CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21698

MEDICAL REVIEW(S)

MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

Date: August 31, 2004

From: Charles J. Ganley, M.D.
Director, Division of Over-the-Counter Drug Products (HFD-560)

Subject: Division Director Memo for NDA 21-698

Recommendation

- After consultation with HFD-180, we agree that NDA 21-698 should be approved for claims and directions of use similar to Zantac 75 mg.
- The descriptor "excellent" can be included in the package insert for the description of the safety record. This descriptor was apparently included in the original approval of Zantac 75 mg.
- The use of the term is not acceptable
- The use of the term ' is not acceptable in the labeling of the products.

Discussion

Prevention of meal Induced Heartburn

Dr. Brodsky describes the studies that support the approval of this application. In two studies (4006 and 3016), Zantac 150 mg met the pre-specified primary endpoint supporting the reduction of meal induced heartburn symptoms compared to placebo. Zantac 75 mg was significantly different from placebo in only one study.[1] Other secondary endpoints support the differential effect of Zantac 150 mg compared to Zantac 75 mg. There was no difference between treatments in the percent of subjects with complete prevention.

FDA did not believe that the sponsor should receive a prevention claim because the data supports only a reduction of symptoms (not complete prevention). The sponsor disagreed because they felt the data was consistent with the data supporting previous prevention claims for other H2 acid reducers. They also wanted parity in labeling with other acid reducers to prevent consumer confusion. Dr. Fan summarized the information from previous reviews of prevention claims of other H2 acid reducers. His review appears to suggest that prevention means reduction of symptoms and complete prevention.[2] After considerable internal discussion, HFD-180 and HFD-560 agreed that

was not supported by the data. It was somewhat disconcerting that there was no differential effect between Zantac and placebo for complete prevention. Two possibilities to explain these results were

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[2] This does not support the sponsors understanding of the data. The primary endpoint was complete prevention in some of the studies of other H2 acid reducers.

considered. First, the populations enrolled in these studies had more severe symptoms of heartburn compared to previous populations. This could have made it more difficult to achieve complete prevention. Second, the drug should not be ingested before a meal but should be ingested at a specified time interval before a meal (such as 30 - 60 minutes as per Zantac 75 mg). Zantac actually may take some time to work.

FDA initially proposed [redacted] the sponsor did not find this acceptable. A compromise was reached that they would get labeling similar to Zantac 75. Even though they had not conducted a study of evaluating Zantac 150 mg 30 – 60 minutes before a provocative meal, it was surmised that they are at least as good as Zantac 75mg in preventing symptoms (complete prevention + reduction of symptoms). In the graphs of the reduction in heartburn severity on page 66 and 67 of Dr. Brodsky's review, Zantac 150 starts to separate from placebo at 60 minutes. This may represent a delayed onset of effect and supports administering the drug 30 – 60 minutes before the meal.

The sponsor also proposed [redacted] This is not an acceptable claim [redacted]

Relief of Heartburn

Dr. Brodsky recommends approval of the relief of heartburn claims for Zantac 150 mg. Zantac 150 mg was significantly better than placebo but not Zantac 75 mg. Some of the secondary analyses demonstrate a mild numerical trend in favor of the Zantac 150 mg over Zantac 75 mg. Although this is not very compelling, the dose response of the prevention data is the primary support for the demonstration of benefit Zantac 150 mg over Zantac 75 mg.

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Charles Ganley
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MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 8/31/04

FROM: Joyce A Korvick, MD, MPH

DGCDP/ODE III

SUBJECT: **Acting Director Summary Approval Comments**
NDA 21-698

APPLICANT: Pfizer Consumer Healthcare

DRUG: Zantac 150 mg™ (ranitidine hydrochloride tablet, 150 mg)

DIVISION RECOMMENDATION:
The Division has reviewed the efficacy portion of this submission in consultation with the Over The Counter (OTC) Division and recommends that the supplemental New Drug Application regarding Zantac 150 mg™ (ranitidine hydrochloride tablet, 150 mg) be approved for over the counter switch for the following OTC indications:

- relieves heartburn associated with acid indigestion and sour stomach
- prevents heartburn associated with acid indigestion and sour stomach brought on by certain foods and beverages

It is important to note the inclusion of a specific time before meals in the direction section of the OTC label with regards to the prevention indication. We agreed upon 30-60 minutes before.

Regulatory History:
Zantac was originally approved in 1983 as a prescription medication, and Zantac 75 mg was first marketed over-the-counter in 1998. Originally, Zantac was developed by Glaxo, Inc.. In January of 1998 Warner-Lambert obtained the rights to Zantac, and in June of 2000 Pfizer, Inc acquired Warner-Lambert.

Zantac 150 mg is approved as a prescription medication for the following indications in adults and pediatric patients over the age of one month:

- Short term treatment of active duodenal ulcer.
- Maintenance therapy for duodenal ulcer patients.
- Treatment of pathological hypersecretory conditions.
- Short term treatment of active, benign, gastric ulcer.
- Maintenance therapy for gastric ulcer patients.
- Treatment of gastro-esophageal reflux disease (GERD).

- Treatment of erosive esophagitis (EE).
- Maintenance of healing of EE.

Zantac 75 mg is currently approved as a prescription medication as well as an over-the-counter preparation. The over the counter indication is for:

- relieves heartburn associated with acid indigestion and sour stomach
- prevents heartburn associated with acid indigestion and sour stomach brought on by certain foods and beverages (It is to be taken 30 to 60 minutes before a meal).

The current NDA was submitted October 31, 2003 and included 2 clinical trials in support of the Relief (treatment of heartburn) indication and 3 clinical trials in support of the Prevention indication.

The Division of Gastrointestinal and Coagulation Drug Products reviewed the results of these studies (see below) as well as the proposed safety labeling. The OTC Drug Division performed the full safety review. The two divisions worked closely regarding the final labeling and the overall approval decision.

Clinical/Statistical Efficacy:

1. Relief:

Two controlled efficacy studies were submitted for the treatment (Relief) of heartburn indication (RAN3013 and RAN3014). These trails are thoroughly reviewed by the statistical and clinical reviewers. The studies were originally designed to test a difference between Zantac 75 and placebo, and Zantac 150 mg and placebo based upon a heartburn relief score (TOTPAR) over a 2 hour period. In both trials Zantac 150 mg was statistically superior to placebo. The Agency was concerned that the TOTPAR score may not be clinically meaningful and suggested several additional *post-hoc* efficacy endpoints (see clinical review for full detail). These analyses did support the approval of the treatment (relief) of heartburn for Zantac 150 mg compared to placebo. However, there was not a statistically significant difference between Zantac 75 mg compared to Zantac 150 mg. There was a numerical trend. Based upon all of these analyses, the clinical reviewer and team leader felt that these data were sufficient to allow the claim of " relieves heartburn associated with acid indigestion and sour stomach" for Zantac 150 mg.

2. Prevention:

Three trials were submitted in support of the use of Zantac 150 in the OTC prevention of heartburn before a provocative meal and beverage in adults and pediatric patients over 12 years of age (RAN3016, RAN3018, RAN4006). The pre-specified efficacy endpoint for these trials was heartburn severity over a 4 hour and 40 minute evaluation period measured by the area under the curve for the Visual Analog Pain Score. Again the Agency was concerned that the AUC endpoint may not adequately represent a clinically meaningful endpoint and the Agency, blinded to the data, created 3 additional endpoints for evaluation:

1) A 40* millimeter • hour or more decrease in overall heartburn severity score (measured by AUC) from the Run-In to the Treatment Meal Visits or the complete prevention of heartburn. The range of possible AUC values were between 0 to 517 millimeter • hours.

2) A 50% decrease or more in heartburn severity (measured by AUC) from the Run-In to he Treatment Meal Visits or the complete prevention of heartburn.

3) Mean heartburn severity pain scores (measured by the 0-100 Visual Analog Scale) of 17 millimeters or less or the complete prevention of heartburn *In 3018 this number was 45 millimeter • hour

Overall, for the pre-specified endpoint, Zantac 150 mg was statistically significantly superior to placebo in 2/3 of these clinical trials. In the three Agency derived endpoints for the three trials, Zantac 150 mg was successful in demonstrating superiority to placebo with a numeric advantage over Zantac 75 mg.

Two concerns remained in the medical review: 1.) for the absolute prevention of symptoms, the efficacy results for Zantac 150 mg were similar to placebo; 2.) the reduction in the severity of heartburn was not immediate and could first occur at 100 mins after dosing.

The Prevention claim involves class labeling where the indication has been historically understood to include prevention of heartburn and the reduction of symptoms, as a combined endpoint. It is important to note that the patients enrolled in these studies were patients with "severe" heartburn where severity was defined by the frequency of heartburn. This definition allowed inclusion of a substantial number of patients with Gastroesophegeal Reflux Disease (GERD). The prescription label recommends the twice-daily use of Zantac therapy for this indication and not the intermittent use as proposed in the OTC label. However, a substantial proportion of patients with this severe heartburn designation was able to obtain clinical relief with a provocative meal, which supports the use in the prevention indication. Finally, it is agreed that 100% prevention of symptoms is not necessary to allow this OTC claim. It is our opinion that the current studies do not support a labeling indication

The timing of the reduction of symptoms does indicate that patients may have to wait a substantial period of time (at least 100 mins) before symptoms start to improve. This may be an artifact of the study design. Studies in support of the previous Zantac 75 mg OTC approval gave Zantac 75 mg to patients 30 to 60 minutes prior to a meal. The studies in support of the Zantac 150 mg administered drug "right before" the meal. This may be why the Zantac 75 mg arm performed poorly in studies 4006 and 3018. Given these data, the Agency advised Pfizer to include a similar timing to that of the current Zantac 75 mg label in the Zantac 150 mg label (30 to 60 minutes prior to a meal). The applicant agreed. (for full details of these trials please refer to the statistical and clinical reviews).

Safety Labeling recommendations:
The prescription label for Zantac 150 mg recommends a dose reduction for patients who have a low creatinine clearance (< 50 mL per minute). We agree that the drug can be safely used over the counter, and agree that the proposed label be strengthened to include a recommendation to consult a physician prior to use if you have kidney disease.

Pediatrics:
The current recommendation regarding pediatrics is outlined in the medical review. The Division of Gastrointestinal and Coagulation Drug Products agrees with the reviewer's recommendations (see below).

> *"In 1999 after GSK (formerly Glaxo Wellcome) submitted pharmacokinetic (PK) and safety information regarding prescription Zantac® in pediatric patients over the age of one month (adolescents, children, and infants), all the Zantac® formulations (at that time) were granted six months of pediatric exclusivity. The safety and efficacy of Zantac in pediatric patients over one month was supported by adequate and well-controlled trials in adult patients and PK and safety information in pediatric patients with several acid-related conditions (including duodenal and gastric ulcers, GERD, and EE). Safety and effectiveness in pediatric patients have not been established for the treatment of pathological hypersecretory conditions and the maintenance of healing of EE.*
>
> *The five trials in this submission excluded patients under 18 years old. However, the approval of medications in pediatric patients can be based on adequate and well-controlled trials in adults and supportive PK and safety information in pediatric patients. Given that adequate PK and safety information exists in pediatric patients with frequent and severe heartburn (GERD patients), it is reasonable to extrapolate this information to a less serious population of episodic heartburn outpatients. According to the Boys and Girls Height/Weight Charts from the National Center for Health Statistics, 95% of 12 year olds are over 30 kilograms (66 pounds). The recommended prescription Zantac dose in pediatric patients with non-erosive GERD and EE is 5-10 mg/kg/day. Therefore, about 95% of 12 year olds will be able to take the maximum recommended Zantac dose for adults (up to 150 mg BID).*
>
> *Therefore, this medical officer recommends the approval of Z 150 in the treatment and prevention of heartburn in pediatric patients from 12 to 18 years old. Furthermore, I recommend a full waiver be given to the sponsor regarding the need for pediatric studies in all age groups."*

Propietary Name: Zantac 150mg was recommended by the DMETs. In several internal discussions during the review of the label the use of the term MAXIUM STRENGTH was felt to be appropriate, as this was probably the highest dose that the Division would recommend for OTC use.

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/s/

Joyce Korvick
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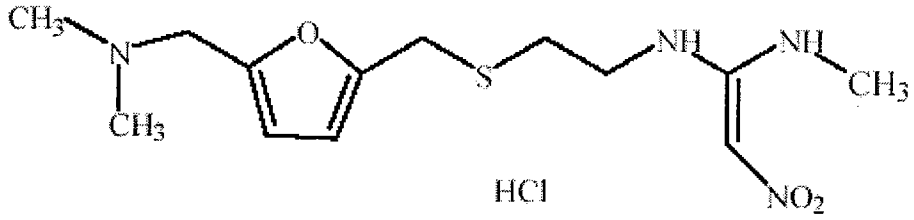
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF GASTROINTESTINAL & COAGULATION DRUG PRODUCTS

Medical Officer's Review of NDA: 21-698

OVER-THE-COUNTER ZANTAC 150™ (Ranitidine 150 mg Tablets)



NDA#:	**21-698**
Proposed Indications:	**The over-the-counter treatment of heartburn and the over-the-counter prevention of heartburn**
Drug Class:	Histamine-2 receptor antagonist
Formulation and Route of administration:	Oral tablet
Proposed regimens:	Treatment: Take one pill (150 mg) for heartburn symptoms Prevention: Take one pill (150 mg) Maximum Dosage for Treatment and Prevention: Two pills per day (300 mg/day)
Applicant:	Pfizer, Inc. (Pfizer)
Documents Reviewed:	Written NDA and Data Sets
Division Director:	Robert Justice, M.D., M.S.
Deputy Director:	Joyce Korvick, M.D., M.P.H.
Medical Team Leader:	Ruyi He, M.D.
Medical Officer:	Eric Brodsky, M.D.
Statistician:	Milton Fan, Ph.D.
Project Manager:	Diane Moore

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-698
Submission Code	000
Letter Date	10/31/03
Stamp Date	10/31/03
PDUFA Goal Date	8/31/04
Reviewer Name	Eric Brodsky, MD
Review Completion Date	8/13/04
Established Name	Ranitidine 150 mg Tablets
(Proposed) Trade Name	Over-the-Counter Zantac 150™
Therapeutic Class	Histamine-2 receptor antagonist
Applicant	Pfizer Consumer Healthcare
Priority Designation	Standard
Formulation	Oral Tablet
Dosing Regimen	150 mg
Proposed Indications	Over-the-counter treatment of heartburn and over-the-counter prevention of heartburn
Intended Population	Adults and pediatric patients 12 years and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, this medical officer recommends the approval of Zantac 150™ (Ranitidine 150 mg Tablets) for the over-the-counter treatment of episodic heartburn and the over-the-counter prevention of heartburn [redacted] in adults and pediatric patients over 12 years old.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

From a clinical perspective, this medical officer does not recommend risk management steps for Zantac 150 in the over-the-counter treatment of episodic heartburn and the over-the-counter prevention of heartburn induced by food or beverages.

1.2.2 Required Phase 4 Commitments

From a clinical perspective, this medical officer does not recommend phase 4 studies for Zantac 150 in the over-the-counter treatment of episodic heartburn and the over-the-counter prevention of heartburn induced by food or beverages.

1.2.3 Other Phase 4 Requests

Not applicable.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Pfizer Inc. (Pfizer) submitted five trials to support the approval of Zantac 150™ (Ranitidine 150 mg Tablets) in two over-the-counter (OTC) indications in adults and pediatric patients over 12 years old: the treatment of episodic heartburn and the prevention of heartburn [redacted] Ranitidine, a histamine-2 receptor antagonist, has been approved in the United States as a prescription medication for multiple acid-related disorders since 1983. Additionally, Zantac 75® (Ranitidine 75 mg Tablets) has been approved for the OTC treatment of episodic heartburn since 1995 and for the OTC prevention of heartburn **30 to 60 minutes** before a provocative meal or beverage since 1998.

For the treatment indication, Pfizer submitted two new, randomized, double-blind, placebo-controlled trials (RANA3013 and RANA3014) to support the OTC treatment of episodic heartburn in adults and pediatric patients over 12 years old. These studies, conducted

exclusively in the United States, randomized a total of 2,020 adult patients with a history of frequent, severe heartburn.

For the prevention indication, Pfizer Inc. submitted three randomized, double-blind, placebo-controlled trials (RANA3016, RANA3018, and RANA 4006) to support the OTC prevention of heartburn [redacted] in adults and pediatric patients over 12 years old. These studies, conducted exclusively in the United States, randomized a total of 2,483 adult patients with a history heartburn frequently stimulated by certain foods and/or beverages.

1.3.2 Efficacy

Treatment Trials: Two identical trials, RANA3013 and RANA3014 (identified as 3013 and 3014, respectively), were conducted to support the use of Zantac 150 in the OTC treatment of episodic heartburn in adults and pediatric patients over 12 years old. The two treatment studies were randomized, double-blind, placebo-controlled, multi-center (24 sites in 3013 and 23 sites in 3014), parallel group trials of Zantac 150 in ambulatory outpatients in the United States. Both trials consisted of three parts: a Screening Phase; a one-week, single- blind Run-In Phase; and a two-week Treatment Phase. In the Treatment Phase, 1013 and 1007 patients in Studies 3013 and 3014, respectively, were randomized (1:1:1) to receive placebo, Zantac 75, or Zantac 150 for severe or very severe heartburn episodes for up to twice-daily use for 14 days.

In both treatment trials, the pre-specified primary endpoint was the total heartburn pain relief (TOTPAR) of the first study drug-treated severe or very severe heartburn episode over the two hour evaluation period. According to the treatment protocols, the primary statistical analysis of the primary endpoint was the pair wise comparison of the Zantac 150 and Zantac 75 treatment groups.

In both treatment trials, Zantac 150 was statistically better than placebo in the total pain relief over the two-hour evaluation period. Furthermore, in both treatment trials, Zantac 150 was numerically better than Zantac 75; however, Zantac 150 was not statistically better than Zantac 75 (the primary statistical comparison).

During several meetings with Pfizer, the Division of Gastrointestinal and Coagulation Drug Products (DGICDP) and Division of Over-The-Counter Drug Products (DOTCDP) stated that the primary efficacy endpoint might not be clinically-meaningful in the efficacy of episodic heartburn treatment. The Agency, blinded to the data, created six additional *post-hoc* efficacy endpoints for the two treatment trials:

#1) After the first episode of severe or very severe heartburn, the percentage of patients that achieved complete relief at the two hour time point after treatment.
#2) After the first episode of severe or very severe heartburn, the percentage of patients that achieved almost complete relief or complete relief at the two hour time point after treatment.
#3) The fraction of episodes of severe or very severe heartburn for each patient with complete relief at the two hour time point after treatment.

#4) The fraction of episodes of severe or very severe heartburn for each patient with almost complete relief or complete relief at the two hour time point after treatment.
#5) After the first episode of severe or very severe heartburn, the time to achieve complete relief in the patients that achieved complete relief.
#6) After the first episode of severe or very severe heartburn, the time to achieve almost complete or complete relief in the patients that achieved almost complete or complete relief.

In 3013, Zantac 150 was statistically better than placebo in the Agency-derived endpoint #1; however, in 3014, Zantac 150 demonstrated only numerical — not statistical — improvement over placebo in the Agency-derived endpoint #1. In both treatment trials, Zantac 150 was statistically better than placebo in the Agency-derived endpoints #2, #3, and #4. The last two Agency-derived endpoints (#5 and #6) are not as clinically-significant as the first four Agency-derived endpoints; therefore, they are not evaluated in this review.

In both treatment trials, there was one major limitation of the efficacy results:

The Zantac 150 treatment groups did not demonstrate statistical significance over the Zantac 75 treatment groups for **all** 21 endpoints (including the 1 pre-specified primary endpoint, the 6 Agency-derived *post-hoc* endpoints, and the 14 pre-specified secondary endpoints).

However, in meetings with the sponsor, the Agency stated that for the approval of Zantac 150 for the over-the-counter treatment of episodic heartburn, Zantac 150 needed only numerical — not necessarily statistical — improvement over Zantac 75 in several efficacy endpoints.

