Gastric Acid Hypersecretion

Preliminary investigations suggest that I.V. RAN may be useful in suppressing gastric acid hypersecretion in pediatric patients with short bowel syndrome who require parenteral nutrition [P.E. Hyman et al., Gastroenterol. 88:A1426 (1985); J. Pediatr, Gastroenterol. Nutr. 4:316-319 (1985)]. An optimal dosage has yet to be determined.

Safety Data

- Review of the evidence presented by the sponsor allows the conclusion that the majority of pediatric clinical trials have reported no side-effects or abnormal laboratory values with parenteral administration of RAN. This included published literature on the parenteral use of the drug in over 550 children ≤16y of age, primarily for the treatment or prevention of acute g.i. hemorrhage or stress ulceration in ca. 450 pediatric patients.

- In addition, case reports of AEs in association with i.v. RAN have been documented in 3 children:

  - Agura et al. [Transplantation 46:53-56 (1988)] reviewed the use of RAN in 223 patients aged 12 to 48y undergoing bone marrow transplantation to determine the incidence of RAN-induced myelosuppression. These authors identified two children aged 12 and 16 out of a total of 137 cases who developed **myelosuppression** while receiving RAN. The two pediatric cases are not well documented and this makes it difficult to assess causality.

  - Nahum et al. [Eur. J. Pediatr. 152:933-934 (1993)] reported a case of bradycardia in a 4-day-old full-term male neonate with massive G.I. bleeding. Two hours after receiving I.V. RAN 1 mg/Kg, patient developed a **sinus bradycardia** of 60 beats/min. with a normal axis and QRS complex on EKG. The bradycardia gradually resolved over the next 24h.

- The following 2 reports of a possible interaction between I.V. RAN and tolazoline have been published.

  - Bush et al. [Arch. Dis. Child. 62:241-246 (1987)] studied the cardiovascular effects of intravenous ranitidine in 12 children with congenital heart disease who had been given tolazoline 1 to 2 mg/Kg as a pulmonary vasodilator. After administration of ranitidine 3 mg/Kg both pulmonary and systemic vascular resistance rose but was not significantly different from baseline. Heart rate also fell and was significantly below baseline values. Further investigation is required to determine if these effects would occur with a lower dose of ranitidine.

  - Initial data from Rylance [sponsor's Ref. 11] suggests that tolazoline may reduce the gastric acid suppressing effects of ranitidine. In the presence of tolazoline, this investigator found it necessary to increase the dose of i.v. RAN every 6h to 2 mg/Kg in one patient and to 4 mg/Kg in a second child to increase the intragastric pH to above 4 within succeeding dose intervals.

- Finally, the following single case report of an interaction with theophylline and RAN in a child has been published.

- Skinner et al. [Amer. J. Med. 86:129-132 (1989)] reported elevated serum theophylline concentrations in an 8y old male during administration of I.V. RAN 20 mg. The child was admitted to the hospital with status asthmaticus unresponsive to therapy with aminophylline and steroids. He was receiving concomitant administration with aminophylline infusion, beta-agonists, cortisone, cefuroxime, ampicillin, as well as fentanyl and lorazepam to induce sedation. Thirty hours after initiation of RAN therapy serum theophylline concentrations rose to 32 μg/mL (compared with 19 μg/mL and 20 μg/mL at 2 and 10h after beginning therapy with RAN). However, the existence of a drug interaction is difficult to assess because the patient received an increase in aminophylline dose over this period.

V. SUMMARY OF DOSE RANGING PKs, PDs AND EFFICACY STUDIES

Oral PKs and PDs

- As shown by Blumer et al. [(locus cited) (1985)], the half-life, volume of distribution and clearance values for RAN•HCl (37.5 mg given orally) were the same after an oral dose (1.8 vs 2h, 2.3 vs 2.5 l/Kg and 794 vs 788 ml/min/1.73m^2, respectively) and an intravenous bolus (see Table 3).

- The efficacy of RAN at suppressing intragastric acidity in children following oral administration was examined by Goudsouzian et al. (1987) and Hartemann et al. (1987). A summary of their findings is presented in Table 4.

