycardia (on i.v.)]. All resolved without stopping treatment
3. de Angelis & Banchini DU=19 72h to 16y	3 to 4 mg/Kg q 12h for unspecified time; maintenance with 3 to 4 mg/Kg/day		100% at end of initial treatment (time not specified)			No side effects attributable to RAN

TABLE 1 (Con't)

6. Accadia et al. DU=12 8 to 13y	RAN 150 mg b.i.d. or CIM 20 mg/Kg/day			80%		No side effects or changes in blood chemistry observed
4. Scorza et al. PU=10 3 mo. to 21y	10 mg/Kg once daily orally for 8 weeks with maintenance of 5 mg/Kg/day for 1y			(9/10) 90%		No side effects or alterations in blood chemistry profiles during treatment or F/U
5. Minella et al. PU=10 4 to 14y (mean 6.8 ± 2.3)	8 to 10 mg/Kg/day in one or two doses for 8 weeks with an additional 4 weeks for those not cured, then 4 to 5 mg/Kg at bedtime for 6 months			(8/10) 80%	Disappearance of symptoms in those healed at 8 weeks	No side effects or alterations of hematology or renal/hepatic function
8. Tadi et al. DU=10 6 to 12y	75 mg b.i.d. for 8 weeks	(6/10 ulcers) 60%	(7/10 ulcers) 70%	(10/10 ulcers) 100%	100% symptomatic relief after 1 weeks' treatment	None reported
7. Deganello et al DU=5 GU=1 PPU=2 0.25 mo to 15.2y	150 mg b.i.d. for 6 weeks then 150 mg daily for 8 weeks		100%			None reported

TABLE 2
NDA 18-703/S-056

Summary of Efficacy and Safety Data from Literature Reports for Oral Ranitidine in Children: GERD

Author (Reference)	Treatment and Duration (oral RAN unless otherwise stated)	Healing	Effects on Symptoms	Side Effects/Adverse Events
3. de Angelis & Banchini [n=185] Reflux esophagitis 72h to 16y	Acute: 3 to 4 mg/Kg b.i.d. maintenance: 3 to 4 mg/Kg/day (for severe GERD: 2 mg/Kg/day in two 6-h I.V. infusions)	All 25 patients with severe esophagitis had re-epithelization. 95% of mild to moderate esophagitis patients had disappearance or marked improvement in lesions.		None attributable to RAN
14. Karjoo & Kane [n=129] Children with abdominal pain due to peptic esophagitis 6 to 18 y	4 mg/Kg b.i.d.; if no relief was seen in 2 weeks the dose was increased to 4 mg/Kg t.i.d. for up to 8 weeks		70% symptomatic improvement at 4 weeks	No apparent side effects to RAN
15. Rosioru et al. [n=109] Esophagitis 12.9 ± 1.5 H. pylori + 10.8 ± 0.6 H. pylori -	RAN 4 mg/Kg/day (150 mg b.i.d. maximum) or CIM 28 mg/Kg/day (300 mg q.i.d. maximum)		72% with clinical response	None reported
5. Minella et al. [n=52] R.E. 4 mo. to 15 y	8 to 10 mg/Kg/day once or twice daily for 8 weeks and continued for 4 more weeks if necessary	After 8 weeks 39/52 (75%) had symptomatic and endoscopic improvement. At 12 weeks - 100% showed symptomatic and endoscopic improvement.		No side effects or alterations to hematology or renal/hepatic function.

TABLE 2 (Con't)