Despite the limitation of the treatment results, this medical reviewer supports the **approval** of Zantac 150 in the OTC treatment of episodic heartburn for several reasons:

1) The two treatment trials were well-conducted; they were large, adequate, and well-controlled.
2) In each treatment trial, in four of the five important endpoints (the one pre-specified primary endpoint and the first four Agency-derived *post-hoc* endpoints), Zantac 150 demonstrated statistical improvement over placebo.
3) In each treatment trial, in four of the five important endpoints (the one pre-specified primary endpoint and the first four Agency-derived *post-hoc* endpoints), Zantac 150 demonstrated numerical improvement over Zantac 75.
4) The Agency should be consistent in its review of drug applications, involving drugs within the same pharmacologic class with identical proposed indications [such as Zantac 150 and Pepcid® (Famotidine) 20 mg Tablets (NDA# 20-325/S-015)]. Zantac 150 appeared to have similar — if not better — efficacy over Zantac 75 in the over-the-counter treatment of episodic heartburn, compared to famotidine 20 mg's efficacy over famotidine 10 mg in the OTC treatment of episodic heartburn. Please see Dr. Lolita Lopez's review of Pepcid® 20 mg Tablets on September 3, 2003 for more details.

Prevention Trials: Three similar trials (RANA3016, RANA3018, and RANA4006 identified as 3016, 4006, and 3018, respectively) were conducted to support the use of Zantac 150 in the OTC prevention of heartburn [redacted] in adults and pediatric patients over 12 years old. The prevention trials were randomized, multi-center, double-blind, double-dummy, placebo-controlled, parallel group trials of Zantac 150 in ambulatory out-patients in the United States. Patients were randomized (1:1:1) to receive placebo, Zantac 75, or Zantac 150 at the beginning of a meal and beverage that was anticipated to provoke heartburn. The patients were allowed to eat the provocative meal for 40 minutes and subsequently patients reported their heartburn severity over a 4 hour evaluation period.

All of the prevention trials had the following pre-specified sponsor-generated primary endpoint: heartburn severity over the 4 hour and 40 minute evaluation period measured by the area under the curve (AUC). The AUC was a complicated measurement based on two values: the Visual Analog Scale and time. The patients rated their heartburn severity on a 0 -100 millimeter Visual Analog Scale (VAS) at each of the 17 time points over the 4 hour and 40 minute evaluation period. The AUC was calculated from the heartburn severity score (VAS) / time curve.

During several meetings with Pfizer, the Agency stated that the primary efficacy endpoint might not adequately represent the efficacy of the treatments. The Agency, blinded to the data, created three additional endpoints that were related to the primary efficacy endpoint. The three Agency-derived endpoints, pre-specified in 3016 and 3018 (and *post-hoc* in 4006), were the following:

1) A 40* millimeter • hour or more decrease in overall heartburn severity score (measured by AUC) from the Run-In to the Treatment Meal Visits or the complete prevention of heartburn. The range of possible AUC values were between 0 to 517 millimeter • hours.
2) A 50% decrease or more in heartburn severity (measured by AUC) from the Run-In to the Treatment Meal Visits or the complete prevention of heartburn.
3) Mean heartburn severity pain scores (measured by the 0-100 Visual Analog Scale) of 17 millimeters or less or the complete prevention of heartburn

*In 3018 this number was 45 millimeter • hour

In summary, Zantac 150 demonstrated efficacy over Zantac 75 in the prevention of heartburn prior to a provocative meal. In the three prevention trials, Zantac 150 was statistically better than Zantac 75 in 5 out of the 12 efficacy endpoints (the one primary endpoint and the three Agency-derived endpoints in each of the three prevention studies). In 5 of the 7 efficacy endpoints (in which Zantac 150 failed to demonstrate statistical significance), Zantac 150 was numerically better than Zantac 75. Additionally, Zantac 150 demonstrated statistical improvement over placebo (100 minutes after dosing) in the reduction of heartburn severity **earlier** than Zantac 75's improvement over placebo (130 minutes after dosing) in two of the three prevention trials (3016 and 4006). From a clinical perspective, this medical officer recommends the **approval** of Zantac 150 in the prevention of heartburn [redacted]

However, there are two important limitations of the prevention trials' results:

1) The efficacy of Zantac 150 in the prevention of heartburn before a provocative meal or beverage is **not** immediate after dosing. In all three prevention trials, both Zantac treatment groups demonstrated no statistical improvement over placebo in heartburn relief during the first 85 minutes after dosing.
2) Zantac 150 was not efficacious at the complete prevention of heartburn taken before a provocative meal and beverage. In 3016, 4006, and 3018, Zantac 150 had complete prevention of heartburn 4%, 8%, and 10% of the times, respectively. Similarly, in 3016, 4006, and 3018, the placebo groups had complete prevention of heartburn 4%, 8%, and 7% of the times, respectively. Thus, 90% to 96% of patients in the prevention studies continued to have heartburn despite Zantac 150 dosing prior to a provocative meal and beverage.

1.3.3 Safety

Please see the July 20, 2004 safety review of Dr. Linda Hu, a medical officer in the Division of Over-The-Counter Drug Products (DOTCDP).

1.3.4 Dosing Regimen and Administration

This medical officer recommends a ranitidine dose of 150 mg once or twice a day as needed for up to 14 days for the OTC treatment of episodic heartburn in adults and pediatric patients over 12 years old. If patients have heartburn [redacted] then they should talk to their doctor. These patients may have a more serious disease such as non-erosive GERD or erosive esophagitis (EE). According to the prescription label, non-erosive GERD and EE patients require 150 mg of ranitidine BID for 4 to 8 weeks and 150 mg of ranitidine QID for 8 to 12 weeks, respectively.

This medical officer recommends a preventive ranitidine dose of 150 mg once or twice a day for up to 14 days to [redacted] in adults and pediatric patients over 12 years old. The label should state [redacted]

1.3.5 Drug-Drug Interactions

Please see Dr. Linda Hu's safety review.

1.3.6 Special Populations

Please see Dr. Linda Hu's review for the safety of Zantac 150 in special populations. Below I will present my efficacy review of the special populations.

Age: In the treatment trials, patients under age 65 in the Zantac 150 groups (n=648) had greater efficacy than patients under 65 in the placebo groups (n=636) in all five of the important efficacy endpoints (the one primary endpoint and four of the Agency-derived endpoints). However, geriatric patients in the Zantac 150 groups (n=29) did not have better efficacy than geriatric patients in the placebo groups (n=35) in four of the five important endpoints in the two treatment trials. In two of the prevention trials (3016 and 4006), similar efficacy of Zantac 150 was demonstrated in geriatric patients (n=1468) and patients under 65 years old (n=95).

Gender: In the two treatment and in two prevention trials, similar efficacy of Zantac 150 was demonstrated in male (n=1667) and female (n=1900) patients.

Race: In the treatment trials, Caucasians in the Zantac 150 groups (n=569) demonstrated improved efficacy over Caucasians in the placebo groups (n=554); however, Non-Caucasians in the Zantac 150 (n=108) and placebo (n=117) groups were not statistically different in the important efficacy endpoints. In two of the prevention trials (3016 and 4006), similar efficacy of Zantac 150 was demonstrated in Caucasians (n=1126) and non-Caucasians (n=437).

Hepatic and Renal Impairment and Pregnancy: In the five Zantac 150 trials, no patient had known hepatic disease, renal disease, and no patient became pregnant.

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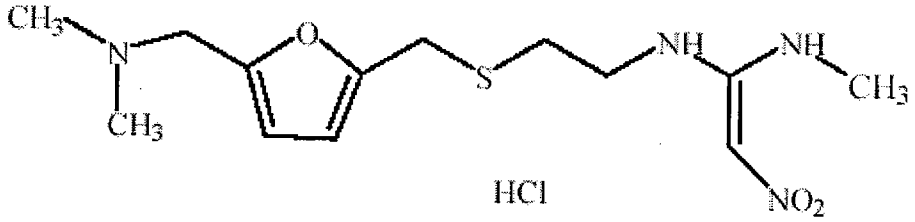
2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Proposed Trade Name (established name): Over-the-counter Zantac 150™ (Ranitidine 150 mg Tablets). In this review, OTC Zantac 150 will be identified as Z 150.



Proposed indications: The OTC treatment of episodic heartburn and the OTC prevention of heartburn

Proposed Treatment Regimen: For episodic heartburn take 150 mg (up to 150 mg BID).

Proposed Prevention Regimen: To prevent heartburn before a provocative meal or beverage take 150 mg

Proposed age group: Adults and pediatric patients over 12 years old

Molecular formula: $C_{13}H_{22}N_4O_3S$-HCl

Chemical name: N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1- ethenediamine, HCl.

Pharmacologic class: Histamine-2 receptor antagonist

Route of administration and formulation: Oral tablet

2.2 Currently Available Treatment for Indications

Multiple OTC histamine-2 receptor antagonists (H_2RAs) and OTC antacids are approved for the treatment of episodic heartburn in the United States (see Table 1). Additionally, one proton pump inhibitor (PPI), prilosec® OTC (omeprazole), was recently approved for the OTC treatment of frequent heartburn (more than two times per week).

Several OTC H_2RAs are approved for the prevention of heartburn prior to a provocative meal and/or beverage (see Table 1). No antacid or PPI is approved for the prevention of heartburn prior to a provocative meal or beverage. All of the OTC H_2RAs have slightly different dosage and administration recommendations to prevent heartburn. The OTC Zantac 75 (Z 75) label recommends taking one pill 30 to 60 minutes prior to a provocative meal and/or beverage.

the proposed Z 150 (Z 150) prevention dose is

All the approved medications in Table 1 are indicated for the OTC self-treatment of heartburn or the OTC self-prevention of heartburn in adolescents; except, prilosec® OTC and rizatidine (axid®) AR are not indicated in the treatment of adolescents. The sponsor proposes a Z 150 population that includes adults and pediatric patients over 12 years old.

Table 1: Recommended doses of FDA-approved medications for the OTC treatment and/or prevention of heartburn in adolescents and adults

DRUG	DRUG CLASS	Treatment of Heartburn	Prevention of Heartburn
Omeprazole (Prilosec® OTC)	PPI	20 mg/day for 14 days[1*]	N/A
Ranitidine (Zantac®) 75; (Z 75)	H_2RA	75 mg prn heartburn (maximum dose is 150 mg/day)	30 to 60 minute prior to eating a provocative meal, take 75 mg (maximum dose is 150 mg/day)
Proposed Zantac 150 mg (Z 150)	**H_2RA**	**Proposed dose is 150 mg prn heartburn (maximum dose is 300 mg/day)**	**Proposed dose is [redacted] take 150 mg (maximum dose is 300 mg/day)**
Famotidine (Pepcid® AC)	H_2RA	10 mg prn heartburn (maximum dose is 20 mg/day)	15 to 60 minutes before eating a provocative meal take 10 mg (maximum dose is 20 mg/day)
Maximum Strength Famotidine (Pepcid®) AC	H_2RA	20 mg prn heartburn (maximum dose is 40 mg/day)	15 to 60 minutes before eating a provocative meal, take 20 mg (maximum dose is 20 mg/day)
Cimetidine (Tagamet®) HB	H_2RA	200 mg prn heartburn (maximum dose is 400 mg/day)	0 to 30 minutes prior to eating a provocative meal, take 200 mg (maximum dose is 400 mg/day)

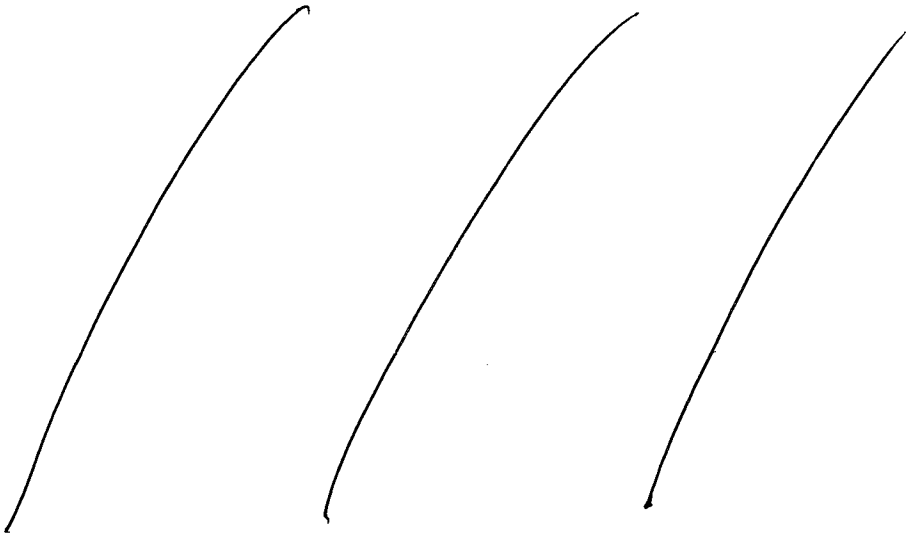
Table 1 Continued: Recommended doses of FDA-approved medications for the OTC treatment and/or prevention of heartburn in adolescents and adults

Rizatidine (Axid®) AR	H_2RA	75 mg prn heartburn (maximum dose is 150 mg/day)*	0 to 60 minutes prior to eating a provocative meal, take 75 mg (maximum dose is 150 mg/day)*
Calcium Carbonate, Magnesium Hydroxide, and Famotidine (Pepcid® Complete)	H_2RA and antacid combination	one tablet (800 mg/165 mg/10 mg) prn heartburn (maximum dose is 2 pills per day)	N/A
Calcium Carbonate and Magnesium Hydroxide (Mylanta®)	Antacid	2 to 4 pills (each pill has 550 mg of calcium carbonate and 125 mg of magnesium hydroxide) prn heartburn (maximum dose 12 pills per day)	N/A
Magnesium Hydroxide (Milk of Magnesia®)	Antacid	1 to 3 teaspoons (each teaspoon has 400 mg) prn heartburn. [maximum dose 12 teaspoons (4800 mg) per day]	N/A
Aluminum Hydroxide and Magnesium Hydroxide (Gaviscon®)	Antacid	15 to 30 mL prn heartburn. (maximum dose is 120 mL per day)	N/A
Calcium Carbonate (Tums®)	Antacid	2 to 4 pills (each pill has 200 mg of elemental calcium) prn heartburn. (maximum dose 16 pills per day)	N/A
Bismuth (Pepto-Bismol®)	Multiple actions Including antacid	2 tablets (each pill has 262 mg) prn heartburn (maximum dose 16 pills per day)	N/A

[1] Prilosec OTC is intended for frequent heartburn (more than 2 episodes per week); * The safety and efficacy in adolescents has not been established; PPI = proton pump inhibitor; H_2RA = histamine-2 receptor antagonist; Reference: Adapted from most recent approved labels

2.3 Availability of Proposed Active Ingredient in the United States

Ranitidine, the active moiety in Z 150, has been marketed in the United States since 1983. The highlights of the regulatory and marketing experience of ranitidine in the United States include the following:

- In 1983, Zantac® was initially approved by the FDA for prescription use (NDA 18-703 sponsored by Glaxo Inc.).
- In 1995, Glaxo Inc and Burroughs Wellcome merged to form Glaxo Wellcome.
- On December 19, 1995, the FDA approved Zantac 75 mg (Z 75) for the OTC treatment of heartburn, acid indigestion, and sour stomach (NDA 20-520 sponsored by Glaxo Wellcome).
- In June 8, 1998, the FDA approved an additional OTC indication for Z 75 for the prevention of heartburn 30 to 60 minutes prior a provocative meal or beverage (supplemental NDA 20-520/S-001 sponsored by Glaxo Wellcome).
- In January of 1999, Warner-Lambert obtained the rights to Z 75 (and NDA 20-520) in the United States from Glaxo Wellcome.
- 
- In June of 2000, Pfizer Inc. (Pfizer) acquired Warner-Lambert.
- In December of 2000, after the merger of Glaxo Wellcome and SmithKline Beecham to form GlaxoSmithKline (GSK), Pfizer acquired the rights to Z 75 and Z 150 for OTC use.

2.4 Important Issues With Pharmacologically Related Products

All of the H_2RA labels recommend dose adjustment in patients with renal insufficiency. For the ranitidine, nizatidine and famotidine labels, the recommendations are to adjust the dose for patients with creatinine clearance < 50 mL per minute. For the cimetidine label, the dose should be reduced in patients with "severely impaired renal function" or a creatinine clearance < 30 mL per minute. Please see Table 2 for the current clinical recommendations for H_2RAs dose adjustment in patients with renal insufficiency.

Table 2: Recommended H_2RA dose adjustment in patients with renal insufficiency

Creatinine Clearance in mL/minute	Cimetidine	Ranitidine	Nizatidine	Famotidine
≥ 50	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed
< 50 and > 30	No dose adjustment needed	Reduce dose by 50% (or extend dosing interval)	150 mg per day	reduce dose by 50% (or extend dosing interval to 36—48 hours)
< 30 and > 20	reduce dose by 50% (or extend dosing interval)	Reduce dose by 50% (or extend dosing interval)	150 mg per day	reduce dose by 50% (or extend dosing interval)
< 20 and > 15	reduce dose by 50% (or extend dosing interval)	Reduce dose by 50% (or extend dosing interval)	150 mg every other day	reduce dose by 50% (or extend dosing interval)
< 15	reduce dose by 75% (or extend dosing interval)	Reduce dose by 50% (or extend dosing interval)	150 mg every other day	reduce dose by 50% (or extend dosing interval)

Reference: Adapted from most recent label and Clinical Pharmacology Online

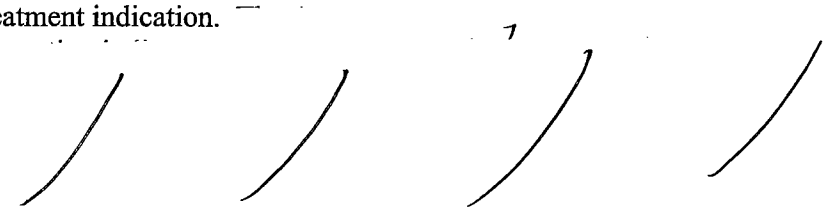
The **PRECAUTIONS** sections of the prescription H2RA labels are very similar. However, cimetidine is more likely than the other H_2RA to provoke drug-drug interactions with hepatically metabolized drugs. The drug interactions subsection of the **PRECAUTIONS** section of the cimetidine label states that cimetidine has been reported to reduce the hepatic metabolism of several medications; thereby, delaying elimination and increasing blood levels of these drugs (including phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam, tricyclic antidepressants, lidocaine, theophylline and metronidazole). Furthermore, the **PRECAUTIONS** section of the cimetidine label, states that reversible delirum has been "observed on occasion, predominantly, but not exclusively, in severely ill patients" with the use of cimetidine. Patients over "50 years old and preexisting liver and/or renal disease appear to be contributing factors. In some patients (this delirum) has been mild and has not required discontinuation of cimetidine therapy. In cases where discontinuation was judged necessary, the condition usually cleared within 3 to 4 days of drug withdrawal."

2.5 Presubmission Regulatory Activity

On January 8, 2003, the Division of Over-The-Counter Drug Products (DOTCDP) had a teleconference with Pfizer. The DOTCDP stated that higher H_2RAs doses were now acceptable to the Agency for OTC approval. Also, the study heartburn patient populations may have more frequent heartburn than prior patient populations. **Additionally, demonstration of**

numerical improvement of a higher H_2RA dose versus a lower H_2RA dose may be acceptable for an approval.

On November 7, 2001, Pfizer met with the DOTCDP and the DGICDP regarding the development of Z 150. After reviewing some preliminary results from the five trials, the divisions stated that the efficacy for the prevention indication looked stronger than the efficacy for the treatment indication.



On May 8, 2003, the DOTCDP and the DGICDP meet with Pfizer to discuss the development of Z 150 in the prevention and treatment of OTC heartburn. The Agency expressed that the primary efficacy endpoint in the important treatment studies (3013 and 3014) were not clinically meaningful. The Agency agreed to retrospectively identify clinically meaningful endpoints in the treatment studies without looking at the clinical data. Subsequently, Pfizer would apply the Agency-derived retrospective endpoints to the data in the two treatment studies. Additionally, the Agency stated that the term "acid reflux" was not an acceptable OTC indication at this time.