  - A dose of 1 to 2 mg/Kg twice daily maintained intragastric pH above 4 for only 50% of the observed time in 14 critically ill children requiring mechanical ventilation. This dosage was not considered by the authors to control intragastric pH adequately.

  - The other study indicated that 2.5 mg/Kg RAN at least an hour but up to 4 hours before the induction of anesthesia can maintain intragastric pH above 4 in pediatric patients who are at risk of acid aspiration.

  - The above-summarized data should be interpreted with caution as this critically ill patient population would not be expected to exhibit the same PD response as less seriously ill children.

  - From their evaluation Blumer et al. [(locus cited) (1985)] predicted that a pediatric oral dosage of 1.25 to 1.90 mg/Kg every 12h should be effective on the basis of an evaluation of the I.V. and oral PKs of RAN and the PD responses to various plasma levels of RAN. However, this was not verified by measurement of intragastric pH following oral administration of RAN.

TABLE 4
NDA 18-703/S-056

Pharmacodynamics of Ranitidine in Pediatric Patients Following Oral Administration of Ranitidine

Population and Age	n	RAN Dose and Presentation	Measurements	Results/Conclusions	AEs	Reference
Anesthetized children (3 to 13y)	8	2.0 mg/Kg 2.5 mg/Kg 3.0 mg/Kg 3.5 mg/Kg 0 (control)	• intragastric pH • aspirate volume hourly for the course of the operation	• all doses effective at increasing the intragastric pH above 4 over the course of the operation • no significant effect was observed on the volume of gastric aspirates	None reported	Goudsouzian et al. (1987)
Critically ill children (2 to 132 mo.)	14 --- 8	1 to 2 mg/Kg twice daily --- 0 (control)	• intragastric pH	• % time pH>4 = 50% --- • % time pH>4 = 0.8% • 1 to 2 mg/Kg twice daily is not optimal at maintaining pH>4	None reported	Hartemann et al. (1987)
[This Table corresponds to sponsor's Table 3, with minor modifications].						

I.V. PKs and PDs

- As shown in Table 3, Leeder et al. [(locus cited) (1986)] reported no significant differences in kinetic parameters between PUD pediatric patients and disease-free adults when corrections for B_{wt} were made. The elimination half-life was ca. 2h and the plasma clearance ca. 10 ml/min/Kg in the two groups.

  - Not included in Table 3 are data from Rylance et al. [(locus cited) (1987)] who studied two neonates, aged 1 day and 1 month who were in intensive care. In these patients, the plasma clearances were reported to be substantially reduced (i.e. 2.2 to 3.1 ml/min/Kg instead of 10.2 ml/min/Kg) and the elimination half-life correspondingly longer than normal (i.e. 3.7 to 4.7h instead of 2.4h).

- Regarding I.V. PDs, Leeder et al [(locus cited) (1986)] suggested that a dose of 2.5 mg/Kg RAN twice daily should provide RAN concentrations comparable to those achieved with the recommended adult dose of 150 mg twice daily on the basis of data from an I.V. PK study (Table 3). However, this group did not confirm whether such a dose in children was likely to produce comparable acid suppression.

  - The efficacy of RAN at suppressing intragastric acidity in pediatric patients following I.V. administration has been examined by Blumer et al. (1985); Rylance et al. (1987); and Hartemann et al. (1987). A summary of their findings is presented in Table 5. Blumer et al. determined the RAN concentration necessary to suppress basal acid secretion by at least 90% to be 40 to 60 ng/mL by monitoring intragastric pH and plasma RAN levels simultaneously following I.V. administration of the drug. Hartemann et al. reported RAN 0.1 mg/Kg/h (i.e., 2.4 mg/Kg/day) to be effective at maintaining intragastric pH above 4 in 11 critically ill children requiring mechanical ventilation. However, a dose of 1 mg/Kg every 6h (equivalent to 4 mg/Kg/day) was reported to produce adequate control of intragastric acidity in only 6 of 10 critically ill children [Rylance et al. (1987)]. As already noted, these results should be interpreted with caution considering the critically ill nature of the patient population studied.