17. Berezin et al. [n=45] Non-specific chest pain with esophagitis	RAN 150 mg for 2 to 4 months or Mylanta 0.5 ml/Kg (up to 30 ml/dose) ac & hs	Simultaneous resolution of chest pain and esophagitis 38/45 (85%) at 8 weeks and 44/45 (98%) at 16 weeks. With RAN the average time to esophagitis resolution was 2.4 months.		None reported
7. Deganello et al. [n=44] Esophagitis 1 mo to 16 y	Acute: RAN 5 to 10 mg/Kg/day in 1 or 2 doses is <30 Kg (300 mg/day if >30 Kg) +/- Al-Mg hydroxide +/- domperidone for 8 weeks in mild esophagitis and 12 weeks in moderate to severe esophagitis	22/26 (85%) with complete healing		None reported
22. Cucchiara et al. [n=25] "Refractory" reflux esophagitis 0.5 to 13.4 y	RAN 10 mg/Kg AM & PM or CIM 40 mg/day/1.73m^2 every AM for 8 weeks	Both treatments produced significant decrease in histological score.	Both groups had improved clinical score. Marked symptomatic relief in 10 of 12 CIM patients and 9 of 13 patients on RAN	No serious AEs required treatment D/C; no lab abnormalities were observed.
19. Mallet et al. [n=20] GERD 1 to 6 mo.	5 mg/Kg q 12h 2h post milk feed for 1 to 3 mo.	Not documented	Not assessed	None noted. One infant had transient in ALT.
4. Scorza et al. [n=20] R.E. 3 mo. to 21 y	10 mg/Kg once daily for 8 weeks with maintenance of 5 mg/Kg/day for 1 year	At 8 weeks: 85% healed		No side effects or alterations in blood chemistry profiles during treatment or follow-up.

TABLE 2 (Con't)

20. Cafferena et al. [n=10] GERD alone & secondary to hiatal hernia, long gap anastomosis, caustic ingestion, tracheoesophageal fistula 2 mo. to 10 y	RAN syrup 10 mg/Kg/day in 2 doses for 2 mo.	Normalization in 3 of 4 with primary GERD and clinical improvement in all others	Symptomatic remission in 3 of 4 patients with primary GERD Symptom improvement in all others	None reported
16. Berezin et al. [n=6] Esophagitis in patients with chest pain of GI origin 8 to 20 y	150 mg b.i.d. for 8 weeks	100% resolution of esophagitis on endoscopy		None reported
18. Berezin et al. [n=5] Esophageal chest pain with esophagitis in patients with asthma 6 to 16 y	150 mg b.i.d. for 3 mo.	4/5 (80%) with endoscopic resolution at 3 months	Simultaneous chest pain resolution with endoscopic resolution	None reported
2. Socha et al. [n=5] R.E. 8 to 11 y	50 to 150 mg b.i.d. orally for 4+ weeks (initially, 0.5 to 1 mg/Kg b.i.d. i.v. infusion given)		All 5 showed good symptomatic response	3 patients reported transient AEs [headache, epistaxis and bradycardia (on I.V.)]. All resolved without stopping treatment.
21. Rylance et al. [n=4] Hiatus hernia, esophagitis and hematemesis	2.5 mg/Kg b.i.d. orally for 3 months	All showed improvement in esophagitis and no further bleeding.		None reported

Hypersecretory Conditions (3 publications)

In the study by R. Zaatar et al. [Gastroenterology, 92:508-512 (1987)] RAN 150 mg b.i.d. was substituted for CIM 300 mg q.i.d. in a 7-y-old boy with pseudo-Zollinger-Ellison syndrome with anemia. The patient's gastric acid outputs at the eleventh and twelfth hour before the next RAN dose showed a marked decrease and he remained asymptomatic with stable Hb and Hct values. In another case [C. De Giacomo et al., J. Pediatr. 117:989-993 (1990)], RAN 10 mg/Kg/day orally initially produced symptomatic improvement in a 3-y-old girl with antral G cell hyperfunction, hyperpepsinogenemia I and severe PUD. However, following two months of therapy, she was readmitted with severe gastrointestinal bleeding. When treatment with high doses of ranitidine (20 mg/Kg/day) did not stop duodenal bleeding, she was successfully treated with I.V. OME. In the third report, Hyman and Hassall [J. Pediatr. Gastroenterol. Nutr. 7:57-63 (1988)] described 3 children with basal gastric acid hypersecretion that required RAN 150 mg every 6h together with an anticholinergic to reduce acid secretion to alleviate symptoms.