2.6 Other Relevant Background Information

Prescription Zantac: Prescription Zantac® 150 mg is approved for the treatment of several acid-related esophageal, gastric, and duodenal disorders in adults and pediatric patients over the age of one month. Prescription Zantac is FDA-approved for the following conditions in the United States:

- Short term treatment of active duodenal ulcer.
- Maintenance therapy for duodenal ulcer patients.
- Treatment of pathological hypersecretory conditions.
- Short term treatment of active, benign, gastric ulcer.
- Maintenance therapy for gastric ulcer patients.
- Treatment of gastro-esophageal reflux disease (GERD).
- Treatment of erosive esophagitis (EE).
- Maintenance of healing of EE.

Prescription Zantac is available by in four oral formulations (tablets, efferdose tablets, efferdose granules, and syrup) and two parental formulations (Zantac injection 25 mg/mL and Zantac injection premixed 50 mg/50 mL).

Worldwide marketing rights to Zantac: Currently, Pfizer holds the rights to Z 75 for OTC use in the United States and Canada. Additionally, Pfizer holds the IND, NDA, and rights to potentially market Z 150 in the United States and the rights to develop Z 150 in Canada. GSK holds the rights to market Z 75 and Z 150 in all countries except the United States and Canada. GSK retains the rights to all the Zantac prescription formulations including all four oral formulations and two parental Zantac formulations in the United States and in the world.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Dr. Ramesh Raghavachari, the chemistry reviewer in the DGICDP, completed his chemistry review for NDA 21-698 on July 6, 2004. From his chemistry perspective, Dr. Raghavachari recommended the approval of this NDA. Please see his review for the details.

3.2 Animal Pharmacology/Toxicology

In this NDA, no new animal pharmacology or toxicology data was submitted; therefore, no non-clinical review was conducted.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Five large, randomized, double-blind, placebo-controlled, parallel-group, multi-center clinical trials were reviewed by this medical officer during this review. Two final study reports were submitted for the OTC treatment of episodic heartburn and three final study reports were submitted for the OTC prevention of heartburn
The five full study reports were submitted in 56 written clinical volumes from the sponsor.

The two treatment studies, Studies RANA3013 and RANA3014, will be identified in this review as 3013 and 3014, respectively. GSK (formerly Glaxo Wellcome) conducted Studies 3013 and 3014; whereas, Pfizer, the sponsor of this NDA (21-698), purchased and subsequently submitted the treatment study reports.

The three prevention studies, coded by the sponsor as Studies RANA3016, RANA3018, and RANA4006, will be identified in this review as 3016, 3018, and 4006, respectively.

GSK (formerly Glaxo-Wellcome) conducted Studies 3016, 3018, and 4006; whereas, Pfizer, the sponsor of this NDA (21-698), purchased and subsequently submitted the prevention study reports.

Meeting minutes from November 7, 2001, January 8, 2003, May 8, 2003, July 17, 2003, and September 11, 2003 meetings between Pfizer, the DGICDP, and the DOTCDP were reviewed.

No INDs were evaluated in my review.

4.2 Tables of Clinical Studies

The two treatment and three prevention study reports, submitted in this NDA, are listed in Table 3. All five trials are important in the review of Z 150 for the proposed treatment and prevention indications.

Table 3: Tabular listing of all the Z 150 trials submitted in this NDA

Trial	Number of Sites	Proposed Indications	Study Design	Treatment Arms	Regimen
RANA 3013	24 (All U.S.)	Treatment	Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center	Z 150 (n=338) Z 75 (n=338) Placebo (n=337)	Take for severe or very severe heartburn episodes; maximum dose is one dose BID for 14 days
RANA 3014	23 (All U.S.)	Treatment	Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center	Z 150 (n=339) Z 75 (n=334) Placebo (n=334)	Take for severe or very severe heartburn episodes; maximum dose is one dose BID for 14 days
RANA 3016	35 (All U.S.)	Prevention	Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center	Z 150 (n=320) Z 75 (n=320) Placebo (n=322)	Single dose; right before a meal and drink likely to induce heartburn (time zero)
RANA 4006	23 (All U.S.)	Prevention	Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center	Z 150 (n=198) Z 75 (n=204) Placebo (n=199)	Single dose; right before a meal and drink likely to induce heartburn (time zero)
RANA 3018	37 (All U.S.)	Prevention	Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center	Z 150 (n=306) Z 75 (n=309) Placebo (n=306)	Single dose; right before a meal and drink likely to induce heartburn (time zero)

Reference: Adapted from Volume 3, Pages 8-000009-13, Table 8.1 and Table 10.1

4.3 Review Strategy

In this review, this medical officer is responsible for the efficacy of Z 150 in the proposed indications and Dr. Linda Hu, a medical officer in the DOTCDP, is responsible for the safety of Z 150 in the proposed outpatient population. We will collaborate equally on the clinical recommendation on regulatory action of Z 150 at the proposed dose in the proposed population for the proposed indications.

For the efficacy review of the treatment indication, both 3013 and 3014 are equally important — both studies are adequate and well-controlled. Furthermore, for the efficacy review of the prevention indication, all three studies (3016, 3018, and 4006) are equally important — all three studies are adequate and well-controlled.

4.4 Data Quality and Integrity

No DSI audits were requested because the five trials had 142 investigative sites and Zantac has great familiarity in the United States. Zantac has been approved for over 20 years as a

prescription medication and over 8 years as an OTC medication. Additionally, the proposed ranitidine dose is double the approved OTC dose and less than the maximum prescription dose recommended in several acid-related conditions.

4.5 Compliance with Good Clinical Practices

According to the sponsor, all five studies were conducted in compliance with good clinical practice (GCP) guidelines and in accordance with GSK (formerly Glaxo Wellcome) Standard Operating Procedures on the conduct and monitoring of clinical studies. A signed informed consent form was obtained for each patient and IRB approval was obtained by the principal investigators in accordance with 21 CFR 50 and 56.

4.6 Financial Disclosures

The sponsor has submitted FDA Form 3454 certifying that the clinical investigators in the five submitted clinical studies:

- Did not participate in any financial arrangement with the sponsor, whereby the value of compensation to the investigators for conducting the study could be affected by the outcome of the study [as defined in 21 CFR 54.2(a)]
- Had no proprietary interest in this product or significant equity interest in the sponsor [as defined in 21 CFR 54.2(b)] and
- Was not the recipient of significant payments of other sorts [as defined in 21 CFR 54.2(f)].

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

In this NDA, no new pharmacokinetic data were submitted.

5.2 Pharmacodynamics

In this NDA, no new pharmacodynamic data were submitted.

5.3 Exposure-Response Relationships

No new exposure-response data were submitted in this NDA.

6 INTEGRATED REVIEW OF EFFICACY

In this submission, the sponsor proposes two OTC indications for Z 150. Section 6.1 is my efficacy review of the first proposed indication — the treatment of episodic heartburn — and section 6.2 is my efficacy review of the second proposed indication — the prevention of heartburn

6.1 Indication - Treatment

6.1.1 Methods

The efficacy evaluation of the proposed treatment indication is based on two identical Z 150 Trials (3013 and 3014). Studies 3013 and 3014 were large, randomized, double-blind, placebo-controlled, parallel-group, multi-center clinical trials. These studies had identical protocols (including the eligibility criteria, procedures, primary endpoint, secondary endpoints, and *post-hoc* Agency-derived endpoints); and had identical protocol amendments. Additionally, in the two treatment trials, the study drugs (Z 150, Z 75, placebo, and maalox) were dispensed from the same drug batches. In this review, this medical officer will detail the design, procedures, and evaluations of 3013 (the design, procedures, and evaluations of 3014 are identical); and will present the results of both 3013 and 3014.

6.1.2 General Discussion of Endpoints

Primary Endpoint: The sponsor's pre-specified primary efficacy endpoint for 3013 and 3014 was the total pain relief (TOTPAR) of the first severe or very severe heartburn episode, treated with study-drug, over the two hour evaluation period. The TOTPAR score was the summation of eight heartburn pain relief scores measured at 15 minute intervals over the two-hour assessment period after taking the study drug. The 7-point heartburn pain relief scores (see Table 4) ranged between 0 (no relief) and 6 (complete relief). Therefore, the TOTPAR score ranged between 0 (no relief at all eight 15-minute intervals over the 2 hours post-treatment evaluation period) and 48 (complete relief at all eight 15-minute intervals over the 2 hours post-treatment evaluation period). A success in the primary efficacy endpoint was defined as the demonstration of statistical improvement of the Z 150 treatment group over the Z 75 treatment group.

Table 4: Heartburn pain relief score after treatment

Heartburn Relief after Treatment	Heartburn Relief Score
No relief	0
Slight relief	1
Some relief	2
Moderate relief	3
Considerable relief	4
Almost complete relief	5
Complete relief	6

Reference: Volume 4, Page 8-000093-94

Agency *Post-Hoc* Specified Endpoints: After the treatment trials were completed (blinded to most of the study results), the DGIDP and the DOTCDP, asked the sponsor to conduct six additional *post-hoc* analyses on the treatment trial data. In the first four *post-hoc* endpoints, patients who took maalox or a second, study-drug dose during the 2 hour evaluation period were included in the denominator and were not included in the numerator. The following are the six, additional, Agency-derived endpoints:

#1 After the **first** episode of severe or very severe heartburn, the percentage of patients that achieved complete relief (a 6 on the heartburn pain relief scale) **at** the two hour time point after treatment.

#2 After the **first** episode of severe or very severe heartburn, the percentage of patients that achieved almost complete relief or complete relief (a 5 or a 6 on the heartburn pain relief scale) **at** the two hour time point after treatment.

#3 The fraction of episodes of severe or very severe heartburn for each patient with complete relief (a 6 on the heartburn relief scale) **at** the two hour time point after treatment.

#4 The fraction of episodes of severe or very severe heartburn for each patient with almost complete relief or complete relief (a 5 or a 6 on the heartburn relief scale) **at** the two hour time point after treatment.

#5 After the **first** episode of severe or very severe heartburn, the **time** to achieve complete relief (a 6 on the heartburn relief scale) in the patients that achieved complete relief. Patients that achieved complete relief, who later took Maalox or a second dose of the study drug would be included in this endpoint. In contrast, patients that did take Maalox or a second dose of the study drug before achieving complete relief would not be included in this endpoint.

#6 After the **first** episode of severe or very severe heartburn, the **time** to achieve almost complete or complete relief (a 5 or a 6 on the heartburn relief scale) in the patients that achieved almost complete or complete relief. Patients that achieved almost complete or complete relief, who later took Maalox or a second dose of the study drug would be included in this endpoint. In contrast, patients that did take Maalox or a second dose of the study drug before achieving almost complete or complete relief would not be included in this endpoint.

Pre-specified secondary efficacy endpoints: The following are the 14 pre-specified secondary efficacy endpoints in 3013 and 3014:

- Over the two hour evaluation period, the total pain relief (TOTPAR) of all severe and very severe drug-treated heartburn episodes
- At the end of each two-hour assessment period, the overall effectiveness (see Table 5) of the study drug for a given severe or very severe drug-treated heartburn episode.
- At the end of the two-week treatment period, the overall effectiveness (see Table 5) of the study medication for treating all severe or very severe heartburn episodes.

Table 5: Overall effectiveness of the study drug

1	Not Effective
2	Poor
3	Fair
4	Good
5	Very Good
6	Excellent

Reference: Volume 4, Page 8-000081

- After the start of each study drug-treated episode, the heartburn relief scores recorded at 15, 30, and 45 minutes (see Table 4)
- The duration of relief for each study drug-treated heartburn episode — the time difference from the beginning of any relief until cessation of relief. The beginning of relief was defined by a rating of at least a "little relief" and followed by a rating of at least "moderate relief". Cessation of relief was to be defined as the earliest occurrence of 1) the patient's indication of less than "moderate relief", 2) the use of the rescue antacid, or 3) re-dosing with the study drug.
- The proportion of study drug-treated severe or very severe heartburn episodes for which maalox was used.
- The total number of maalox tablets used after severe or very severe heartburn episodes in which study drug was taken.
- The total number of maalox tablets used in non-study drug-treated heartburn episodes
- The total amount of maalox used for each severe or very severe heartburn episode and for each non-severe heartburn episode
- The proportion of patients who experienced insomnia (difficulty falling asleep or waking up during the night) due to their heartburn episodes.
- The mean change from baseline (the end of the Run-In Phase) in the Abdominal Gastric Index of Digestive Annoyances (AGIDA). The AGIDA is an index composed of 10 common digestive symptoms (heartburn, acid/sour taste, sour stomach, stomach ache, upset stomach, nausea, stomach fullness/bloating, feeling gassy inside, passing gas, and belching). Each symptom in the AGIDA is graded on a 0 to 10 ordinal scale with the total AGIDA score ranging from 0 to 100.
- For all study-drug treated, severe or very severe heartburn episodes, the peak heartburn relief score — the maximum heartburn pain relief score over the two-hour assessment period. This computation was based on the last observation carried forward (LOCF) heartburn pain relief scores. The LOCF methodology was used to replace missing and non-meaningful relief scores.

Medical Reviewer's Comments: Multiplicity adjustment may be needed with one pre-specified primary endpoint, six *post-hoc* Agency-derived endpoints, and 14 pre-specified secondary endpoints. Treatment trials of episodic heartburn with H_2RAs have had similar secondary

endpoints including the total number of rescue antacid used, global assessment of study drug efficacy, and the proportion of heartburn episodes completely relieved.

6.1.3 Study Design

Study RANA3013: "A randomized, double-blind, placebo-controlled, parallel-group, multi-center evaluation of ranitidine for the treatment of severe heartburn episodes."

Study Design: Study 3013 was a randomized, double-blind, placebo-controlled, multi-center (24 sites), parallel group trial of Z 150 in ambulatory outpatients in the United States. The trial consisted of three parts: a Screening Phase; a one-week, single blind Run-In Phase; and a two-week Treatment Phase. In the Treatment Phase, patients were randomized (1:1:1) to receive placebo, Z 75, or Z 150 for severe or very severe heartburn episodes for up to twice-daily use for 14 days. During the Treatment Phase, patients were permitted to take maalox, a rescue antacid, to treat heartburn episodes not relieved by the study drug.

Medical Reviewer's Comments: Study 3013 was a well-controlled study; it was placebo controlled and dose-comparison controlled. The two week duration for the treatment of episodic heartburn is similar to the duration of other H_2RAs treatment trials and it is acceptable.

Eligibility Criteria: Table 6 displays the eligibility criteria of Study 3013.

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Table 6: Eligibility criteria

Inclusion Criteria: To be eligible to participate in the study, patients had to have met the following criteria:	**Exclusion Criteria:** If patients had the following conditions, they were not eligible to participate in the study:
➢ At least 18 years of age ➢ Signed written informed consent ➢ Generally healthy, with no unstable/uncontrolled significant medical conditions ➢ At least a 6-month history of heartburn, sour stomach, and/or acid indigestion which was typically brought on by eating, stress, or postural changes (i.e., lying down) ➢ Reported the occurrence of at least four heartburn episodes per week over the past 2 weeks (i.e., prior to Visit 1) ➢ described his/her almost daily heartburn episodes over the 2 weeks prior to Visit 1 as being severe or very severe most of the time, on a five-point heartburn pain intensity scale ➢ An ambulatory outpatient ➢ If female, was surgically sterilized (bilateral tubal ligation or hysterectomy), or was at least 1 year post-menopausal, or was using an acceptable method of contraception in the presence of childbearing potential and not pregnant as determined by the urine pregnancy test performed at Visit 1.	➢ Currently wider the care of a physician for, or had been diagnosed with an ulcer or Zollinger Ellison Syndrome within the past year ➢ Used a PPI for the treatment of GERD or heartburn ➢ Had a diagnosis of erosive esophagitis or symptoms associated with more serious GERD (i.e., dysphagia, odynophagia, hoarseness, or wheezing) ➢ Had a history of significant gastrointestinal hemorrhage ➢ Had taken non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, on a chronic basis in tile last 3 months [low dose aspirin (≤325 mg/day) for coronary artery disease was permissible] ➢ had a medical history and physical examination conducted at screening which demonstrated a clinically significant disease which was not adequately controlled ➢ An active substance abuser (e.g., marijuana, alcohol), excluding tobacco use ➢ A woman who was pregnant or lactating ➢ Had a known hypersensitivity or intolerance to cimetidine (Tagamet®), ranitidine (Zantac®), famotidine (Pepcid®), or nizatidine (Axid®) ➢ Had previously participated in this protocol ➢ Had participated in a study with an investigational drug within 30 days prior to Visit 1 ➢ Demonstrated an inability to comprehend or correctly use the diary card booklet ➢ Was an immediate family member of a participating investigator, sub investigator or study coordinator. ➢ The use of the following medications was not permitted: OTC or prescription H2RAs, PPIs, metoclopramide, misoprostol, sucralfate, cisapride, and non-study antacids

Reference: Volume 3, Pages 8-000086-88

Medical Reviewer's Comments: The inclusion criteria selected for adult GERD patients (patients with frequent and severe heartburn for over 6 months). The patients in this treatment trial are likely to have more severe disease than the proposed population of episodic heartburn outpatients. However, enrichment of the study population in this clinical trial is reasonable. The eligibility criteria appropriately excluded the use of concomitant medications that treat episodic heartburn (including other antacids, H_2RAs,PPIs) and properly prohibited patients with other upper gastrointestinal disease.

The current ranitidine prescription label states that patients with a creatinine clearance less than 50 mL per minute should start on a lower dose of ranitidine (150 mg per day). The eligibility criteria did not exclude patients with moderate to severe renal insufficiency. Therefore, patients with chronic renal insufficiency may have received a higher dose of ranitidine (150 twice a day).

Premature discontinuation of patients: A patient could withdraw from the study at any time at the investigator's discretion or the patient's request. Reasons for withdrawing a patient could include one of the following:

- An adverse event
- The concomitant use of excluded medication during the study
- The patient did not wish to continue participating in the study
- The patient failed to comply with protocol dosing instructions, or
- Any condition or circumstance that would jeopardize the welfare of the patient if he/she were to continue in the trial.

Drugs used in study: During the Run-In Phase, all eligible patients were allowed to treat their first heartburn episode (regardless of severity) with the single-blind study drug (placebo). Similarly, patients were allowed to treat their second heartburn episode of the day with a second dose of the single-blind study drug (placebo). If their heartburn continued after treatment with the study drug (placebo), then the patients were allowed to take maalox, the rescue antacid. Patients were allowed to use a maximum of two doses of study drug and a maximum of 16 tablets of maalox each day.

During the Treatment Phase, patients were allowed to treat their heartburn with one of three study treatments: placebo, Z 75, or Z 150. If their heartburn persisted despite study drug treatment, the patients were allowed to take maalox, the rescue antacid. Patients were allowed to use a maximum of two doses of study drug and a maximum of 16 tablets of maalox each day.

Schedule of Procedures and Evaluations: Studies 3013 and 3014 each consisted of three phases: a Screening Phase, a Run-In Phase (one week), and a Treatment Phase (two weeks). Please see Table 7 for the Schedule of Procedures and Evaluations during both of these treatment studies.