TABLE 5
NDA 18-703/S-056

PDs of RAN in Pediatric Patients Following I.V. Administration

Population and Age	n	Dose	Measurements	Results/Conclusions	AEs	Reference
Peptic ulceration (3.5-16y)	12	Variable I.V. infusion or 0.13 to 0.80 mg/Kg 6-hourly	• basal intragastric pH • $C_{90\%}$*	• $C_{90\%}$ = 40 to 60 ng/ml ranitidine • recommends oral dose of 1.25 to 1.90 mg/Kg twice daily for control of intragastric acidity on basis of calculated $C_{90\%}$ and bioavailability	None Reported	Blumer et al. (1985)
Critically ill children (1 day-12.6y)	20	1 mg/Kg	• intragastric pH	• pH=1 at onset (n=10) • pH ≥5 within 2h (n=6) • no evidence of ulceration found in any patient • 1 mg/Kg 6-hourly may not be sufficient to control intragastric pH in some patients	None Reported	Pylance et al. (1987)
Critically ill children (2 mo. to 11y)	11 --- 8	0.1 mg/Kg/h --- 0 (control)	• intragastric pH	• % time pH > 4 = 94.2% • no hemorrhage observed --- • % time pH > 4 = 0.8%	None Reported	Hartemann et al. (1987)

[This Table corresponds to sponsor's Table 2, with minor modifications].

*$C_{90\%}$ = plasma RAN concentration required to suppress basal acid secretion by at least 90%

Efficacy Trials

- The efficacy of RAN in the treatment of DU and GU disease has been evaluated in the three studies summarized in Table 6. For all three trials, endoscopic evaluations were considered the primary measure of efficacy.

  - One study (RAN M15) evaluated 194 children, 7 to 16y of age, for acute DU healing followed by a 12 month follow-up to assess ulcer recurrence. Open-label treatment with RAN 150 mg twice daily resulted in 91% healing by 4 weeks and 100% healing by 8 weeks.

    Following the acute healing phase, 189 patients were randomized to either RAN 150 mg nocte or PL for 12 months to assess ulcer relapse. By 12 months, RAN-treated patients experienced significantly fewer relapses (9%) compared to PL-treated patients (30%, $p<0.001$).

- A second study (145) evaluated 12 patients with duodenal or gastric ulcers, 3.5 to 16y of age, for I.V. dose ranging and PKs in order to choose an appropriate dose for a 6-week acute oral treatment phase. All patients were healed after 6 weeks of treatment. Follow-up in these patients for up to 12 months revealed no ulcer recurrences.

- The third and last study (145A) was identical in design to Study 145. Three patients, 5 to 8y of age, were evaluated for peptic ulcer healing; 3 patients had a 10 mm PU at baseline. By week 6, two patients had healed ulcers and one patient had a 5 mm ulcer.

- From the results of these three studies, the sponsor concluded that RAN (in doses up to a maximum of 150 mg twice daily) is efficacious in healing acute PU in patients 3.5 to 16y of age. Additionally, RAN (in doses up to a maximum of 150 mg per day) is effective in maintaining healed PUs.

TABLE 6
NDA 18-703/S-056

Clinical Efficacy Studies: Identification, Design, Study Population and Brief Summary of Results