PK/PD Studies

- Mallet et al. [Eur. J. Clin. Pharmacol. 36:641-642 (1989)] administered the I.V. European formulation (without phenol) of RAN•HCl orally at a dose of 5 mg/Kg. The mean peak plasma concentration for RAN was 476 ng/mL at around 1.2h after ingestion. The half-life was 2.8h and clearance was 664 mL/min/m^2. Twenty-four-hour gastric pH monitoring showed a positive correlation between the plasma RAN concentration and gastric pH. Gastric pH in these infants fell below 4 when the plasma RAN level decreased below 100 ng/mL, which occurred at around 9h post-ingestion. A dosage regimen of RAN 5 mg/Kg at twelve-hourly intervals was therefore proposed.

  - As a follow-up, these investigators treated 20 infants, aged 1 to 6 mo., with this regimen for 1 to 3 months [Mallet et al. (locus cited) (1989)]. No untoward effects were noted. Occasional checks of gastric pH and RAN concentrations showed values consistent with the initial study. Since a bottle of formula milk feed raises gastric pH above 4 for 2 to 3h after the feed, the investigators suggest that the dose of RAN be given 2h after a feeding.

- Sutphen and Dillard [J. Pediatr. 114:472-474 (1989)] studied the effects of RAN on 24-h gastric acidity in infants.

  - 23 full-term and 10 pre-term infants, aged 7 days to 8 mo., had both intra-esophageal and intra-gastric pH monitoring. Baseline pH values in the pre-term infants were not significantly different from those in the full-term infants. A number of dosage regimens were investigated: 2 mg/Kg b.i.d., 3 mg/Kg b.i.d., 4 mg/Kg b.i.d. and 2 mg/Kg t.i.d. All dosages increased the intragastric pH over control values, but the 8-hourly schedule was the most effective. Comparing regimens of 6 mg/Kg/day, a significant improvement in terms of the number of hours with pH<3 was found for the 8-hourly

regimen over the 12-hourly regimen (0.2h vs 2.3h, respectively; $p<0.05$) and similarly for the number of hours with a pH<4 (1.4h vs 5.1h; $p=0.02$).

Safety Data

- The majority of pediatric clinical trials with RAN have reported no side-effects or abnormal laboratory values. In over 30 published studies of oral RAN in pediatric practice in for both labeled (see Tables 1 and 2) and unlabeled indications and including over 350 children, very few AEs have been recorded. Most were mild and transient. Acute treatment has ranged from a single dose to a total of 8 weeks. A small number of children have received long-term treatment up to 5 to 6y.

- In addition, the following 4 reports of AEs in association with RAN in children have been published:

  - Balestrazzi et al. [Amer. J. Dis. Child. 139:442 (1985)] observed a **sudden alteration in consciousness** in a 4-y-old boy who had received RAN, 8 mg/Kg/day, for ten months for esophagitis. He was not taking any other medications. His symptoms occurred 12h after his last RAN dose and included bradycardia and neurological symptoms of drowsiness, dysarthria and hyporeflexia. The symptoms disappeared spontaneously without sequelae after discontinuation of therapy: bradycardia within 8h and neurological symptoms within 24h of admission.

  - De Giacomo et al. [Lancet 2:47 (1984)] reported the **intermittent loss of color vision**, together with symptoms of confusion, disorientation in time and space, aggressiveness and self injury in a 10-y-old child after 2 days' treatment with 150 mg RAN twice daily. The symptoms resolved on D/C of treatment, but a latter rechallenge again produced a short episode of loss of color vision.

  - Maak and Spiller [Vet. Hum. Toxicol. 35:343 (1993)] reported an acute dystonic reaction after an accidental overdose of RAN. A **3-month-old girl** weighing 5 Kg was prescribed 0.5 mL (0.5 mg [sic]) q.i.d. of RAN for GERD. The child inadvertently received two doses of 2.5 mL the day prior to hospitalization and four doses of 2.5 mL (total 10 mg) on the day of arrival. Two of these four doses were given only 15 min. apart and 1h before presentation to the hospital where she received 5 g of activated charcoal. Ca. 4h later, she experienced a dystonic reaction, exhibiting opisthotonos and oculogyric crisis. One mg/Kg (6 mg) of diphenhydramine was given intramuscularly and she promptly recovered within 5 min.