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Table 7: Schedule of procedures and evaluations during Studies 3013 and 3014

	Visit 1* Screening Day 0	Visit 2 Randomization 7+3 days after Visit 1	Visit 3 Termination 14+5 days after Visit 2	Early Termination Procedures
Informed consent	X			
Medical/heartburn history	X			
Abbreviated physical exam	X			
Urine pregnancy (if applicable)	X			
AGIDA symptom questionnaire	X[a]	X[a]	X,[a,b]	
Prior/concurrent medication assessment	X	X	X	X
Dispense Run-In medication	X			
Dispense treatment medication		X		
Dispense open-label antacid	X	X		
Dispense heartburn diary booklet[b]	X	X		
Review heartburn diary booklet[b] completed during previous phase		X	X	X
Adverse events assessments		X	X	X
Drug accountability		X	X	X
Schedule return appointment	X	X	X[c]	X[c]
Complete study summary			X	X

* Subjects were screened via telephone prior to their first office visit to determine if they met the heartburn history requirements (i.e., 6-month history of frequent heartburn, and having almost daily heartburn (at least 4 of 7 days/week in the past 2 weeks) and describe most of their heartburn episodes as having been severe or very severe in the 2 weeks prior to Visit 1.) In order to confirm appointments and reiterate instructions, research personnel telephoned subjects within 5 days of Visit 1

b Diaries were to be completed by subjects during the 7 (+3) days following Visit 1 and during the 14 (+5) days following Visit 2. Diaries were to be reviewed by study personnel with subjects before the completion of the visit.

a These assessments were to be reviewed by clinic personnel with subjects before the completion of the visit.

b Global evaluation of study drug efficacy for severe or very severe episodes.

c To be scheduled for follow-up evaluation of any ongoing adverse event.

Reference: Volume 3, Page 8-000131, Table 1 and Volume 19, Page 8-006338, Table 1

Screening Phase: Patients were screened by telephone prior to their first office visit to determine if they met the heartburn history requirement as follows: they had a 6-month history of heartburn, sour stomach, or acid indigestion; their symptoms were typically brought on by eating, stress, or postural changes (i.e., lying down); they had heartburn symptoms at least 4 of 7 days during the 2 weeks prior to Visit 1; and they described most of their heartburn episodes as being severe or very severe in the 2 weeks prior to Visit 1.

Run-In Phase: During the Run-In Phase, all eligible screened patients had the following evaluations: they had a medical history recording their tobacco use, heartburn symptoms, and concurrent and prior medications; a physical examination; and a urine pregnancy test for female patients of childbearing potential.

Patients who qualified for entry into the Run-In Phase were given a supply of the single-blind Run-In Phase study drug (placebo), a supply of open-label chewable maalox tablets, a heartburn diary booklet, and a timer. Patients were instructed to grade the severity of their heartburn on a five-point intensity scale prior to treatment (see Table 8).

Table 8: Heartburn symptom patient intensity scale

0	None	My heartburn does not hurt
1	Very mild	My heartburn hurts very little
2	Mild	My heartburn hurts a little
3	Moderate	My heartburn hurts
4	Severe	My heartburn hurts a lot
5	Very Severe	My heartburn hurts very much

Reference: Volume 1, Page 8-000081

Patients were instructed to self-administer one dose of the Run-In Phase study drug (placebo), if they had a heartburn episode (regardless of severity) during the Run-In Phase. Patients were instructed to self-administer a second dose of the study drug (placebo) for a second heartburn episode (regardless of severity). During the first two heartburn episodes, patients were instructed to refrain from taking additional study drug or maalox during the 2 hours post-treatment period. Additionally, they were instructed not to eat or drink during the 2 hours post-treatment period.

Two hours after study drug treatment, the patients were instructed to take one to two rescue maalox tablets if they still needed heartburn relief. The maximum amount of maalox permitted was up to 16 maalox tablets per day. During the third episode of heartburn, patients were allowed to self-administer one to two maalox tablets as needed until their heartburn was relieved.

Patients recorded the following information about their heartburn in their diaries:

- The overall effectiveness of the study drug at the end of each 2-hour heartburn episode assessment period (see Table 5)
- For every study drug-treated heartburn episode, the relief over 15 minute intervals during the two-hour evaluation period (see Table 4),
- The time that maalox was taken (if applicable)
- The total number of maalox tablets taken for each heartburn episode.
- If nighttime heartburn interfered with their sleep
- For every heartburn episode (not treated with study drug), the heartburn severity and the number of maalox tablets taken.

During Visit 2, (between Days 8 and 11 of the Run-In Phase), the run-in diary was reviewed with each patient. Any missing or conflicting information on the diary was clarified with the patient and corrected by the patient on the diary booklet at the time of the visit. Furthermore, study personnel interviewed patients regarding the following during the Run-In Phase: concomitant medication use, drug accountability and compliance, and the Abdominal Gastric

Index of Digestive Annoyances (AGIDA) symptom questionnaire – a survey regarding gastrointestinal symptoms.

In order for patients to qualify for the Treatment Phase, patients must have complied with the procedures and evaluations during the Run-In Phase in all of the following ways:

- Completed their diary booklets according to instructions
- Followed study drug and antacid dosing instructions
- Used antacid tablets as recorded in their diary (the returned antacid inventory must have been within 30% of that recorded on the diary)
- Used study drug tablets as recorded in their diaries (the number of study tablets in the inventory must have been within 20% of that recorded on the diary)
- Treated a heartburn episode on at least 4 of the first 8 days during the Run-In Phase
- Rated severe or very severe at least 50% of the heartburn episodes recorded on the diary during the first 8 days of the Run-In Phase or had a severe or very severe episode on at least 4 days during the first 8 days of the Run-In Phase.

Patients who failed to meet the above criteria because of compliance reasons or patients who did not have frequent, severe heartburn were terminated from the study.

Medical Reviewer's Comments: The enrichment procedures during the Run-In Phase increased the likelihood that patients who continued in the Treatment Phase would be more compliant and would have more frequent, severe disease then the terminated patients. This enrichment was acceptable for these clinical trials.

Treatment Phase: In the Treatment Phase, patients were randomized (1:1:1) to self-administer placebo, Z 75, or Z 150 for severe or very severe heartburn episodes for up to twice-daily use for 14 days. In the Treatment Phase, patients received written instructions to self-administer study drug as follows:

- Swallow (do not chew) one dose of study drug with 2 ounces of water for each severe or very severe heartburn episode
- Only take one dose of study medication for the first two severe or very severe heartburn episodes
- Do not take a second dose of study medication until your previous heartburn episode is relieved.
- After the first two severe or very severe heartburn episodes, do not take a second dose of study medication or maalox
- Do not eat or drink anything else during the 2-hour heartburn evaluation period.
- Treat no more than two severe or very severe heartburn episodes per day
- After completing the 2 hour assessment, if you still need relief of your heartburn episode chew the maalox tablets
- If you already treated two episodes of severe or very severe heartburn, then you are allowed to chew one to two maalox tablets as needed until your heartburn is relieved (up to 16 maalox tablets per day).

- If you do not consider your heartburn to be severe or very severe, then chew the maalox tablets as needed until your heartburn is relieved.

The following concomitant medication during the Run-In and Treatment Phases were not permitted: OTC or prescription H_2RAs, PPIs, metoclopramide, misoprostol, sucralfate, cisapride, and non-study antacids. Patients were not permitted to take any drug during the study for the relief of their heartburn, except the study drug and maalox provided.

Similar to the Run-In Period, the patients recorded information in their diaries about the severity of their heartburn episodes, the relief of the episodes, and the treatments administered during the Treatment Period.

Medical Reviewer's Comments: The procedures and evaluations in 3013 are acceptable.

The treatment heartburn studies did not provide a procedure for counseling patients on non-pharmacologic methods for treating heartburn including the following: decreasing alcohol, caffeine, and tobacco consumption; decreasing spicy food, peppers, tomatoes, grapefruit, oranges, and peppermint; eating slowly; eating less quantities of food at each meal; loosing weight (if applicable); and elevating the head of the bed at night. Standard medical practice in the treatment of heartburn includes non-pharmacologic therapy.

Statistical Methods: For all efficacy endpoints, success was obtained if the Z 150 treatment group was statistically superior to the Z 75 treatment group. If the Z 150 treatment group was statistically superior to the placebo group, the Z 75 group was not statistically superior to placebo, and the Z 150 group was not statistically superior to the Z 75 group; then this was a failure.

The LOCF (Last Observation Carried Forward) methodology was used to replace missing and non-meaningful relief scores (i.e., scores following rescue antacid or re-dosing with the study drug). For assessment periods during which the patient was asleep, the most immediately preceding, non-missing score was carried forward into the missing pain relief scores. In addition, all scores following the use of antacid or the patient's re-dosing with the study drug were replaced with the pain relief score immediately preceding the supplemental drug use.

6.1.4 Efficacy Findings

Baseline Demographics: Of the 2,554 patients enrolled in the Run-In Phase of Study RANA3013, 1,013 (40%) patients were randomized in the Treatment Phase. Plus, 1,541 (60%) patients were not randomized to the Treatment Phase because 975 (63%), 304 (20%), 185 (12%), and 77 (5%) patients did not meet randomization criteria, were lost to follow up, withdrew their consent, or had other reasons, respectively. Of the 1,013 patients enrolled in the Treatment Phase, 338, 338, and 337 patients were randomized to the Z 150, Z 75, and placebo groups, respectively, in 24 investigative sites in the United States. Nine hundred seventy-six (976/1013, 96%) patients completed the study, with study completion evenly distributed among treatment groups. Table 9 delineates the baseline patient demographics including: gender, age, height, weight, ethnic origin, and tobacco use in 3013.

Table 9: Baseline demographics for Study 3013

	Placebo	Z 75	Z 150	p-value
Number of patients	337	338	338	
Sex N (%)				
Female	169 (50%)	167 (49%)	157 (46%)	0.60
Male	168 (50%)	171 (51%)	181 (54%)	
Age in years				
Mean (SE)	42.8 (0.66)	40.8 (0.60)	40.9 (0.65)	0.06
Min-Max	18-79	20-75	18-81	
Height in inches				
Mean (SE)	67.3 (0.23)	67.6 (0.22)	67.6 (0.22)	0.66
Min-Max	54-80	55-78	56-77	
Weight in lbs				
Mean (SE)	196.4 (2.37)	194.7 (2.30)	193.4 (2.17)	0.78
Min-Max	92-355	100-370	104-309	
Ethnic Origin N (%)				
White	276 (82%)	271 (80%)	285 (84%)	
Black	44 (13%)	52 (15%)	40 (12%)	0.74
Asian	1 (<1%)	0 (0%)	2 (<1%)	
Latin	14 (4%)	13 (4%)	9 (3%)	
Other	2 (<1%)	2 (<1%)	2 (<1%)	
Tobacco Use N (%)				
No	232 (69%)	232 (69%)	221 (65%)	0.56
Yes	105 (31%)	106 (31%)	117 (35%)	

P-values represent comparison of treatment groups
Reference: Adapted from Volume 3, Page 8-000138-139, Table 7

Of the 2,057 patients enrolled in the Run-In Phase of Study RANA3014, 1,007 (49%) patients were randomized in the Treatment Phase. Plus, 1,050 (51%) patients were not randomized to the Treatment Phase because 652 (62%), 206 (20%), 146 (14%), and 46 (4%) did not meet randomization criteria, were lost to follow up, withdrew their consent, and had other reasons, respectively. Of the 1,007 patients enrolled in the Treatment Phase, 339, 334, and 334 patients were randomized to the Z 150, Z 75, and placebo groups, respectively, in 23 investigative sites in the United States. Nine hundred seventy-seven (977/1007, 97%) patients completed the study, with study completion evenly distributed among treatment groups. Table 10 delineates the baseline patient demographics including: gender, age, height, weight, ethnic origin, and tobacco use in 3014.

Table 10: Baseline demographics for Study 3014

	Placebo	Z 75	Z 150	p-value
Number of patients	334	334	339	
Sex N (%)				
Female	149 (45%)	155 (46%)	158 (47%)	0.85
Male	185 (55%)	179 (54%)	181 (53%)	
Age in years				
Mean (SE)	42.5 (0.68)	43.4 (0.66)	41.6 (0.62)	0.14
Min-Max	18-80	20-78	18-82	
Height in inches				
Mean (SE)	67.7 (0.21)	67.5 (0.22)	67.6 (0.21)	0.82
Min-Max	58-78	56-83	58-78	
Weight in lbs				
Mean (SE)	194.5 (2.50)	196.5 (2.37)	195.5 (2.43)	0.55
Min-Max	115-450	103-360	92-365	
Ethnic Origin n (%)				
White	278 (83%)	271 (81%)	284 (84%)	
Black	47 (14%)	51 (15%)	44 (13%)	0.90
Asian	0 (0%)	1 (<1%)	0 (0%)	
Latin	8 (2%)	10 (3%)	9 (3%)	
Other	1 (<1%)	1 (<1%)	2 (<1%)	
Tobacco Use N (%)				
No	235 (70%)	237 (71%)	223 (66%)	0.28
Yes	9 (30%)	97 (29%)	116 (34%)	

P-values represent comparison of treatment groups
Reference: Adapted from Volume 19, Page 8-006345, Table 7

Medical Reviewer's Comments: Overall, the baseline demographics of the study populations in 3013 and 3014 were acceptable. The average age of the heartburn patients in both studies was approximately 42 years old. The racial diversity of the study populations were similar to the racial diversity in the United States in the mid 1990's (when the study was conducted); except the study populations had a lower percentage of Latinos and a slightly higher percentage of Caucasians (whites). In both studies, no statistical differences were seen in the demographics (gender, age, height, weight, ethnic origin, and tobacco use) in the three treatment groups.

Additional baseline demographics and behaviors may have been helpful. The sponsor did not calculate the average Body Mass Index (BMI) and did not record other non-pharmacologic behaviors (including caffeine and alcohol ingestion, eating peppers, tomatoes, grapefruit, oranges, and spicy food) that may influence the frequency and severity of heartburn in the patient populations.

The two treatment trials randomized 92 patients who were over 65 years of age. Typically the Agency recommends that a drug development program contain over 100 geriatric patients to assess their safety and efficacy. If a disease state is more common in the elderly (including episodic heartburn), then the drug development program should contain a larger number of

geriatric patients. Therefore, the treatment indication had a fewer number of geriatric patients than desired.

Baseline heartburn history: In 3013, all three treatment groups (placebo, Z 75, and Z 150) had similar extensive heartburn histories (see Table 11).

Table 11: Past medical history of heartburn in Study 3013

	Placebo	Z 75	Z 150
Length of Time (yrs) with heartburn, acid indigestion, or sour stomach [1]			
N	337	338	338
Mean (SE)	11.0 (0.60)	10.1 (0.50)	9.5 (0.50)
Min - Max	0.5 - 58.0	0.5 - 47.0	0.5 - 46.0
How many days did you experience heartburn over the last week? [1]			
N	337	338	338
Mean (SE)	6.1 (0.06)	6.1 (0.06)	6.2 (0.06)
Min - Max	4 - 7	4 - 7	4 - 7
How many days did you experience heartburn the week before? [1]			
N	337	338	338
Mean (SE)	6.1 (0.06)	6.1 (0.06)	6.2 (0.06)
Min - Max	4 - 7	4 - 7	2 - 7
On a typical day how many episodes of heartburn do you have? [1]			
N	337	338	338
Mean (SE)	2.6 (0.09)	2.7 (0.09)	2.7 (0.10)
Min - Max	1 - 20	1 - 12	1 - 20
Describe most of your heartburn episodes over the last two weeks [2][3]			
Very mild	0	0	0
Mild	0	0	0
Moderate	0	0	0
Severe	281 (83%)	269 (79%)	280 (83%)
Very severe	56 (17%)	70 (21%)	58 (17%)
Frequency of Heartburn Medication			
Not every day	74 (22%)	76 (22%)	69 (20%)
Daily - Once per day	64 (19%)	53 (16%)	66 (20%)
Daily - More than once per day	199 (59%)	205 (61%)	199 (59%)

Reference: Adapted from Volume 3, Pages 8-000142-144, Tables 10, 11, and 12

In 3014, all three treatment groups (placebo, Z 75, and Z 150) also had similar extensive heartburn histories (see Table 12).

Table 12: Past medical history of heartburn in Study 3014

	Placebo	Z 75	Z 150
Length of Time (yrs) with heartburn, acid indigestion, or sour stomach [1]			
N	334	334	339
Mean (SE)	10.9 (0.54)	10.3 (0.55)	10.1 (0.50)
Min - Max	0.5 - 51.0	0.5 - 61.0	0.5 - 50.0
How many days did you experience heartburn over the last week? [1]			
N	334	334	339
Mean (SE)	6.1 (0.06)	6.2 (0.06)	6.3 (0.06)
Min - Max	3 - 7	4 - 7	3 - 7
How many days did you experience heartburn the week before? [1]			
N	334	334	339
Mean (SE)	6.1 (0.06)	6.3 (0.06)	6.3 (0.05)
Min - Max	4 - 7	3 - 7	3 - 7
On a typical day how many episodes of heartburn do you have? [1]			
N	338	334	339
Mean (SE)	2.5 (0.08)	2.7 (0.10)	2.6 (0.07)
Min - Max	1 - 12	1 - 15	1 - 10
Describe most of your heartburn episodes over the last two weeks [2][3]			
Very mild	0	0	0
Mild	0	0	0
Moderate	0	1 (<1%)	0
Severe	279 (84%)	275 (82%)	269 (79%)
Very severe	55 (16%)	58 (17%)	70 (21%)
Frequency of Heartburn Medication			
Not every day	104 (31%)	97 (29%)	103 (30%)
Daily - Once per day	71 (21%)	74 (22%)	63 (19%)
Daily - More than once per day	150 (45%)	157 (47%)	163 (48%)

Reference: Adapted from Volume 19, Pages 8-006349-6351, Tables 10, 11, and 12

Medical Reviewer's Comments: In 3013 and 3014, patients (on average) had at least 6 days of heartburn per week, had over 2.5 episodes of heartburn per day, had a past medical history of heartburn for over 10 years, had taken medication to relieve their heartburn approximately 73% of the time, and had characterized the majority of their heartburn episodes as severe or very severe. Therefore, most patients in these treatment studies had GERD; not episodic heartburn.

The enrichment of the study heartburn population was acceptable. However, the appropriate ranitidine dose for treatment non-erosive GERD and EE patients is 150 mg BID for 4 to 8 weeks and 150 mg QID for 12 weeks, respectively. Consumers with frequent and severe heartburn (GERD) should not self-administer ranitidine OTC; rather, they should see their doctor for treatment.

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Efficacy Results:

Pre-specified primary efficacy endpoint: In the treatment studies, the pre-specified primary efficacy endpoint was the total pain relief (TOTPAR) of the first study drug-treated severe or very severe heartburn episode over the two hour evaluation period (see Table 13 for 3013 and Table 14 for 3014). The TOTPAR score was the summation of eight heartburn pain relief scores measured at 15 minute intervals over the two-hour assessment period after taking the study drug. The 7-point heartburn pain relief scores (see Table 4) ranged between 0 (no relief) and 6 (complete relief).

Table 13: The TOTPAR scores during the first episode of severe or very severe heartburn in Study 3013

	Placebo	Z 75	Z 150
Number of patients[1] whose first heartburn episode was rated as severe or very severe	320	323	313
Mean (SE) TOTPAR Score over two hours	17.5 (0.69)	20.1 (0.72)	20.6 (0.72)
Median TOTPAR Score over two hours	16.0	19.0	21.0
p-value* (comparison with placebo)		0.015	0.005
p-value* (comparison of Z 150 to Z 75)			0.567

[1] Two patients in the Z 150 treatment group had a missing pain relief score at 15 minutes and were excluded from the TOTPAR analysis
* P-values were calculated using the Wilcoxon Rank sum-test
Reference: Adapted from Volume 3, Page 8-000149, Table 17

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Table 14: The TOTPAR scores during the first episode of severe or very severe heartburn in Study 3014

	Placebo	Z 75	Z 150
Number of patients[1] whose first heartburn episode was rated as severe or very severe	315	313	324
Mean (SE) TOTPAR Score over two hours	19.1 (0.73)	20.7 (0.70)	21.1 (0.68)
Median TOTPAR Score over two hours	18.0	21.0	20.0
p-value* (comparison with placebo)		0.093	0.042
p-value* (comparison of Z 150 to Z 75)			0.980

[1] Two patients in the Z 75 treatment group and three patients in the placebo treatment group had a missing LOCF pain relief score at 15 minutes and were excluded from the TOTPAR analysis
* P-values were calculated using the Wilcoxon Rank Sum test
Reference: Adapted from Volume 19, Page 8-006356, Table 17

Medical Reviewer's Comments: In both treatment studies, Z 150 demonstrated statistical improvement in the first episode TOTPAR score (the primary efficacy endpoint) compared to placebo. In contrast, Z 75 only demonstrated statistical improvement in the TOTPAR score compared to placebo in Study 3013, not Study 3014. Additionally, Z 150 demonstrated numerical improvement over Z 75 in the primary efficacy endpoint in both treatment trials.