Study Identification Location Number of Pts. Age Range	Main Features of Design	Study Population	Summary of Results/ Details of Regimens Used	Safety
RAN M15 (Single Center in Russia) [n=194] (7 to 16y)	Phase 1 Open-label, 150 mg oral RAN for 4 w. If ulcer not healed, pts. were given an additional 8 w of RAN. Maintenance Phase (Double blinded) 12-month follow-up, randomized 1:1 to double-blind treatment with either RAN 150 mg or PL (once a day)	Mean age=13y M-2/3; F=1/3 Mean Wt=47.5 Kg Mean Height=159 cm All caucasians All (n=194) had at least one DU of median size 7 mm.; 23% had esophagitis	Endoscopically-proven Healing of DU Week 4 = 177/194 (91%) 8 = 16/16 (100%) Endoscopically-proven DU Recurrence Month: PL / RAN / p-value 4: 17/93 (18%) / 5/95 (5%) / 0.006 8: 26/93 (28%) / 8/95 (8%) / <0.001 12: 28/93 (30%) / 9/95 (9%) / <0.001	Well Tolerated
145 (Single U.S. Center) [n=12] (3.5 to 16y)	Open label, individualized dose based on pharmaco-kinetic calculations, RAN 0.3 to 2.1 mg/Kg for 1 to 2 days then oral for 6 weeks, 2-month follow-up period	Mean age=12y M=7 F=5 All had Hx of epigastric pain, 9 had N&V, 4 had hematemesis and 1 had melena. GU=8 DU=3 DU+GU=1	All ulcers healed on repeat endoscopic evaluation at 6 weeks Follow-up endoscopy for up to 12 mo. (no pharmacological treatment) revealed no recurrences	Well Tolerated

TABLE 6 (Con't)

145A (Single U.S. Center) [n=3] (5 to 8y)	Open label, individualized dose based on PK calculations. After I.V. RAN, pts. received an oral syrup formulation of the drug instead of RAN tablets	Pt. 01: 7y-old WF (10 mm GU) Pt. 02: 8y-old BF (10 mm DU) Pt. 03: 5y-old BM	7 mg, i.v., q6h x 2 days 42 mg, po, bid for 5 days then 58 mg, po bid for the remainder of 6 weeks (non-healed at 6w) 6.3 mg, i.v., q6h x 2 days 25 mg, po, bid for remaining 6 weeks (Healed at 6w) 3.3 mg, i.v., q6h x 4 days 4 mg, i.v., q6h x 36 days* (Healed at 6w)	Well Tolerated

[Reviewer's Table]

*Pt. maintained on I.V. therapy because of severe esophagitis and inability to swallow. He received I.V. treatment for 40 days.

VI. SAFETY

A. Safety Data From Controlled Clinical Trials

These data are summarized in Table 7. Included are AE and laboratory findings from six clinical trials conducted by the sponsor. These trials enrolled patients under the age of 16 years. The design and characteristics of the study population of three of these studies (RAN-M15, RAN-145 and RAN-145A) were described in Table 6. These three trials evaluated the use of RAN in conditions included in the currently approved labeling. The remaining three studies (RAN-147, RAN-701 and RAN-1149), listed in Table 7, assessed the use of the drug in conditions outside of the currently approved labeling. These three studies were not assessed for efficacy. The main features of the design of these three studies are summarized below.

RAN-147

This was a trial in 10 male patients with cystic fibrosis and pancreatic insufficiency. The patients were randomized to receive either RAN 3 mg/Kg b.i.d. or PL for Days 1 through 5 of the study. During the second 5-day period (Days 7 through 11) the patients were crossed over to the alternative treatment. Enteric-coated Pancrease® capsules were also taken on Days 1 through 11.

RAN-701

- This single center study assessed inhibition of gastric acid production in critically ill pediatric patients.
  - 51 in-patients were enrolled and randomized to either a RAN continuous infusion regimen of 0.2 mg/Kg/h (n=24) or a bolus RAN infusion of 1.6 mg/Kg every 8h (n=27).
  - 20/24 (83%) patients in the continuous infusion treatment group and 19/27 (70%) patients in the bolus treatment group completed the study.
  - 35 patients received the maximum exposure to RAN provided by the protocol with 19 patients (79%) receiving the continuous infusion regimen for 48 to 71h and 16 patients (59%) receiving the bolus regimen for 48 to 72h.
  - 2 patients in each group received 72 to 96h of RAN.

RAN-1149

This single center, open label, multidose trial was designed to assess the PKs and safety of RAN syrup in children. Patients who required H_2-receptor antagonists as part of their normal clinical management were enrolled in the study and received ca. 2 mg/Kg RAN syrup (15 mg/mL) twice daily for as long as it was considered therapeutic by the investigator.