  - Dubois et al. [Pediatrie 48:335-336 (1993)] reported a case of lethargy in a associated with RAN administration 3.5 mg/Kg/24h in

a 15-h-old neonate being treated for hematemesis and esophagitis. The neonate received RAN for at least 16 days prior to admission to hospital for routine endoscopic follow-up for the earlier hematemesis and esophagitis. At the time of admission, lethargy and weight loss of 50 g was noted. Endoscopy revealed an improvement in the esophagitis. RAN was stopped. The child gradually improved and was discharged 4 days later.

IV. REVIEW OF THE LITERATURE (PARENTERAL RANITIDINE)

I.V. PKs (Table 3)

- Leeder et al. [Acta Pharmacol. Topxicol. 59:A79 (1986)] reported no significant differences in kinetic parameters between pediatric patients and disease free adults when body weight corrections were made. Following a 2.5 mg/Kg dose of I.V. RAN, the elimination half-life was ca. 2h with a plasma clearance of ca. 10 mL/min/Kg in both children and adult subjects. Similar results were reported in children aged 6 to 16y and adults in an earlier report by Leeder et al. [Clin. Pharmacol. Therap. 37:201(A23) (1985)].

- Blumer et al. [J. Pediatr. 107:301-306 (1985)] observed that peak serum concentrations after I.V. bolus dosing (0.13 to 0.80 mg/Kg) ranged from 50 to 968 ng/ml, occurred within 30 min. after completion of the bolus infusion and correlated directly with the dose administered. The AUC after I.V. bolus administration also correlated directly with the dose administered.

I.V. PDs

- Blumer et al. [(locus cited) (1985)] examined the efficacy of I.V. RAN in suppressing intragastric acidity in 12 pediatric patients aged 3.5 to 16y with documented duodenal or gastric ulcer disease. RAN was administered by a continuous infusion at doses ranging from 0.3 to 2.1 mg/Kg until gastric acid secretion was inhibited by ≥90%. Serum levels of RAN measured immediately on D/C of the infusion averaged 182 ng/mL (range of 75 to 419 ng/mL). In all patients, at least 90% gastric acid suppression was achieved by 45 min. after the start of the infusion. RAN serum concentrations necessary to suppress gastric acid by ≥90% was 40 to 60 ng/mL with a threshold effect noted at 20 to 25 ng/mL. Bolus doses of 0.13 to 0.8 mg/Kg of RAN administered over 15 min. produced maximal acid suppression at 1.5 to 3h with return to baseline acid secretion by 5 to 6h. Peak serum concentrations ranged from 50 to 968 ng/mL within 30 min. of administration, with a 6h trough concentration averaging 12 ng/mL.

TABLE 3
NDA 18-703/S-056

Published Data: Ranitidine PKs in Pediatric Patients With PUD Following I.V. Administration

Ref.	Age (years)	n	RAN Dose (mg/Kg Bwt)	T1/2 (h) Mean±SD	Vd (L/Kg) Mean±SD	Vss (L/Kg) Mean±SD	Clp (mL/min/Kg) Mean±SD	AEs
Leeder et al. (1986)	<6	6[a]	2.5	2.2±2.1		1.29±0.83	11.41±6.86	None reported
	6 to 11.9	11	2.5	2.1±1.0		1.14±0.52	8.96±3.36	
	>12	6	2.5	1.7±0.5		0.98±0.26	9.89±3.0	
	Adults	6	2.5	1.9±0.3		1.04±0.10	8.77±0.72	
Blumer et al. (1985)	3.5 to 16	12	0.13 to 0.80	1.8±0.3	2.3±0.9		795±334[b]	None reported

[This Table corresponds to sponsor's Table 1, with minor modifications]

a) Variability in estimated parameters may be related to severity of illness in these ICU patients
b) Clp=mL/min/1.73m²

Key: T1/2 = Terminal half-life
Vd = Volume of distribution calculated
Vss = Volume of distribution calculated at steady state
Clp = Plasma clearance of RAN