Agency-derived *post-hoc* efficacy endpoints #1 and #2: Two hours post-treatment, the proportion of patients that achieved complete relief (a 6 on the heartburn pain relief scale) and the proportion of patients that achieved almost complete relief or complete relief (a 5 or a 6 on the heartburn pain relief scale) of the first drug-treated heartburn episode. Please see Tables 15 and 16 for these efficacy results for 3013 and 3014, respectively).

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Table 15: Two hours post-treatment, the proportion of patients with (at least) almost complete relief of the first drug-treated heartburn episode in Study 3013

	Placebo	Z 75	Z 150
Number of patients with a first heartburn episode that was severe or very severe	320	323	315
Number (%) of patients with almost complete relief (5) or complete relief (6)	120 (38%)	155 (48%)	154 (49%)
p-value (comparison with placebo)		0.009	0.003
p-value (comparison of Z 150 to Z 75)			0.783
Number (%) of patients with complete relief (6)	83 (26%)	114 (35%)	113 (36%)
p-value (comparison with placebo)		0.012	0.007
p-value (comparison of Z 150 to Z 75)			0.871

* p-values were calculated using Cochran-Mantel-Haenszel test
Reference: Adapted from Volume 3, Page 8-000302, Table 18.7

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Table 16: Two hours post-treatment, the proportion of patients with (at least) almost complete relief of the first drug-treated heartburn episode in Study 3014

	Placebo	Z 75	Z 150
Number of patients with a first heartburn episode that was severe or very severe	318	315	324
Number (%) of patients with almost complete relief (5) or complete relief (6)	121 (38%)	144 (46%)	151 (47%)
p-value (comparison with placebo)		0.057	0.036
p-value (comparison of Z 150 to Z 75)			0.775
Number (%) of patients with complete relief (6)	86 (27%)	106 (34%)	103 (32%)
p-value (comparison with placebo)		0.082	0.221
p-value (comparison of Z 150 to Z 75)			0.623

* p-values were calculated using Cochran-Mantel-Haenszel test
Reference: Adapted from Volume 19, Page 8-006551, Table 18.7

Medical Reviewer's Comments: In both treatment studies, the Z 150 treatment groups had statistically higher proportions of patients (compared to the placebo groups) that achieved almost complete relief or complete relief of the first drug-treated heartburn episode at the two hour time point after treatment. In 3013, the Z 150 treatment group had a statistically higher proportion of patients (compared to the placebo group) that achieved complete relief of the first drug-treated heartburn episode at the two hour time point after treatment. In 3014, the Z 150 treatment group was numerically — not statistically — better than the placebo group in the complete relief of the first drug-treated heartburn episode at the two hour time point after treatment.

The Z 150 and the Z 75 treatment groups were not statistically different from one another in the Agency-derived *post-hoc* efficacy endpoints #1 and #2.

Agency-derived *post-hoc* efficacy endpoint #3 and #4: Two hours post-treatment, the proportion of patients that achieved complete relief (a 6 on the heartburn pain relief scale) and the proportion of patients that achieved almost complete relief or complete relief (a 5 or a 6 on the heartburn pain relief scale) of all the drug-treated heartburn episodes. Please see Tables 17 and 18 for these efficacy results for 3013 and 3014, respectively).

Table 17: Two hours post-treatment, the proportion of patients with complete relief of all the drug-treated heartburn episodes in Study 3013

	Placebo	Z 75	Z 150
Number of patients	337	338	338
Number of severe or very severe drug-treated heartburn episodes	4724	5102	5093
Number (%) of patients with almost complete relief (5) or complete relief (6)	1573 (33%)	2224 (44%)	2308 (45%)
p-value (comparison with placebo)		< 0.001	< 0.001
p-value (comparison of Z 150 to Z 75)			0.523
Number (%) of patients with complete relief (6)	1084 (23%)	1569 (31%)	1712 (34%)
p-value (comparison with placebo)		0.004	< 0.001
p-value (comparison of Z 150 to Z 75)			0.439

* p-values were calculated using generalized estimating equations
Reference: Adapted from Volume 3, Page 8-000318, Table 18.15

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Table 18: Two hours post-treatment, the proportion of patients with complete relief of all the drug-treated heartburn episodes in Study 3014

	Placebo	Z 75	Z 150
Number of patients	334	334	339
Number of severe or very severe drug-treated heartburn episodes	4633	4814	4928
Number (%) of patients with almost complete relief (5) or complete relief (6)	1638 (35%)	2079 (43%)	2135 (43%)
p-value (comparison with placebo)		0.015	0.004
p-value (comparison of Z 150 to Z 75)			0.630
Number (%) of patients with complete relief (6)	1098 (24%)	1385 (29%)	1466 (30%)
p-value (comparison with placebo)		0.052	0.013
p-value (comparison of Z 150 to Z 75)			0.549

* p-values were calculated using generalized estimating equations
Reference: Adapted from Volume 19, Page 8-006567, Table 18.15

Medical Reviewer's Comments: In both treatment studies, the Z 150 treatment groups had statistically higher proportion of patients (compared to the placebo groups) that achieved almost complete relief or complete relief of all the drug-treated heartburn episodes at the two hour time point after treatment. Similarly, the Z 150 treatment groups in both treatment studies had statistically significant higher proportion of patients (compared to the placebo groups) that achieved complete relief of all the drug-treated heartburn episodes at the two hour time point after treatment.

In both treatment trials, the Z 150 groups were numerically — not statistically — better than the Z 75 groups in the Agency-derived *post-hoc* efficacy endpoints #3 and #4.

The Agency-derived efficacy endpoints #5 and #6 were not evaluated in this review because they were not as clinically-significant as the first four Agency-derived endpoints. Additionally, more endpoints would increase the multiplicity.

Pre-specified secondary efficacy endpoints (overall effectiveness): At the end of each two-hour assessment period, the overall effectiveness of the study drug for the first severe or very severe drug-treated heartburn episode and for all of the severe or very severe drug-treated heartburn episodes. Please see Tables 19 and 20 for these efficacy results in 3013 and 3014, respectively).

Table 19: Patient's evaluation of the overall effectiveness of treatment on the first and all severe or very severe heartburn episodes in Study 3013

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	337	338	338
First Episode: Number of episodes	320	323	315
0=Not effective	29 (9%)	25 (8%)	14 (4%)
1=Poor	57 (18%)	42 (13%)	46 (15%)
2=Fair	91 (28%)	68 (21%)	60 (19%)
3=Good	82 (26%)	98 (30%)	92 (29%)
4=Very Good	44 (14%)	63 (20%)	71 (23%)
5=Excellent	15 (5%)	24 (7%)	28 (9%)
Unknown	2 (<1%)	3 (<1%)	4 (1%)
Comparison with Ranitidine 75mg [1]			0.215
Comparison with Placebo [1]		0.002	<0.001
All Episodes: Number of episodes	4724	5102	5093
0=Not effective	504 (11%)	337 (7%)	281 (6%)
1=Poor	801 (17%)	645 (13%)	522 (10%)
2=Fair	1162 (25%)	1030 (20%)	1170 (23%)
3=Good	1176 (25%)	1415 (28%)	1398 (27%)
4=Very Good	796 (17%)	1077 (21%)	1124 (22%)
5=Excellent	212 (4%)	510 (10%)	519 (10%)
Unknown	73 (2%)	98 (2%)	79 (2%)
Comparison with Ranitidine 75mg [2]			0.390
Comparison with Placebo [2]		<0.001	<0.001

[1] P-values were calculated using Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren)
[2] P-values were calculated using General Estimating Equations with investigator in the model.

Reference: Adapted from Volume 3, Page 8-000152, Table 19

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Table 20: Patient's evaluation of the overall effectiveness of treatment on the first and all severe or very severe heartburn episodes in Study 3014

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	334	334	339
First Episode: Number of episodes	318	315	324
0=Not effective	38 (12%)	24 (8%)	16 (5%)
1=Poor	58 (18%)	32 (10%)	35 (11%)
2=Fair	66 (21%)	62 (20%)	77 (24%)
3=Good	80 (25%)	101 (32%)	104 (32%)
4=Very Good	55 (17%)	64 (20%)	63 (19%)
5=Excellent	19 (6%)	27 (9%)	26 (8%)
Unknown	2 (<1%)	5 (2%)	3 (<1%)
Comparison with Ranitidine 75mg [1]			0.925
Comparison with Placebo [1]		<0.001	0.002
All Episodes: Number of episodes	4633	4814	4928
0=Not effective	668 (14%)	284 (6%)	270 (5%)
1=Poor	672 (15%)	571 (12%)	499 (10%)
2=Fair	923 (20%)	958 (20%)	1085 (22%)
3=Good	1199 (26%)	1368 (28%)	1547 (31%)
4=Very Good	749 (16%)	1097 (23%)	1012 (21%)
5=Excellent	369 (8%)	456 (9%)	440 (9%)
Unknown	53 (1%)	70 (1%)	75 (2%)
Comparison with Ranitidine 75mg [2]			0.942
Comparison with Placebo [2]		<0.001	<0.001

[1] P-values were calculated using Wilcoxon Rank Sum test stratified by investigator (i.e., van Elteren).
[2] P-values were calculated using General Estimating Equations with investigator in the model.

Reference: Adapted from Volume 19, Page 8-006359, Table 19 .

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Medical Reviewer's Comments: In both treatment studies, the overall effectiveness of Z 150 was statistically better than placebo in the treatment of the first severe or very severe heartburn episode. Furthermore in both treatment studies, the overall effectiveness of Z 150 was statistically better than placebo in the treatment of all the severe or very severe heartburn episodes during the two week treatment period. The Z 150 and Z 75 treatment groups did not differ in their effectiveness to treat the first severe heartburn episode or all the severe heartburn episodes.

6.1.5 Clinical Microbiology

There have been no clinical microbiology issues with this application.

6.1.6 Efficacy Conclusions – Treatment

This medical officer supports the efficacy of Zantac 150 (Ranitidine 150 mg Tablets, Z 150) for the over-the-counter treatment of episodic heartburn in adults and pediatric patients over 12 years old. In two large, adequate, and well-controlled treatment trials, Zantac 150, in comparison to the placebo, demonstrated statistical improvement in four of the five important efficacy endpoints (the one pre-specified primary efficacy endpoint and the first four Agency-derived endpoints). In addition, Zantac 150 demonstrated numerical improvement over Zantac 75 in four of those five efficacy endpoints.

Limitations of the treatment trial results include the inability of Zantac 150 to demonstrate the following:

1) The complete resolution of episodic heartburn in more than a third of the Zantac 150 treated patients
2) Unequivocal superior efficacy over Zantac 75

6.2 Indication – Prevention

6.2.1 Methods

The efficacy evaluation of the proposed prevention indication is based on three very similar Z 150 Trials – Study RANA3016 (identified as 3016), Study RANA3018 (identified as 3018), and Study RANA4006 (identified as 4006). The three prevention studies were large, randomized, double-blind, placebo-controlled, parallel-group, multi-center clinical trials.

In this review, this medical officer will detail the design, procedures, and evaluations of 3016; summarize the design differences in 3018 and 4006; and present the results in all three of the prevention trials.

6.2.2 General Discussion of Endpoints

Primary Efficacy Endpoint for 3016: The primary efficacy parameter was heartburn severity at the Treatment Meal Visit (Visit 4) as measured by area under the curve (AUC). The AUC was calculated from each patient's VAS scores (graded on a 0 to 100 scale) and the patient's use of rescue antacid over the 4-hour and 40-minute evaluation period.

Medical Reviewer's Comments: The DGICDP and the DOTCDP felt that the heartburn severity measured by AUC may not be an acceptable primary endpoint because it may not be clinically meaningful.

During a July 18, 1997 meeting between Glaxo Wellcome (the sponsor of Z 75 at the time) and the Agency, three additional Agency-derived endpoints in the three prevention heartburn studies were agreed upon. These clinical endpoints categorize study treatment effect on a per

patient basis of either success or failure and are all related to the primary endpoint of heartburn severity as measured by the AUC.

Agency-Derived Endpoints: In 3016, the three pre-specified Agency-Derived endpoints were the following:

#1 A 40* millimeter•hour or more decrease in heartburn severity (measured by AUC) from the Run-In to the Treatment Meal Visits or the complete prevention of heartburn.
#2 A 50% decrease or more in heartburn severity (measured by AUC) from the Run-In to the Treatment Meal Visits or the complete prevention of heartburn
#3 Mean heartburn severity scores (measured by VAS) of 17 mm or less or the complete prevention of heartburn
* In 3018, this number is 45; not 40.

Medical Reviewer's Comments: In the prevention studies, these three Agency-derived efficacy endpoints were characterized by the following:

- In Study 3016, the endpoints were pre-specified
- In Study 4006 the endpoints became *post-hoc* analyses because Study 4006 was completed before these analyses were recommended by the Agency.
- In Study 3018, the endpoints became additional pre-specified co-primary endpoints; therefore, Study 3018 had four co-primary endpoints

Secondary Efficacy Endpoints for 3016: The following are the 14 secondary endpoints for 3016:

- Percentage reduction of heartburn severity was calculated by subtracting the heartburn severity AUC at the Treatment Meal Visit from the AUC at the Run-In Meal Visit and then dividing by the Run-In Meal AUC. Means of these percent reductions were compared to assess treatment differences.
- The reduction of heartburn severity was calculated by subtracting the heartburn severity AUC at the Treatment Meal Visit from the AUC at the Run-In Meal Visit
- Peak heartburn severity score (post-meal): Each patient's highest, post-meal LOCF heartburn severity score was to be determined. The median of the individual peak severity scores was to be used to assess treatment group differences.
- Percent decrease in peak heartburn severity: The percentage reduction in peak heartburn severity from Run-In to Treatment Meal Visits was calculated.
- The median duration of time without heartburn symptoms was calculated from the beginning of the meal (time zero) to the time patients experienced their first heartburn symptoms or the time the rescue antacid was taken. Patients who did not develop heartburn during the session were to be assigned the maximum duration (240 minutes). Only patients who reported no heartburn symptoms at the beginning of the meal were included in the analysis. Durations were to be calculated after assigning each patient the midpoint of the time interval during which the heartburn began. For instance, a patient who indicated the first experience of heartburn symptoms at 55 minutes (the second post-meal observation point) would be assigned a duration of 47.5 minutes.

- The longest duration of no heartburn
- Median number of consecutive time points without heartburn
- Median number of time points without heartburn
- The proportion of patients who used maalox, the rescue antacid
- The mean time that maalox was taken for patients who used maalox
- Patient global heartburn evaluations: At the end of the 4-hour and 40-minute evaluation period patients answered the following question: "How would-you rate the effectiveness of the study medication?" The 6-point overall effectiveness score was used (see Table 4). Median scores for the global ratings were compared for treatment group differences.
- At the end of the 4-hour and 40-minute evaluation period patients answered the following question: "From the time you took your medication until now, how would you rate the discomfort level you experienced due to each of the following 11 symptoms" including (acid indigestion, acid reflux, acid taste, belching/burping, burning feeling, gas, heartburn, indigestion, sour stomach, stomach ache/pain, and stomach fullness/bloating)? The symptoms were rated on a six-point scale (see Table 6). Median scores for the individual symptom ratings were compared for treatment group differences.
- The proportion of patients with complete prevention ("success") of heartburn episodes. If patients took maalox, then they were failures. Only patients who reported no baseline heartburn symptoms at the start of the provocative meal were included.
- The proportion of patients who had insomnia due to heartburn symptoms (were kept from sleeping or were awakened) or who experienced heartburn symptoms upon awakening.

Medical Reviewer's Comments: Multiplicity adjustment may be needed with one pre-specified primary endpoint, three *post-hoc* Agency-derived endpoints, and 14 pre-specified secondary endpoints. H_2RAs prevention trials of episodic heartburn have had similar secondary endpoints including the peak heartburn after the meal; the proportion of patients with complete heartburn prevention; proportion of patients with excellent good, very good, or excellent heartburn relief; proportion of patients with no awakenings from heartburn; and the proportion of patients using rescue antacids.

6.2.3 Study Design

Study RANA3016: "A randomized, double-blind, double-dummy, placebo-controlled, parallel evaluation of ranitidine for the reduction of severity or prevention of meal-induced heartburn."

Study Design: Study 3016 was a randomized, multi-center (35 sites), double-blind, double-dummy, placebo-controlled, parallel group trial of Z 150 in ambulatory out-patients in the United States. Patients were randomized (1:1:1) to receive placebo, Z 75, or Z 150 at the beginning of a meal and beverage that was anticipated to provoke heartburn. The patients were allowed to eat the provocative meal for 40 minutes and subsequently patients reported their heartburn severity over a 4 hour evaluation period. Anytime after the provocative meal during the Treatment Meal Visits, patients were allowed to request open-label, rescue maalox tablets to relieve their heartburn. Patients could chew one to four maalox tablets as needed for heartburn, but no more than 16 tablets per day.

Medical Reviewer's Comments: Study 3016 was a well-controlled (placebo and dose-comparison controlled) study. The four hour evaluation period after the meal was similar to other H_2RAs prevention trials and it is acceptable.

Eligibility Criteria: Table 21 displays the eligibility criteria of 3016.

Table 21: Eligibility criteria

Inclusion Criteria: To be eligible to participate in the study, patients had to have met the following criteria:	**Exclusion Criteria:** If patients had the following conditions, they were not eligible to participate in the study:
➢ At least 18 years of age ➢ Signed an informed consent form ➢ Had a history of at least five episodes of meal-induced heartburn per week over the last two months ➢ Had identified at least two types of food and/or beverage, which were similar to the test meal and caused their meal-induced heartburn symptoms ➢ Had a current six month history of heartburn which required treatment ➢ Had used antacids to treat heartburn for the six months prior to enrollment and achieved relief from antacid use ➢ Was a current user of antacids ➢ Had properly completed the heartburn diary for seven consecutive days prior to the Screening Visit. ➢ Had recorded experiencing meal-induced heartburn symptoms a minimum of four out of the seven consecutive days on the seven day Screening Diary ➢ Had rated at least 60% of all meal-induced heartburn episodes as 3 or above in severity on the seven day Screening Diary ➢ If female, was surgicially sterilized (bilateral tubal ligation or hysterectomy), or was at least 1 year post-menopausal, or was using an acceptable method of contraception in the presence of childbearing potential and not pregnant as determined by the urine pregnancy test.	➢ Was currently under the care of a physician for, or had been diagnosed with an "ulcer" within the past year ➢ Had any history of gastrointestinal hemorrhage or upper gastrointestinal surgery (ulcer or acid-reflux) ➢ Had a medical history and physical examination conducted at the Screening Visit (Visit 2) which demonstrated a clinically significant disease, which was not adequately controlled, including a current history of significant abdominal condition or pain not related to heartburn ➢ Had taken an OTC H_2RA after 12:01 AM the day before the Run-In Meal Visit (i.e., within the past 36 hours) and for the duration of the study ➢ Had taken a prescription H_2RA, metoclopramide, sucralfate, misoprostol, or cisapride between the Prescreening Visit (Visit 1) and the end of the study ➢ Had ever taken omeprazole or lansoprazole ➢ Was an active substance abuser (e.g., marijuana, alcohol), excluding tobacco use ➢ Was a current methadone user ➢ Was breastfeeding. ➢ Had a known hypersensitivity or intolerance to cimetidine, ranitidine, famotidine, nizatidine, or magnesium or aluminum hydroxide ➢ Had participated in a study with an investigational drug within 30 days prior to Screening or had ever participated in a Glaxo Wellcome gastrointestinal study where a meal had been served ➢ Had any objections to consuming any portion of the test meal. ➢ Had a history of allergies to any portion of the test meal. ➢ Had an infirmity, disability, or geographic location, which was likely to limit compliance for scheduled visits. ➢ Was a study staff member or an immediate family member of a participating investigator, sub-investigator, or study coordinator.