TABLE 7
NDA 18-703/S-056

Summary of Safety Data From Controlled Clinical Trials With Ranitidine in Pediatric Patients

Study Identific. [n on RAN]	Deaths/Serious AEs	Withdrawals Due to AEs	Laboratory Data	Summary of AEs
RAN-M15 [n=195]	RAN=NONE PL=1 Pt. (K8282) D/C because of mod. abd. pain, nausea, an 8 mm DU and erosive esophagitis. He was hospitalized. No F/U available.	Acute Phase RAN 150 mg b.i.d. [n=3] - 13y-old F: pain in the throat. N&V mod. esophagitis (UNL D/C) - 14y-old F: mod. allergic rash (PROB) - 14y-old F: mild esophagitis (UNREL) Maintenance Phase RAN 150 mg hs - 15y-old M mod. erosive esophagitis (UNLIK) - 14y-old M mild epileptic seizures (UNREL) PL (n=5) 3= mod. esophagitis 1= mild esophagitis 1= mild allergic rash	Acute Phase Some abnormal lab. values were observed, considered of no clinical relevance Maintenance Phase Values outside threshold range in the RAN group were similar to those seen in the PL group.	Acute Phase RAN: 6/195 pts. (3%): esophagitis (n=2); N&V; head injury (concussion); dizziness; allergic rash (one pt. each). All except allergic rash considered unrelated to test med. Maintenance Phase RAN: 2/191 pts. (2%) PL : 6/191 pts. (6%)
RAN-145 [n=12]	NONE	NONE	Clinically unimportant changes	Oral Pt. No. 4: (11y-old M) two separate mild episodes of loose tarry stools and one episode of vomiting (NOT REL) Intravenous Pt. No. 6: (15y-old M) mild abdominal pain (NOT REL)

TABLE 7 (Con't)

RAN-145A [n=3]	NONE	NONE	Subject 02 All total BIL values were reported as above ULN (ca. 1.8 x UL) (NOT REL)	NONE
RAN-147 [n=10]	NONE	UNKNOWN	No statistical analyses were performed	RAN-treatment Phase (n=6) Most frequently reported AEs: headache, nausea, diarrhea and bloating (UNK or NOT REL) PL-treatment Phase (n=2) These 2 pts. reported headache; stomach cramping and heartburn (UNK or NOT REL)
RAN-701 [n=51]	Continuous Infusion Group: 3 deaths: (UNREL) Bolus Dosing Regimen One serious AE (hypotension and ↑ cranial pressure in a pt. hospitalized in the ICU for severe open head trauma (UNREL)	3 pts. (see Deaths/Serious AEs column)	No significant changes between treatment groups	Both regimens were well tolerated. Incidence of AEs: Continuous Infusion: 5/24 (21%) Bolus: 2/27 (7%) (p=N.S.)
RAN-1149 [n=30]	NONE	NONE	For both, oral and injectable treatment groups, changes in lab. values in some pts. were attributable to the patients' medical condition (e.g. esophageal varices, anemia, viral infection, hypersplenism)	Oral Pt. 0001 (14y-old M): intermittent dizziness for 2 to 3 weeks prior to the post-study assessment. An ear infection was diagnosed (UNREL) Pt. 0002 (10 mo. old M): acute rash (UNREL) Injectable No AEs reported.

[Reviewer's Table]

- The information detailed in Table 7 allows the conclusion that whether oral or parenteral RAN is used for indications included in the currently approved labeling RAN•HCl is safe when administered to pediatric patients. In addition, both the oral and parenteral forms of the drug also appear to be safe when administered to children for conditions not included in the currently approved labeling.

B. Overview of Spontaneous AEs

This section addresses AEs reported to the sponsor from marketed product use, as of May 1, 1996.

- A total of 264 case reports involving AEs following the use of RAN in patients under the age of 16y have been received.

- These cases were reported from worldwide sources including health care providers, consumers, medical sales representatives, published literature and regulatory agencies.

- The sponsor provided the information on these 264 cases in their Tables 2 through 13 which included patient testing by body system of the primary event separated by age and formulation. From these Tables, the MO has assembled summary Table 8. Included in this Table are:

  - 193 cases received in conjunction with oral RAN (sponsor's Tables 2, 5, 8 and 11).

  - 54 cases reported for injectable RAN (sponsor's Tables 3, 6, 9 and 12)

  - 17 cases of unknown formulations (sponsor's Tables 4, 7, 10 and 13)

  - A total of 61 15-day Alert Reports.

  The origin of these 264 cases was:

  - 145 domestic cases

  - 119 foreign cases

- Among the reports listed in reviewer's Table 8, there were reports on 2 patients who, on follow-up, had not received the drug. However, those two patients are included in the computations because they were initially reported in association with RAN.

  - G0007956: an 8y-old F with hemorrhagic pancreatitis and subsequent death.

  - G0004981: 30-month old F with an overdose but no symptoms

TABLE 8
NDA 18-703/S-056

Number of Spontaneous Reports and 15-Day Alert Reports Reported to Glaxo Wellcome North American Product Surveillance Department per Ranitidine Formulation by Age

Age[a]	No. of Reports	15-Day Alert Reports[b]	Table
I. All Oral Formulations			
Neonates	6	3	2
Infants	62	16	5
Children	80	12	8
Adolescents	45	5	11
Total	193	36	
II. Injectable Formulation			
Neonates	7	2	3
Infants	11	3	6
Children	26	11	9
Adolescents	10	4	12
Total	54	20	
III. Unknown Formulation			
Neonates	2	1	4
Infants	3	1	7
Children	8	2	10
Adolescents	4	1	13
Total	17	5	
GRAND TOTAL	**264**	**64**	

IV. Most Commonly Reported Primary AEs

Body System	n
Neurologic	36
Non-site specific	33
Gastrointestinal	30
Hepatobiliary & Pancreas	26
Drug Interaction, Overdose and Trauma	24
Blood and Lynophatic, Psychiatry and Integumentqry	19 each
Reproduction	12
Urology	10
Lower Respiratory	9
Cardiovascular	7
Musculoskeletal	6
ENT	5
Endocrine and Eye	4 each
Pregnancy	1

[Reviewer's Table]
a) Age Categories:
Neonates (birth to <1 month)
Infants (1 month to <2y)
Children (2y to <12y)
Adolescents (12y to <16y)
b) Identified on sponsor's Tables with an asterisk (*)

Deaths

- 11 fatal cases (4 domestic, 7 foreign) were reported following the use of RAN. These 11 cases were reported to the FDA as 15-day alert reports.

  - In all cases, the pts. received concomitant medications; 10 of these pts. were on multiple prescription medications.

  - 4 of the cases reported at least a possible causal relationship to RAN.

A very short clinical summary of each case, individually, is given below.

DEATHS [domestic, n=4]

- B0003855: cerebral hemorrhage (death)

  This 12y old M received I.V. RAN as well as ceftazidine, vancomycin, amikacin and amphotericin.

- B0006331: death

  This 2-y old F received I.V. RAN and subsequently died. Cause of death was thought to be related to a) sudden onset diabetic ketoacidosis; b) an undiagnosed metabolic disorder; or c) stress hyperglycemia.

  According to the reporting physician, RAN was probably not implicated, but may have been a contributing factor.

- G0013743: hepatic failure (death)

  This case, with minimal information available, involved a 5-y old that received I.V. RAN.

- W0003677: acute liver failure (death)

  This case involved a 4-y old M with cystic fibrosis, lactose intolerance and a history of ileus. He received oral RAN.

DEATHS [foreign, n=7]

- The following two Australian cases were extracted from the line listings circulated by the ADRAC, the local regulatory authority. It should be noted that a drug is included on this list whenever it is used and is not necessarily implicated.

  - G0007605 involved a 12-y old F on multiple medications who received an unknown formulation of RAN and experienced intracranial hemorrhage.

  - G0013740 involved a 5-y old M that received an unknown formulation of RAN and experienced hepatic failure.

- RAN was determined not to be implicated when the causes of death were clarified in the following foreign cases: -A0009345
  -B0005057
  -G0007956 and
  -G0015834/5
  and in case G0007957 it was later established that the pt. never received RAN.