Reference: Volume 33, Pages 8-011704-11707

Medical Reviewer's Comments: The inclusion criteria selected for adult GERD patients (patients with frequent and severe heartburn for over six months). This enrichment is acceptable.

The eligibility criteria appropriately excluded the use of concomitant medications that can prevent heartburn (including other H_2RAs, PPIs) and properly prohibited patients with other upper gastrointestinal disease.

The current ranitidine prescription label states that patients with a creatinine clearance less than 50 mL per minute should initially take only 150 mg of ranitidine per day. However, the eligibility criteria did not exclude patients with moderate to severe renal insufficiency. Furthermore, patients with chronic renal insufficiency were allowed to take up to 300 mg of ranitidine per day (two doses of Z 150 for two episodes of severe heartburn).

Premature Discontinuation of Patients: Patients could withdraw from the study at any time at the investigator's discretion or the patient's request. Reasons for withdrawal from the trial included, but were not limited to, the following:

- An adverse event
- Failure to comply with the protocol
- Concomitant use of excluded medications during the study
- VAS score > 10 mm just prior to eating the Run-In Meal
- Maximum VAS score < 34mm at all time points within the first 90 minutes after completing the Run-In Meal
- Within the first 90 minutes of completing the Run-In Meal Visit, responded "no" to having heartburn, acid indigestion, or acid stomach at each evaluation time point.
- Not consuming the minimum required portions at the Run-In Meal Visit
- Lost to follow-up
- Use of rescue antacid within the first 90 minutes of the Run-In Meal Visit AND before achieving a VAS score ≥ 34 mm
- Withdrawal of consent

Medical Reviewer's Comments: The withdrawal criteria appropriately discontinued patients for noncompliance with the study procedures and patients with no significant heartburn symptoms following the Run-In Meal.

Drugs used in study: At the Run-In Meal Visit, all patients who qualified were given one dose of single-blind placebo. At the Treatment Meal Visit, all qualified patients were randomized to three treatments: Z 150, Z 75, or placebo. Open-label rescue antacid, maalox, was available to patients upon their request at the Run-In and Treatment Meal Visits. Patients could chew one to four maalox tablets as needed for heartburn, but no more than 16 tablets per day.

Schedule of Procedures and Evaluations: The study consisted of four on-site study visits: the Prescreening Visit (Visit 1), the Screening Visit (Visit 2), the qualifying Run-In Meal Visit (Visit 3), and the Treatment Meal Visit (Visit 4). Please see Table 22 for the schedule of procedures and evaluations during Study 3016.

Table 22: Schedule of procedures and evaluations during Study 3016

	VISIT 1	VISIT 2	VISIT 3	VISIT 4
	PRESCREENING[a]	SCREENING	RUN-IN MEAL VISIT (MEAL 1)	TREATMENT MEAL VISIT (MEAL 2)
	Day 0	8-34 days from Visit 1	8-34 days from Visit 1	4-22 days from Visit 3
Informed consent	X			
Dispense diary card and review directions for completion	X[b]			X[c]
Review diary card		X		X[d]
Physical examination		X	X[e]	X[e]
Medical/heartburn history		X		
Pregnancy test		X[f]		
Adverse events assessment			X	X
Concurrent medications assessment		X	X	X
Randomization				X
Test Meal			X	X
Dispense study drug			X[g]	X
Dispense open-label rescue antacid			X[h]	X[h]
Heartburn symptom evaluation			X	X
Global subject evaluation			X	X
Drug accountability			X	X
Schedule return appointment	X	X	X[i]	X[i]

Reference: Volume 33, Page 8-011760, Table 1

In 3018, the Run-In Meal took place ≤ 30 days from Visit 2 and the Treatment Meal took place 4 to 60 days from the Run-In Meal. In 4006, the Screening Visit took place 8 to 26 days from Visit 1, the Run-In Meal took place 0 to 30 days from the Screening Visit, and the Treatment Visit took place 4 to 16 days from the Run-In Meal. Furthermore, in 3018, patients took home a diary to report their heartburn symptoms after the Treatment Meal and they mailed the diary back to the investigators.

Pre-Screening Visit (Visit 1): After providing written informed consent, patients were trained on the proper completion of a seven day screening diary card. Patients received a seven day screening diary on which they recorded information about each of their heartburn episodes on a daily basis (i.e., severity of the episode, its cause, whether or not it was treated, and if treated then the time of treatment).

Screening Visit (Visit 2): Patients returned to the study site (8 to 34 days after the Prescreening Visit) with their completed seven day screening diary. The diary information was reviewed to determine if the patients met the heartburn history requirements. Patients must have had experienced meal-induced heartburn on at least four out of the seven consecutive days and had

at least 60% of all meal-induced episodes rated as moderate, severe, or very severe on the heartburn symptom intensity scale (see Table 8).

Patients could only use antacids to treat heartburn during the seven-day Screening Diary Period and between the qualifying Run-In Meal Visit and the Treatment Meal Visit. OTC H_2RAs were not allowed from 36 hours prior to the Run-In Meal through the duration of the study. Prior to the Run-In and Treatment Meal Visits, patients could not take antacids after midnight, or eat or drink (except water) after 7:00 AM. Alcohol intake was restricted to 1-2 beverages within 24 hours, and was prohibited after 11:59 PM the evening prior to the Run-In and Treatment Meal Visits.

Run-In Meal Visit (Visit 3): Patients, who qualified, received one dose of single-blind placebo at the beginning of the qualifying Run-In Meal. Patients were instructed to swallow the study drug (placebo) with coke® classic at the beginning of the heartburn provocative meal. The meal consisted of a minimum of approximately 10-ounces (280 grams) of chili, one approximately 3-ounce (84 grams) portion of tortilla chips, one 12-ounce (355 mL) can of coke® classic, and one 0.325-ounce (10.7 grams) ghirardelli® mint chocolate square. Additional full portions of coke classic and chocolate squares and additional half portions of chili and tortilla chips were given to patients who requested additional food. Patients had to consume all the food within 40 minutes; no extra time was allowed to consume the additional portions. No additional food or drink was allowed during the evaluation period. Patients were not allowed to recline, use tobacco products, chew gum, eat candy, watch television, or listen to sports radio during the evaluation period. Conversation among patients regarding their heartburn, treatment, or study procedures was prohibited.

Patients recorded the presence of heartburn just prior to eating the meal, 40 minutes later (at the end of the meal period), and at 15-minute intervals thereafter for a total evaluation time of 4-hour and 40 minutes from the time of dosing (for a total of 18 evaluations). At these same time points, patients with heartburn recorded their level of heartburn severity on a 100 mm visual analog scale (VAS), with higher scores indicating increased severity. Global assessments were made by the patients at the end of the evaluation period.

Open-label rescue antacid, maalox tablets, was available to patients upon their request at the Run-In Meal Visit. Patients could chew one to four maalox tablets as needed for heartburn, but no more than 16 tablets per day. Patients were not allowed to use any other medications to relieve their heartburn symptoms during the study meal.

Treatment Meal Visit (Visit 4): Patients who met the minimum requirements at the Run-In Meal Visit were scheduled to return for the Treatment Meal Visit, within 4 to 22 days after the Run-In Meal visit. At the Treatment Meal Visit, the same procedures and assessments were performed as at the Run-In Meal Visit. However, at the beginning of the Treatment Meal, patients were randomized and then received a double-blind, double-dummy, study drug dose of Z 150, Z 75, or placebo. The patients were instructed to swallow the study drug with coke® classic at the beginning of the heartburn provocative meal. Furthermore, during the 40 minute Treatment Meal, patients were instructed to consume the same number of portions of chili, tortilla chips, coke classic, and mint chocolate squares as they consumed at the Run-In Meal

Visit. Open-label maalox was available to patients upon their request at the Treatment Meal Visit. Patients could chew one to four maalox tablets as needed for heartburn, but no more than 16 tablets per day. Patients were not allowed to use any other medications to relieve their heartburn symptoms during the study meal.

Patients were to complete a take-home Post-Treatment Meal Diary to assess their heartburn from the end of the visit (4 hours and 40 minutes after taking the study drugs) until the following morning. Patients were to record insomnia due to heartburn and heartburn upon awakening in the morning.

Medical Reviewer's Comments: The procedures and evaluations in 3016 are acceptable for a heartburn prevention study.

Studies 3016 and 4006 had identical eligibility criteria, designs, procedures (the same provocative meal and drink was administered), evaluations, and primary efficacy endpoints. Furthermore, both studies used the same Z 150, Z 75, and maalox batches. However, 3016 and 4006 differed in the following ways:

- They used different placebos batches
- The three Agency-derived endpoints were pre-specified in 3016; whereas, these three Agency-derived endpoints were *post-hoc* in 4006.
- Study 3016 included an extended evaluation of heartburn symptoms (nighttime and post-treatment day evaluations); whereas, the total evaluation period in 4006 was four hours and 40 minutes.
- Patients in 3016 assessed specific symptoms (including acid indigestion, acid reflux, acid taste, belching/burping, burning feeling, gas, heartburn, indigestion, sour stomach, stomach ache/stomach pain, stomach fullness/bloating) over the evaluation period; whereas, patients in 4006 did not assess these symptoms.
- Different patients were randomized and different investigative sites were used.

Study 3018 was very similar to 3016 and 4006. Study 3018 used the same study batches as 3016 for the following study drugs: the placebo, Z 75 and Z 150. In 3018, the provocative meal and drink (tortilla chips, chocolate, chili, and coke) were qualitatively the same as in 3016 and 4006. However, 3018 differed from 3016 and 4006 in the following ways:

- During the 3018 study meal, fewer tortilla chips were administered: two ounces (56 grams) of tortilla chips were provided instead of three ounces (84 grams) in 3016 and 4006.
- In 3018, rescue antacid could not be used during the 4 hour and 40 minute evaluation period during the Run-In and Treatment Periods; whereas in 3016 and 4006, maalox was available to the patients during the evaluation period.
- In 3018, heartburn symptoms were assessed over 15 minute periods; while in 3016 and 4006, symptoms were assessed at the time the question was asked.

Statistical Methods: For the efficacy endpoints, the Z 150 was to be considered superior to the Z 75 group if the Z 150 groups were statistically better than the placebo groups and if the Z 75 and the placebo groups were not significantly different from one another. Alternatively, if both ranitidine treatment groups were significantly more efficacious than placebo, then the Z 150 group must also reveal significantly greater efficacy than the Z 75 group to be considered superior.

Medical Reviewer's Comments: The statistical analysis in the prevention trials was different than the treatment trials. Z 150 had a lower threshold to achieve statistical significant over Z 75 in the prevention trials (compared to the treatment trials).

6.2.4 Efficacy Findings

Baseline Demographics: Of the 2,784 patients enrolled in the Run-In Meal of Study RANA3016, 962 (35%) patients were randomized to the Treatment Meal and 1,822 (65%) patients were not randomized to the Treatment Phase. Most of the patients were not randomized because they did not meet the randomization criteria, they were lost to follow up, or they withdrew their consent.

Of the 962 randomized patients enrolled in the Treatment Meal, 322 (34%), 320 (33%), and 320 (33%) patients were randomized to the placebo, Z 75, and Z 150 treatment groups, respectively, in 35 investigative sites in the United States. All of the patients enrolled in the Treatment Meal completed the study (962/962). Table 23 delineates the baseline patient demographics in 3016 including: gender, age, height, weight, ethnic origin, and tobacco use. P-values were calculated with the Mantel-Haenszel test for the sex, ethnic origin, and tobacco use variables and with the Kruskal-Wallis test for age, height, and weight parameters.

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Table 23: Baseline demographics for Study 3016

	Placebo		Ranitidine 75mg		Ranitidine 150mg	
Number of Subjects	322		320		320	
Sex, n (%)						
Male	127	(39%)	115	(36%)	111	(35%)
Female	195	(61%)	205	(64%)	209	(65%)
Age (years)						
Mean	41.8		40.8		41.9	
Std Error	0.69		0.72		0.68	
Min-Max	18-74		18-81		19-84	
N	322		320		320	
Males, age (years)						
Mean	40.9		39.5		41.4	
Std Error	1.14		1.17		1.22	
Min-Max	18-74		18-79		20-79	
N	127		115		111	
Females, age (years)						
Mean	42.4		41.5		42.1	
Std Error	0.87		0.92		0.82	
Min-Max	18-72		18-81		19-84	
N	195		205		209	
Height (inches)						
Mean	66.7		66.3		66.5	
Std Error	0.22		0.21		0.22	
Min-Max	56-80		57-77		54-76	
N	322		320		320	
Weight (pounds)						
Mean	188.2		187.9		191.9	
Std Error	2.50		2.51		2.73	
Min-Max	97-356		99-356		95-435	
N	322		320		320	
Ethnic Origin, n (%)						
Black	80	(25%)	86	(27%)	68	(21%)
Hispanic	19	(6%)	23	(7%)	25	(8%)
Oriental	2	(1%)	0	(0%)	0	(0%)
White	220	(68%)	210	(66%)	225	(70%)
Other	1	(0%)	1	(0%)	2	(1%)
Tobacco Use Status, n (%)						
Daily User	85	(26%)	88	(28%)	81	(25%)
Non-Daily User	237	(74%)	232	(73%)	239	(75%)

Mantel-Haenszel test was used for sex, ethnic origin, and tobacco use status; Kruskal-Wallis test was used for age, height, and weight.
Reference: Adapted from Volume 33, Page 8-011764, Table 4

Of the 2,116 patients enrolled in the Run-In Meal of Study RANA4006, 601 (28%) patients were randomized to the Treatment Meal and 1,515 (72%) patients were not randomized to the Treatment Phase. Most of the non-randomized patients did not meet the randomization criteria because 1084 patients (72%) did not have a heartburn severity VAS score < 34 mm within the first 90 minutes after completing the Run-In Meal and 272 patients (18%) did not have a heartburn VAS score > 10 mm just prior to eating the Run-In Meal.

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Of the 601 randomized patients enrolled in the Treatment Meal, 199 (33%), 204 (34%), and 198 (33%) patients were randomized to the placebo, Z 75, and Z 150 treatment groups, respectively, in 23 investigative U.S. sites. All of the patients enrolled in the Treatment Meal completed the study (601/601). Table 24 delineates the baseline patient demographics in Study 4006 including: gender, age, height, weight, ethnic origin, and tobacco use. P-values were calculated with the Mantel-Haenszel test for the sex, ethnic origin, and tobacco use variables and with the Kruskal-Wallis test for age, height, and weight parameters.

Table 24: Baseline demographics for Study 4006

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	199	204	198
Sex, n (%)			
Male	81 (41%)	88 (43%)	80 (40%)
Female	118 (59%)	116 (57%)	118 (60%)
Age (years)			
Mean	43.7	45.4	43.3
Std Error	0.94	0.93	1.01
Min-Max	19-80	18-81	18-76
N	199	204	198
Males, age (years)			
Mean	44.6	44.5	44.1
Std Error	1.62	1.41	1.70
Min-Max	21-80	18-74	19-74
N	81	88	80
Females, age (years)			
Mean	43.1	46.0	42.8
Std Error	1.14	1.25	1.25
Min-Max	19-75	18-81	18-76
N	118	116	118
Height (inches)			
Mean	66.6	66.3	66.6
Std Error	0.27	0.28	0.27
Min-Max	58-75	56-78	60-76
N	199	204	198
Weight (pounds)			
Mean	188.9	187.9	190.9
Std Error	3.17	3.33	3.29
Min-Max	105-339	96-380	99-328
N	199	204	198
Ethnic Origin, n (%)			
Black	23 (12%)	21 (10%)	20 (10%)
Hispanic	16 (8%)	19 (9%)	19 (10%)
Oriental	0	1 (<1%)	1 (<1%)
White	155 (78%)	161 (79%)	155 (78%)
Other	5 (3%)	2 (<1%)	3 (2%)
Tobacco Use Status, n (%)			
Daily User	66 (33%)	49 (24%)	47 (24%)
Non-Daily User	133 (67%)	155 (76%)	151 (76%)

Mantel-Haenszel test was used for sex, ethnic origin, and tobacco use status; Kruskal-Wallis test was used for age, height, and weight.
Reference: Adapted from Volume 41, Page 8-014399, Table 4

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Of the 2,306 patients enrolled in the Run-In Meal of Study RANA3018, 921 (40%) patients were randomized to the Treatment Meal and 1,385 (60%) patients were not randomized to the Treatment Phase. Most of the patients were not randomized because they did not meet the randomization criteria, they were lost to follow up, or they withdrew their consent.

Of the 921 randomized patients enrolled in the Treatment Meal, 306 (33%), 309 (34%), and 306 (33%) patients were randomized to the placebo, Z 75, and Z 150 treatment groups, respectively, in 37 investigative sites in the United States. Almost all of the patients enrolled in the Treatment Meal completed the study (918/921; 99.67%). Table 25 delineates the baseline patient demographics in 3018 including: gender, age, height, weight, ethnic origin, and tobacco use. P-values were calculated with the Mantel-Haenszel test for the sex, ethnic origin, and tobacco use variables and with the Kruskal-Wallis test for age, height, and weight parameters.

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Table 25: Baseline demographics for Study 3018

	Placebo	Ranitidine 75mg	Ranitidine 150mg
Number of Subjects	306	309	306
Sex, n (%)			
Male	99 (32%)	110 (36%)	114 (37%)
Female	207 (68%)	199 (64%)	192 (63%)
Age (years)			
Mean	41.5	41.7	43.2
Std Error	0.71	0.75	0.73
Min-Max	18-82	18-80	18-80
N	306	309	306
Males, age (years)			
Mean	40.2	40.1	42.3
Std Error	1.20	1.29	1.24
Min-Max	18-79	18-76	18-75
N	99	110	114
Females, age (years)			
Mean	42.2	42.6	43.7
Std Error	0.88	0.91	0.95
Min-Max	18-82	18-80	19-80
N	207	199	192
Height (inches)			
Mean	66.2	66.2	66.5
Std Error	0.23	0.22	0.23
Min-Max	54-80	56-76	52-79
N	306	309	305
Weight (pounds)			
Mean	190.4	189.5	189.4
Std Error	2.75	2.79	2.60
Min-Max	103-350	98-350	84-380
N	305	309	305
Ethnic Origin, n (%)			
Black	63 (21%)	58 (19%)	54 (18%)
Hispanic	13 (4%)	6 (2%)	11 (4%)
Oriental	0 (0%)	0 (0%)	2 (1%)
White	224 (73%)	241 (78%)	235 (77%)
Other	6 (2%)	4 (1%)	4 (1%)
Tobacco Use Status, n (%)			
Daily User	76 (25%)	81 (26%)	87 (28%)
Non-Daily User	230 (75%)	228 (74%)	219 (72%)

Mantel-Haenszel test was used for sex, ethnic origin, and tobacco use status; Kruskal-Wallis test was used for age, height, and weight.
Reference: Adapted from Volume 50, Page 8-017662, Table 4

No statistical differences between the groups were found for each reported demographic in the three prevention studies; except, the Z 75 and Z 150 treatment groups in 4006 contained a statistically higher percentage of patients who used daily tobacco compared to the placebo group.
The average age of the heartburn patients in the study was approximately 41 years old.

Medical Reviewer's Comments: Overall, the baseline demographics of the study population in 3016 were acceptable.

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The racial diversities in the three prevention studies were similar to the diversity in the U.S. population in the mid 1990's (when the studies were conducted). However, Study 3016 had a slightly higher percentage of African-Americans and 3018 had a higher percentage of African Americans and a lower percentage of Latinos compared to the U.S. population in the mid 1990's.

Additional baseline demographics and behaviors may have been helpful. The sponsor did not calculate the average Body Mass Index (BMI) and did not record other non-pharmacologic behaviors (including caffeine and alcohol ingestion, eating peppers, tomatoes, grapefruit, oranges, and spicy food) that may influence the frequency and severity of heartburn in the patient populations.