Alerts

- As summarized in Table 8, 61 of the 264 cases were reported to the FDA as 15-day alert reports via Form 3500A.
- 33 (54%) were reported in the U.S.
- Primary AEs were reported most commonly in the non-site specific body system (11), followed by hepatobiliary & pancreas (10), neurologic (9), blood & lymphatic (7), g.i. and lower respiratory (5 each), integumentary (4), ENT and drug interaction/overdose & trauma (3 each), cardiovascular (2) and reproduction and urology (1 each).
- 19 alert reports did not identify any concomitant medications; one report identified only TPN as a concomitant medication; and another report indicated the patient was receiving vitamin K.
- 40 patients (66%) were receiving at least one other prescription medication.
- 17 patients were receiving a least four prescription drugs concomitantly; and one patient received 29 other medications concomitantly (B0005057).
- 10 alert reports did not cite the indication/symptoms necessitating the use of RAN. With respect to the remaining 51 alert reports; 28 (55%) received RAN for either GERD or PUD; 15 (29%) for other g.i. symptoms; and 6 (12%) for other indications (prophylaxis, pre-surgery); 2 reports indicated accidental ingestion (4%).

VII. REVIEWER'S OVERALL SUMMARY AND CONCLUSIONS

The sponsor of NDA 18-703/S-056 (Zantac® 150/300 tablets) has submitted this Pediatric-Use Labeling Supplement 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. The data contained in the sponsor's application and reviewed by the MO were derived from a number of sources including published literature, clinical trials and the Glaxo Wellcome worldwide spontaneous AE reporting system.

The evidence submitted by the sponsor in support of the requested labeling changes was organized and evaluated by the MO under the following headings. Where possible, the data were analyzed by age group (birth to <1 month; 1 month to <2y; 2y to <12y; 12y to <16y). One of the objectives of the review was to carry out comparisons of the PKs of RAN in children vs adults to allow for extrapolation of a pediatric dosage recommendation based on the currently approved adult doses: Summary of Current Clinical Practice, which included evidence of disease similarity between adults and children; a Review of the Literature, first for oral then for parenteral RAN; this included efficacy data as well as PK/PD and safety data from published studies; Summary Clinical Studies, including PK/PD and efficacy studies for both oral and I.V. formulations. The efficacy data originated from three clinical trials (RAN-M15, RAN-145 and RAN-145A) that studied the effects of the drug for conditions included in the currently approved labeling and finally, an assessment of safety. The safety data originated from two main sources; one of these sources was data from six trials. In three of these, the safety data was obtained from studies where the effects of the drug were assessed for indications included in the currently approved labeling (studies RAN-M15, RAN-145 and RAN-145A). In the remaining three trials, the effects of RAN were assessed in conditions not included in the currently approved labeling (Studies RAN-147, RAN-701 and RAN-1149). Together these clinical trials amounted to a total of 301 patients on RAN. The other source was the Glaxo Wellcome spontaneous AE data database which as of the cut-off day of May 1, 1996 contained 264 case reports involving AEs following the use of the drug in patients up to 16y of age.

The MO conclusions from the review of the available evidence noted above are: 1) more information is needed to elucidate the role of H. Pylori in PUD in children, but the available initial information - based on pathophysiology, current medical practice and response to H_2-receptor antagonists - suggests that adult efficacy data with H_{2s} may be extrapolated to children;

2) except for critically-ill children where the pathophysiology appears to be different to other children (a phenomenon also seen in the adult population) PK/PDs on RAN•HCl gastric acid suppression in children and adults are similar; for example;

3) the average bioavailability of RAN•HCl given orally to pediatric patients is 48% (±20±SD) and this is comparable to that of RAN±HCl in the adult population;

4) there seems to be no significant differences in the PK parameter values for orally administered RAN•HCl in pediatric patients (up to 16y of age) and healthy adults when correction is made for B_{wt}. However, the plasma and renal clearance of parenterally administered RAN•HCl may be substantially reduced in the neonate (<1 month old);

5) The literature clinical trial data on orally or parenterally administered RAN•HCl use in PUD and GERD in the pediatric population is limited. It is not possible to ascertain percent response with specific duration of therapy. Based on studies in adults as well as some available trials of PKs in children

it seems reasonable to recommend, as the sponsor proposes, treating children based on adult duration of therapy recommendations: oral dose of RAN•HCl of 2 to 4 mg/Kg per day twice daily to a maximum of 300 mg/day for the treatment of active DU and GU; and oral doses of RAN•HCl of 2 to 4 mg/Kg once daily to a maximum of 150 mg/day for the maintenance of healing of DU and GU. There exists more limited data for oral RAN•HCl treatment of GERD and Erosive Esophagitis in children but the published literature appears to support a dosage of 5 to 10 mg/Kg per day as two divided doses;

6) the safety and effectiveness of parenteral RAN•HCl in the age group 1 month to 16y was tested only for the treatment of DU. The use of the I.V. drug in this age group seems however supported by adequate and well-controlled studies in adults, as well as published literature of additional PK data after parenteral RAN•HCl in pediatric patients. From this rather limited information, a recommendation for the use of I.V. RAN•HCl in children is derived - as proposed by the sponsor - of 2 to 4 mg/Kg/day, given every 6 to 4h, up to a maximum of 50 mg given every 6 to 8h. It is important to emphasize individualization of treatment, based on the expanded use of endoscopy and gastric/esophageal pH monitoring rather than radiography in the pediatric population; and finally;

7) the overall safety information on oral and parenteral RAN•HCl in the pediatric population supports the conclusion that this H_2 can be safely used in children over the proposed age range.

VIII. RECOMMENDATIONS FOR REGULATORY ACTION

The sponsor of NDA 18-703/S-056 (Zantac®) has provided adequate information in support of the requested labeling changes for oral and parenteral RAN•HCl use in children. Approval of the proposed labeling revisions, including dosing recommendations is recommended. These labeling changes are in accordance with the intent of the FDA regulation to provide health care practitioners with more reliable information on which to base a decision to prescribe a drug to pediatric patients.

Listed below are justifications for the labeling revisions proposed by the sponsor. These changes match the changes in the submitted draft labeling identified in the Project Manager's review by Mrs. M. Walsh (March 18, 1997).

A. Proposed Labeling Changes for RAN•HCl Oral Dosage Forms

1. CLINICAL PHARMACOLOGY, Pharmacokinetics

The following statements were added at the end of this subsection:

DRAFT LABELING

- This revision is justified on the basis of the information evaluated in the present review (Sections IV and V).

2. PRECAUTIONS, Pediatric Use.

This subsection was revised

from: DRAFT LABELING

TO:

- This revision is justified on the basis of the information assessed in the present review (Sections III through VI).

3. **DOSAGE AND ADMINISTRATION**

The following subsection has been added:

DRAFT LABELING

- This revision is supported by data assessed under Section III through V of the present review.

B. Proposed Labeling Changes for RAV•HCl Parenteral Dosage Forms

1. **CLINICAL PHARMACOLOGY, Pharmacokinetics**

The following statements were added at the end of this subsection:

DRAFT LABELING

- This labeling revision is supported by the data reviewed in Sections III through V of this review.

2. **PRECAUTIONS, Pediatric Use**

This subsection was revised

from: DRAFT LABELING

to:

- These proposed labeling revisions are justified on the basis of the information evaluated in the present review (Sections III through VI).

3. **DOSAGE AND ADMINISTRATION**

The following subsection has been added:

DRAFT LABELING

- This addition to the labeling is justified on the basis of the information evaluated in the present review and the conclusions reached by the MO (Section VII).

Finally, the MO recommends to include, in the letter to sponsor, any recommendations - if any - emanating from the Biopharm. review.

/S/ May 21, 1997

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 18-703/S-056
HFD-180
HFD-180/LTalarico
HFD-180/HGallo-Torres
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
r/d 3/26/97 jgw
f/t 5/20/97 jgw
MED\N\18703703.0HG

/S/ 5-21-97

APPEARS THIS WAY ON ORIGINAL