Baseline heartburn history: All three treatment groups (placebo, Z 75, and Z 150) had similar heartburn histories. Tables 26, 27, and 28 demonstrate the baseline heartburn history of patients in Studies 3016, 4006, and 3018, respectively.

Table 26: Past medical history of heartburn in Study 3016

	Placebo	Z 75	Z 150	p-value Z 75 versus placebo	p-value Z 150 versus placebo	p-value Z 150 versus Z 75
Number of patients	322	320	320			
Number of days in a typical month with heartburn						
Mean (SE)	25.4 (0.23)	25.2 (0.23)	25.6 (0.22)	0.482*	0.671*	0.181*
Min - Max	15-31	20-31	20-31			
Over the past two months, the number of days/week of meal related heartburn episodes						
5 days/week	116 (36%)	125 (39%)	103 (32%)	0.167[a]	0.498[a]	0.037[a]
6 days/week	64 (20%)	76 (24%)	74 (23%)			
7 days/week	141 (44%)	119 (37%)	143 (45%)			

* p-values were calculated by the Kruskal-Wallis test; [a] p-values were calculated by the Mantel-Haenszel test
Reference: Adapted from Volume 33, Page 8-011769, Table 9

Table 27: Past medical history of heartburn in Study 4006

	Placebo	Z 75	Z 150	p-value Z 75 versus placebo	p-value Z 150 versus placebo	p-value Z 150 versus Z 75
Number of patients	199	204	198			
Number of days in a typical month with heartburn				0.254*	0.017*	0.187*
Mean (SE)	26.3 (0.27)	26.6 (0.29)	27.1 (0.27)			
Min - Max	18-31	15-31	20-31			
Over the past two months, the number of meal related heartburn episodes				0.528[a]	0.414[a]	0.148[a]
5 times/week	37 (19%)	40 (20%)	31 (18%)			
6 times/week	26 (13%)	25 (12%)	19 (10%)			
7 times/week	33 (17%)	42 (21%)	26 (13%)			
> 7 times/week	103 (52%)	97 (48%)	122 (62%)			

* p-values were calculated by the Kruskal-Wallis test; [a] p-values were calculated by the Mantel-Haenszel test
Reference: Adapted from Volume 41, Page 8-014404, Table 9

Table 28: Past medical history of heartburn in Study 3018

	Placebo	Z 75	Z 150	p-value Z 75 versus placebo	p-value Z 150 versus placebo	p-value Z 150 versus Z 75
Number of patients	306	309	306			
Number of days in a typical month with heartburn				0.712*	0.972*	0.891*
Mean (SE)	25.1 (0.24)	25.0 (0.23)	25.0 (0.24)			
Min - Max	15-31	15-31	16-31			
Over the past two months, the number of days/week of meal related heartburn episodes				0.920[a]	0.745[a]	0.668[a]
5 days/week	126 (41%)	123 (40%)	127 (42%)			
6 days/week	71 (23%)	78 (25%)	76 (25%)			
7 days/week	109 (36%)	108 (35%)	103 (34%)			

* p-values were calculated by the Kruskal-Wallis test; [a] p-values were calculated by the Mantel-Haenszel test
Reference: Adapted from Volume 50, Page 8-017667, Table 9

Table 30: After a provocative meal and a preventive medication, the heartburn severity in AUC (mm • hour) in Study 4006

	Placebo	Z 75	Z 150	p-value Z 75 versus placebo	p-value Z 150 versus placebo	p-value Z 150 versus Z 75
Number of patients	199	204	198			
Run-In Meal						
Mean (SE)	159.8 (6.1)	157.2 (5.7)	174.0 (6.3)	0.780	0.093	0.050
Median	149.7	147	168.5			
Min - Max	20-391	0-370	14-394			
Treatment Meal						
Mean (SE)	85.0 (5.8)	75.9 (5.7)	63.8 (5.2)	0.259	0.006	0.102
Median	62.3	42.2	36.6			
Min - Max	0-364	0-418	0-343			

P-values used Analysis of Variance; * One patient was excluded from the analysis because no VAS score was recorded at 40 minutes after dosing for the Run-In Meal and two patients were excluded because they took maalox less than 40 minutes after dosing.
Reference: Adapted from Volume 41, Page 8-014405, Table 10

Table 31: After a provocative meal and a preventive medication, the heartburn severity in AUC (mm • hour) in Study 3018

	Placebo	Z 75	Z 150	p-value* Z 75 versus placebo	p-value* Z 150 versus placebo	p-value* Z 150 versus Z 75
Number of patients	306	309	306			
Run-In Meal						
Mean (SE)	174.4 (4.9)	176.0 (5.3)	178.3 (5.3)	0.821	0.683	0.855
Median	164.8	166	167.9			
Min - Max	28-425	13-412	12-433			
Treatment Meal						
Mean (SE)	98.8 (4.8)	88.6 (5.0)	94.6 (5.9)	0.114	0.372	0.491
Median	79.8	79.8	54.5			
Min - Max	0-408	0-379	0-431			

* p-values used Analysis of Variance
Reference: Adapted from Volume 50, Page 8-017668, Table 10

Medical Reviewer's Comments: In 3016 and 4006, the Z 150 groups had statistically significant lower heartburn severity scores (the primary efficacy endpoint), compared to the placebo groups, over the four hour evaluation periods after the Treatment Meals. In contrast,

the Z 150 treatment group in Treatment Study 3018 did not have statistically significant lower heartburn severity scores, compared to the placebo group, over the four hour evaluation period after the Treatment Meal.

The Z 75 treatment group in 3016 had statistically significant lower heartburn severity scores (the primary efficacy endpoint), compared to the placebo group, over the four hour evaluation period after the Treatment Meal. However, in 4006 and 3108, Z 75 failed to achieve the primary efficacy endpoint.

Therefore, Z 150 achieved the primary efficacy endpoint in two out of the three prevention studies.

Agency-derived prevention efficacy endpoints #1, #2, and #3: Tables 32, 33, and 34 demonstrate the results of Agency-derived prevention efficacy endpoints #1, #2, and #3. The three Agency-Derived endpoints were the following:

#1 A 40* mm•hour or more decrease in heartburn severity (measured by AUC) from the Run-In to the Treatment Meal Visits or the complete prevention of heartburn. * In 3018, this number is 45; not 40.
#2 A 50% decrease or more in heartburn severity (measured by AUC) from the Run-In to the Treatment Meal Visits or the complete prevention of heartburn
#3 Mean heartburn severity scores (measured by VAS) of 17 mm or less or the complete prevention of heartburn

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Table 32: Three, Agency-derived, pre-specified, efficacy endpoints in Study 3016

Agency-Derived Efficacy Endpoint	Placebo	Z 75	Z 150	p-value* Z 75 versus placebo	p-value* Z 150 versus placebo	p-value* Z 150 versus Z 75
Number of Patients	322	320	320			
N (%) of patients with a reduction in heartburn severity (AUC) by at least a 40 mm•hours or the complete prevention of heartburn	168 (52%)	191 (60%)	213 (67%)	0.048	<0.001	0.099
N (%) of patients with at least a 50% reduction in heartburn severity (AUC) or the complete prevention of heartburn	121 (38%)	145 (45%)	161 (50%)	0.029	0.002	0.254
N (%) of patients with mean heartburn severity scores (VAS) of 17 mm or less or the complete prevention of heartburn	130 (40%)	155 (48%)	165 (52%)	0.020	0.006	0.550

* P-values were calculated using the Mantel-Haenszel test
Reference: Adapted from Volume 33, Pages 8-011773-1775, Table 13, 14, and 15

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Table 33: Three, Agency-derived, *post-hoc,* efficacy endpoints in Study 4006

Agency-Derived Efficacy Endpoint	Placebo	Z 75	Z 150	p-value* Z 75 versus placebo	p-value* Z 150 versus placebo	p-value* Z 150 versus Z 75
Number of Patients	199	204	198			
N (%) of patients with a reduction in heartburn severity (AUC) by at least a 40 mm•hours or the complete prevention of heartburn	112 (56%)	133 (65%)	146 (74%)	0.082	<0.001	0.062
N (%) of patients with at least a 50% reduction in heartburn severity (AUC) or the complete prevention of heartburn	105 (53%)	117 (57%)	131 (66%)	0.395	0.007	0.077
N (%) of patients with mean heartburn severity scores (VAS) of 17 mm or less or the complete prevention of heartburn	108 (54%)	119 (58%)	133 (67%)	0.438	0.008	0.054

* P-values were calculated using the Mantel-Haenszel test; Patients who used maalox during the Treatment Meal were classified as failures
Reference: Adapted from Volume 41, Pages 8-014408-14410, Table 13, 14, and 15

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Table 34: Three, Agency-derived, pre-specified, co-primary, efficacy endpoints in Study 3018

Agency-Derived Efficacy Endpoint	Placebo	Z 75	Z 150	p-value* Z 75 versus placebo	p-value* Z 150 versus placebo	p-value* Z 150 versus Z 75
Number of Patients	306	309	306			
N (%) of patients with a reduction in heartburn severity (AUC) by at least a 45 mm•hours or the complete prevention of heartburn	196 (64%)	192 (62%)	198 (65%)	0.476	0.816	0.486
N (%) of patients with at least a 50% reduction in heartburn severity (AUC) or the complete prevention of heartburn	145 (47%)	165 (53%)	173 (57%)	0.202	0.016	0.455
N (%) of patients with mean heartburn severity scores (VAS) of 17 mm or less or the complete prevention of heartburn	148 (48%)	175 (57%)	176 (58%)	0.039	0.017	0.801

* P-values were calculated using the Mantel-Haenszel test
Reference: Adapted from Volume 50, Pages 8-017670-17672, Table 12, 13, and 14

Medical Reviewer's Comments: In **two** prevention studies (3016 and 4006), the Z 150 groups achieved statistical success, in comparison to the placebo groups, in the Agency-derived endpoint #1 (a 40 mm•hours or more decrease in heartburn severity from the Run-In to the Treatment Meal Visits or the complete prevention of heartburn). In **all three** prevention studies, the Z 150 groups achieved statistical success, in comparison to the placebo groups, in the Agency-derived endpoint #2 (a 50% decrease or more in heartburn severity from the Run-In to the Treatment Meal Visits or the complete prevention of heartburn) and the Agency-derived endpoint #3 (mean heartburn severity scores of 17 mm or less or the complete prevention of heartburn).

The Z 150 groups achieved statistically success over the placebo groups in 8 out of 9 Agency-derived prevention endpoints (3 Agency-derived endpoints in 3 prevention studies). In contrast, the Z 75 groups achieved statistically success over the placebo groups in 4 out of 9 Agency-derived prevention endpoints (3 Agency-derived endpoints in 3 prevention studies).

In the three prevention trials, the Z 150 groups was numerically better than the Z 75 groups in 8 out of 9 Agency-derived prevention endpoints (3 Agency-derived endpoints in 3 prevention studies).

Clinically-important secondary efficacy endpoint: A very clinically-important pre-specified secondary efficacy endpoint was the complete prevention of heartburn following a provocative meal and drink (see Tables 35, 36, and 37 for these efficacy results in 3016, 4006, and 3018, respectively).

Table 35: Complete prevention of heartburn in Study 3016

	Placebo	Z 75	Z 150	p-value[a] Z 75 versus placebo	p-value[a] Z 150 versus placebo	p-value[a] Z 150 versus Z 75
Run-In Meal						
Number of patients*	304	296	305			
Complete prevention				0.386	N/A	0.480
Yes	0 (0%)	1 (<1%)	0 (0%)			
No	304 (100%)	295 (>99%)	305 (100%)			
Treatment Meal						
Number of patients*	283	262	283			
Complete prevention				0.272	0.683	0.580
Yes	11 (4%)	13 (5%)	12 (4%)			
No	272 (96%)	271 (96%)	271 (96%)			

[a] p-values were calculated by a Wilcoxon rank-sum test; * Only patients who reported having no heartburn symptoms at the start of the meal were included in this analysis
Reference: Adapted from Volume 33, Page 8-011778, Table 18

Table 36: Complete prevention of heartburn in Study 4006

	Placebo	Z 75	Z 150	p-value[a] Z 75 versus placebo	p-value[a] Z 150 versus placebo	p-value[a] Z 150 versus Z 75
Run-In Meal						
Number of patients*	187	192	182			
Complete prevention				0.328	N/A	0.317
Yes	0 (0%)	1 (<1%)	0 (0%)			
No	187 (100%)	191 (>99%)	182 (100%)			
Treatment Meal						
Number of patients*	188	177	181			
Complete prevention				0.701	0.971	0.704
Yes	15 (8%)	16 (9%)	15 (8%)			
No	173 (92%)	161 (93%)	166 (92%)			

[a] p-values were calculated by a Wilcoxon rank-sum test; * Only patients who reported having no heartburn symptoms at the start of the meal were included in this analysis
Reference: Adapted from Volume 41, Page 8-014413, Table 18

Table 37: Complete prevention of heartburn in Study 3018

	Placebo	Z 75	Z 150	p-value[a] Z 75 versus placebo	p-value[a] Z 150 versus placebo	p-value[a] Z 150 versus Z 75
Run-In Meal						
Number of patients*	284	287	300			
Complete prevention				N/A	N/A	N/A
Yes	0 (0%)	0 (0%)	0 (0%)			
No	284 (100%)	287 (100%)	300 (100%)			
Treatment Meal						
Number of patients*	270	275	277			
Complete prevention				0.631	0.328	0.519
Yes	20 (7%)	24 (9%)	28 (10%)			
No	250 (93%)	251 (91%)	249 (90%)			

[a] p-values were calculated by a Wilcoxon rank-sum test; * Only patients who reported having no heartburn symptoms at the start of the meal were included in this analysis
Reference: Adapted from Volume 50, Page 8-017675, Table 17

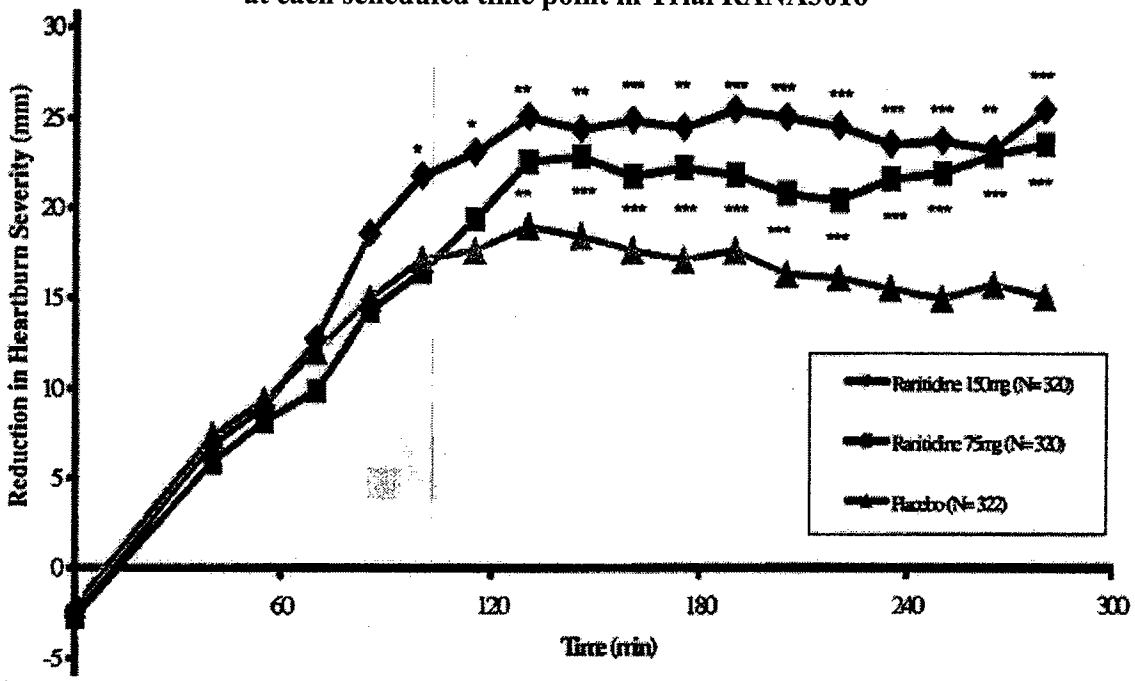
During the Treatment Meal, the proportions of patients who had complete prevention of heartburn from the placebo groups were 4%, 8%, and 7% in 3016, 4006, and 3018, respectively. Whereas during the Run-In Meal, the proportions of patients who had complete prevention of heartburn from the placebo groups were 0%, 0%, and 0% in 3016, 4006, and 3018, respectively.

The proportions of patients who had complete prevention of heartburn from Z 150 were 4%, 8%, and 10% in 3016, 4006, and 3018, respectively. These proportions are not numerically or statistically different than the placebo treatments.

Medical Reviewer's Comments: This medical officer recommends that the label

Important secondary efficacy endpoints: Important secondary endpoints in the prevention trials are the reduction of heartburn severity at each time point during the 4 hour and 40 minute, post-dosing evaluation period (see Figures 1, 2, and 3 for 3016, 4006, and 3018, respectively). These endpoints can elucidate the time after dosing when Z 150 reduces heartburn severity compared to placebo (if applicable).

Figure 1: Reduction in heartburn severity at Treatment Meal, compared to the Run-In Meal, at each scheduled time point in Trial RANA3016



* $p \leq 0.05$ versus placebo; ** $p \leq 0.01$ versus placebo; and *** $p \leq 0.001$ versus placebo
Reference: ISE, Volume 1, Page 3-0110, Figure 2

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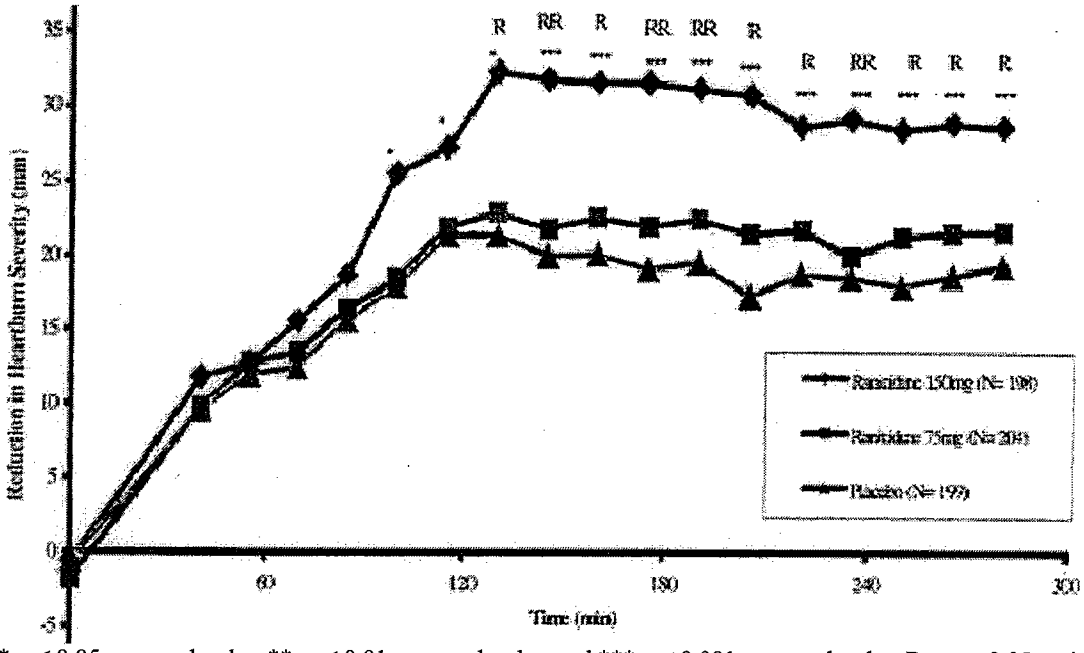
Figure 2: Reduction in heartburn severity at Treatment Meal, compared to the Run-In Meal, at each scheduled time point in Trial RANA4006



* $p \leq 0.05$ versus placebo; ** $p \leq 0.01$ versus placebo; and *** $p \leq 0.001$ versus placebo; R = $p \leq 0.05$ ranitidine 150 mg versus ranitidine 75 mg; RR = $p \leq 0.01$ ranitidine 150 mg versus ranitidine 75 mg
Reference: ISE, Volume 1, Page 3-0114, Figure 3

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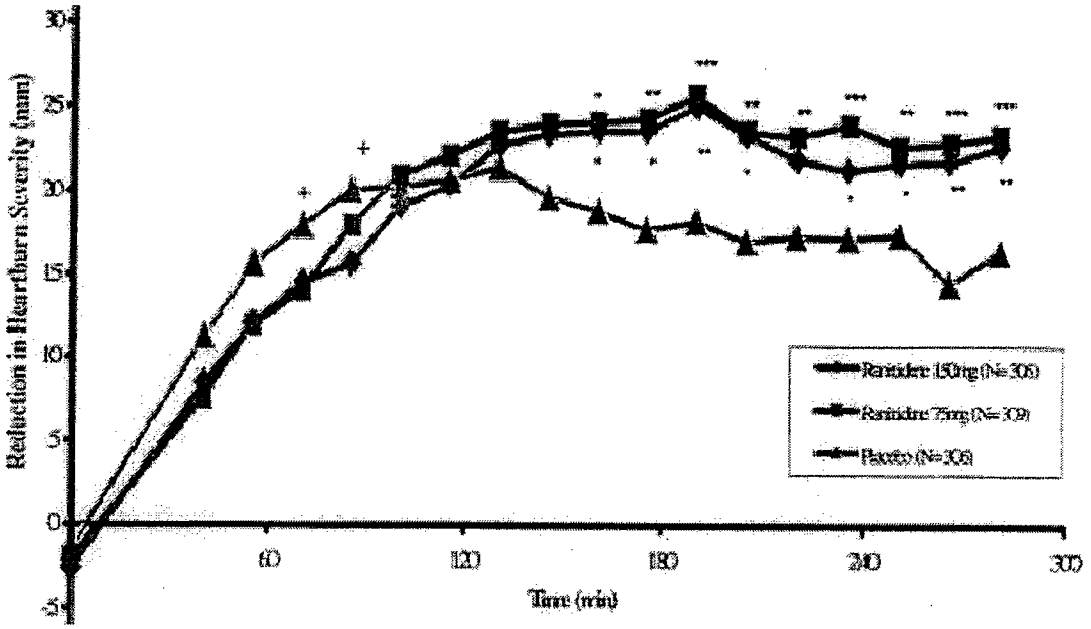
Figure 2: Reduction in heartburn severity at Treatment Meal, compared to the Run-In Meal, at each scheduled time point in Trial RANA4006



* $p \leq 0.05$ versus placebo; ** $p \leq 0.01$ versus placebo; and *** $p \leq 0.001$ versus placebo;
+ $p \leq 0.05$ placebo versus ranitidine 150 mg
Reference: ISE, Volume 1, Page 3-0118, Figure 4

In 3016 and 4006, Z 150 began to demonstrate greater effectiveness over placebo in the reduction of heartburn starting at 100 minutes after dosing (60 minutes after the 40 minute meal period) until 280 minutes after dosing (4 hours after the 40 minute meal period). In 3018, Z 150 began to demonstrate greater effectiveness over placebo starting at 145 minutes after dosing until 280 minutes after dosing; however, between the 12th 15 minute interval (between 205 to 220 minutes post-dosing), Z 150 was not more effective than placebo. Furthermore, in 3018, the placebo demonstrated greater efficacy compared to Z 150 between 55 minutes to 85 minutes after dosing.

In 3016 and 3018, Z 75 began to demonstrate greater effectiveness over placebo in the reduction of heartburn starting at 130 minutes and 145 minutes post-dosing, respectively, until 280 minutes after dosing. In 4006, Z 75 failed to demonstrate efficacy over placebo at all time points after dosing.

In 4006, Z 150 began to demonstrate greater effectiveness over Z 75 in the reduction of heartburn starting at 130 minutes after dosing until 280 minutes after dosing.

Medical Reviewer's Comments: This medical officer recommends that the label ——

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6.2.5 Clinical Microbiology

There have been no clinical microbiology issues with this application.

6.2.6 Efficacy Conclusions - Prevention

This medical officer supports the efficacy of approval of Zantac 150 (Ranitidine 150 mg Tablets) for the over-the-counter prevention of heartburn — — in adults and pediatric patients over 12 years old. In the three prevention trials, Zantac 150 was statistically better than Zantac 75 in 5 out of the 12 important efficacy endpoints (the one primary endpoint and the three Agency-derived endpoints in each of the three prevention trials). In 5 of the 7 efficacy endpoints (in which Zantac 150 failed to demonstrate statistical significance), Zantac 150 was numerically better than Zantac 75. Additionally, Zantac 150 demonstrated statistical improvement over placebo (100 minutes after dosing) in the reduction of heartburn severity **earlier** than Zantac 75's improvement over placebo (130 minutes after dosing) in two of the three prevention trials (3016 and 4006). Therefore, Zantac 150 demonstrated statistical improvement over Zantac 75 in decreasing overall heartburn severity during the four hour evaluation period and demonstrated statistical improvement over Zantac 75 in the time to decrease heartburn severity.

Limitations of the prevention trial results include the inability of Zantac 150 to demonstrate the following:

1) Absolutely prevent heartburn prior to a provocative meal and/or beverage
2) Reduce the severity of heartburn during the first 85 minutes after dosing

7 INTEGRATED REVIEW OF SAFETY

Please see the July 2004 review of Dr. Linda Hu for the integrated review of safety of Z 150.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

This medical officer recommends a ranitidine dose of 150 mg once or twice a day as needed for up to 14 days for the OTC treatment of episodic heartburn in adults and pediatric patients over 12 years old. If patients — — then they should talk to their doctor. These patients may have a more serious disease such as non-erosive GERD or EE. Non-erosive GERD and EE patients require 150 mg of ranitidine BID for 4 to 8 weeks and 150 mg of ranitidine QID for 8 to 12 weeks, respectively.

This medical officer recommends a preventive ranitidine dose of 150 mg once or twice a day for up to 14 days in adults and pediatric patients over 12 years old. The label

Medical Reviewer's Comments: The recommended adult ranitidine dose for the treatment of episodic heartburn is 150 mg per episode — the maximum daily dose is 150 mg for two heartburn episodes for a total of 300 mg per day. Since the recommended ranitidine dose in the treatment of GERD (non-erosive GERD and EE) in adults is higher and for a longer duration than the recommended ranitidine dose in the treatment of episodic heartburn in adults; I recommend

8.2 Drug-Drug Interactions

Please see Dr. Linda Hu's review for the recommended drug-drug interactions in the OTC label.

8.3 Special Populations

Age: In the two treatment trials (3013 and 3014), patients under age 65 in the Z 150 group (n=648) had greater efficacy than patients under 65 in the placebo group (n=636) in all five of the important efficacy endpoints (the one primary endpoint and four of the Agency-derived endpoints).

Medical Reviewer's Comments: To help elucidate the efficacy of Z 150 in geriatric patients in the two treatment trials, this medical officer analyzed the pre-specified primary endpoint and three additional important efficacy endpoints that included more information from all the severe or very severe heartburn episodes over the two week treatment period rather than limited results from one (the first) severe or very severe heartburn episode. The three additional important endpoints were the mean TOTPAR score for **all** severe or very severe heartburn episodes, the mean proportion of patients with complete relief of **all** the heartburn episodes at two hours post-treatment (Agency-derived efficacy endpoint #3), and the mean proportion of patients with almost complete or complete relief of **all** the heartburn episodes at two hours post-treatment (Agency-derived efficacy endpoint #4).

Geriatric patients in the Z 150 group (n=29) did not demonstrate statistical improvement over geriatric patients in the placebo group (n=35) in these four important endpoints in the two treatment trials. However, geriatric patients in the Z 150 group demonstrated numerical improvement over geriatric patients in the placebo group in three of those four important efficacy endpoints (the pre-specified primary endpoint, the mean TOTPAR score for all severe or very severe heartburn episodes, and the Agency-derived efficacy endpoint #3). In contrast, the placebo group demonstrated numerical — not statistical — improvement over the Z 150

group in geriatric patients in one of the four important efficacy endpoints (the Agency-derived efficacy endpoint #4). Please see Table 38.

Table 38: Four important efficacy endpoints for geriatric patients in Studies 3013 and 3014

Efficacy Endpoint	Placebo (n=35)	Z 75 (n=28)	Z 150 (n=29)	p-value Z 150 v. placebo
Mean TOTPAR* scores for the first severe or very severe heartburn episode (the pre-specified primary endpoint)	**21.1**	**24.4**	**23.6**	**0.366[A]**
Mean TOTPAR* scores for all severe or very severe heartburn episodes; total pain relief scale is from 0 to 48 (an important pre-specified secondary endpoint)	**22.4**	**25.1**	**23.5**	**0.234[B]**
The mean proportion of patients with complete relief of all the heartburn episodes at two hours post-treatment (Agency-derived efficacy endpoint #3)	**35.2%**	**38.7%**	**35.9%**	**0.224[A]**
The mean proportion of patients with (at least) almost complete relief of all the heartburn episodes at two hours post-treatment (Agency-derived efficacy endpoint #4)	**53.6%**	**58.5%**	**45.7%**	**0.036[A]**

The data in this data represents pooled information from Studies 3013 and 3014.
*TOTPAR is the total heartburn pain relief from 0 to 48 (0 represents no relief at all 8 time intervals and 48 represents complete relief at all 8 time intervals)
[A] p-values were calculated using Wilcoxon Rank Sum test stratified by investigator
[B] p-values were calculated using Generalized Estimating Equations
Reference: Adapted from ISE, Volume 57, Page 8-020206 (Table C. 26), Page 8-020214 (Table C. 30), Page 8-020314 (Table C. 80), and Page 8-020324 (Table C. 85)

Medical Reviewer's Comments: The pooled treatment trials included more than 600 patients in each treatment group; whereas, the geriatric subpopulation included less than 36 patients in each treatment group. Potentially the modest total number of geriatric patients (N=92) in the treatment trials lowered the power of the geriatric efficacy analysis. Therefore, it is difficult to make an conclusion regarding the efficacy of Z 150 in the geriatric subpopulation in the treatment of heartburn. However, Z 150 did demonstrate numerical improvement over placebo in geriatric patients in three out of the four important efficacy endpoints.

In two of the prevention trials (3016 and 4006), patients under age 65 in the Z 150 group (n=484) had greater efficacy than patients under 65 in the placebo group (n=487) in all four of the important efficacy endpoints (the one primary endpoint and the three Agency-derived endpoints). Geriatric patients in the Z 150 group (n=34) had greater efficacy than geriatric patients in the placebo group (n=34) in three of the four of the important efficacy endpoints and approached statistically-significant efficacy in the remaining efficacy endpoint in the two

prevention trials. Therefore, geriatric patients (compared to patients under 65 years old) had similar efficacy in the prevention of heartburn prior to a provocative meal and beverage.

Gender: In the two treatment trials, men in the Z 150 group (n=362) had greater efficacy than men in the placebo group (n=353) in four out of five important efficacy endpoints (the one primary endpoint and four of the Agency-derived endpoints). Women in the Z 150 group (n=315) had greater efficacy than women in the placebo group (n=318) in four out of five important efficacy endpoints in the two treatment trials. Therefore, men and women had similar efficacy in the treatment of episodic heartburn.

In two of the prevention trials (3016 and 4006), men in the Z 150 group (n=191) had greater efficacy than men in the placebo group (n=208) in three of the four important efficacy endpoints (the one primary endpoint and the three Agency-derived endpoints). Women in the Z 150 group (n=327) had greater efficacy than women in the placebo group (n=313) in all four of the important efficacy endpoints in the two prevention trials. Therefore, no gender differences existed in the effectiveness of Z 150 in the prevention of heartburn prior to a provocative meal and beverage.

Race: In the two treatment trials, Caucasians patients in the Z 150 group (n=569) had greater efficacy than Caucasians patients in the placebo group (n=554) in all five important efficacy endpoints (the one primary endpoint and four of the Agency-derived endpoints).

In the two treatment trials, Non-Caucasians (mostly Black patients with some Latinos) in the Z 150 group (n=108) demonstrated numerical improvement over non-Caucasians in the placebo group (n=117) in the primary endpoint (TOTPAR in the first severe or very severe heartburn episode). In the two treatment trials, Non-Caucasians in the Z 150 group demonstrated numerical — and approached statistical — improvement over non-Caucasians in the placebo group for the important secondary efficacy endpoint (the mean TOTPAR score in all the severe or very severe heartburn episodes; see Table 39).

Table 39: For non-Caucasians, the TOTPAR scores for all heartburn episodes in Studies 3013 and 3014

	Placebo (N=117)	Ranitidine 75mg (N=130)	Ranitidine 150mg (N=108)
TOTPAR Score over 2 hours [1]			
Number of Episodes	2009	2091	1770
Mean (SE)	17.4 (0.27)	20.4 (0.23)	20.4 (0.28)
Median	16.0	21.0	20.0
Min-Max	0-48	0-48	0-48
Comparison with Ranitidine 75mg [2]			0.441
Comparison with Placebo [2]		0.223	0.064

TOTPAR is the total heartburn pain relief from 0 to 48; Only severe or very severe heartburn episodes are included in this table; p-values were calculated using Generalized Estimating Equations; The data in this data represents pooled information from Studies 3013 and 3014. Reference: Adapted from ISE, Volume 57, Page 8-020218, Table C. 32

Additionally, in the two treatment trials, Non-Caucasians in the Z 150 group demonstrated numerical improvement over Non-Caucasians in the placebo group for the Agency-derived efficacy endpoint #4 (the proportion of patients with almost complete or complete relief of all the heartburn episodes at two hours post-treatment; see Table 40).

Table 40: The proportion of non-Caucasians with (at least) almost complete relief of all the heartburn episodes at two hours post-treatment, the in Studies 3013 and 3014

	Placebo (N=117)	Ranitidine 75mg (N=130)	Ranitidine 150mg (N=108)
Number of Subjects with a Severe or Very Severe Episode	113	122	108
Percent of Severe or Very Severe Episodes with Complete or Almost Complete Relief within 2 Hours			
N	113	122	108
Mean (SE)	33.8 (3.46)	43.0 (3.41)	44.5 (3.95)
Median	18.8	41.4	34.8
Min-Max	0-100	0-100	0-100
Comparison with Ranitidine 75mg [1]			0.425
Comparison with Placebo [1]		0.239	0.186

p-values were calculated using Wilcoxon Rank Sum test stratified by investigator; The data in this data represents pooled information from Studies 3013 and 3014.
Reference: Adapted from ISE, Volume 57, Page 8-020328, Table C. 87

Medical Reviewer's Comments: Potentially the small number of Non-Caucasians in the treatment trials (the lack of power) influenced these results. If there were more Non-Caucasians in the treatment trials, conceivably the efficacy of the Z 150 groups would demonstrate statistical improvement over the placebo groups.

In Non-Caucasians, the Z 150 groups did demonstrate numerical improvement over the placebo groups for several important efficacy endpoints. Therefore, the efficacy results of Z 150 in Non-Caucasians in the over-the-counter treatment of episodic heartburn are acceptable.

In two of the prevention trials (3016 and 4006), Caucasians in the Z 150 group (n=380) had greater efficacy than Caucasians in the placebo group (n=375) in all of the four important efficacy endpoints (the one primary endpoint and the three Agency-derived endpoints). Non-Caucasians in the Z 150 group (n=138) had greater efficacy than non-Caucasians in the placebo group (n=146) in three out of the four important efficacy endpoints in the two prevention trials. Therefore, no race differences existed in the effectiveness of Z 150 in the prevention of heartburn prior to a provocative meal and beverage.

Renal Insufficiency: Please see Dr. Linda Hu's excellent comments regarding dose adjustment in patients with chronic renal insufficiency. The treatment and prevention studies did not perform laboratory tests; therefore, efficacy of the treatments in patients with renal insufficiency could not be assessed.

Hepatic Insufficiency: Please see Dr. Linda Hu's excellent comments regarding patients with hepatic insufficiency. The treatment and prevention studies did not perform laboratory tests;

therefore, efficacy of the treatments in patients with hepatic insufficiency could not be assessed.

Pregnancy: Please see Dr. Linda Hu's excellent comments regarding the use of Z 150 in pregnant patients.

8.4 Pediatrics

In 1999 after GSK (formerly Glaxo Wellcome) submitted pharmacokinetic (PK) and safety information regarding prescription Zantac® in pediatric patients over the age of one month (adolescents, children, and infants), all the Zantac® formulations (at that time) were granted six months of pediatric exclusivity. The safety and efficacy of Zantac in pediatric patients over one month was supported by adequate and well-controlled trials in adult patients and PK and safety information in pediatric patients with several acid-related conditions (including duodenal and gastric ulcers, GERD, and EE). Safety and effectiveness in pediatric patients have not been established for the treatment of pathological hypersecretory conditions and the maintenance of healing of EE.

The five trials in this submission excluded patients under 18 years old. However, the approval of medications in pediatric patients can be based on adequate and well-controlled trials in adults and supportive PK and safety information in pediatric patients. Given that adequate PK and safety information exists in pediatric patients with frequent and severe heartburn (GERD patients), it is reasonable to extrapolate this information to a less serious population of episodic heartburn outpatients. According to the Boys and Girls Height/Weight Charts from the National Center for Health Statistics, 95% of 12 year olds are over 30 kilograms (66 pounds). The recommended prescription Zantac dose in pediatric patients with non-erosive GERD and EE is 5-10 mg/kg/day. Therefore, about 95% of 12 year olds will be able to take the maximum recommended Zantac dose for adults (up to 150 mg BID).

Therefore, this medical officer recommends the approval of Z 150 in the treatment and prevention of heartburn in pediatric patients from 12 to 18 years old. Furthermore, I recommend a full waiver be given to the sponsor regarding the need for pediatric studies in all age groups.

8.5 Advisory Committee Meeting

No advisory committee meetings were held for this NDA.

8.6 Literature Review

Please see Dr. Linda Hu's excellent literature review regarding the safety of Z 150.

8.7 Postmarketing Risk Management Plan

This medical officer recommends no post-marketing risk management plan for these OTC indications.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

This medical officer recommends the **approval** of Zantac 150™ (Ranitidine 150 mg Tablets) for the over-the-counter treatment of episodic heartburn in adults and pediatric patients over 12 years old. In two large, adequate, and well-controlled treatment trials, Zantac 150, in comparison to the placebo, demonstrated statistical improvement in four of the five important efficacy endpoints (the one pre-specified primary efficacy endpoint and the first four Agency-derived endpoints). In addition, Zantac 150 demonstrated numerical improvement over Zantac 75 in four of those five efficacy endpoints.

Zantac 150 demonstrated a reasonable safety profile in the treatment trials and a literature review by Dr. Linda Hu.

Limitations of the treatment trial results include the inability of Zantac 150 to demonstrate the following:

1) The complete resolution of episodic heartburn in more than a third of the Zantac 150 treated patients
2) Unequivocal superior efficacy over Zantac 75

This medical officer recommends the approval of Zantac 150™ (Ranitidine 150 mg Tablets) for the over-the-counter prevention of heartburn [redacted] in adults and pediatric patients over 12 years old. In the three prevention trials, Zantac 150 was statistically better than Zantac 75 in 5 out of the 12 important efficacy endpoints (the one primary endpoint and the three Agency-derived endpoints in each of the three prevention trials). Zantac 150 was numerically better than Zantac 75 in 11 out of those 12 important efficacy endpoints. Additionally, Zantac 150 demonstrated statistical improvement over placebo (100 minutes after dosing) in the reduction of heartburn severity earlier than Zantac 75's improvement over placebo (130 minutes after dosing) in two of the three prevention trials (Studies RANA3016 and RANA4006). Therefore, Zantac 150 demonstrated statistical improvement over Zantac 75 in decreasing overall heartburn severity during the four hour evaluation period and demonstrated statistical improvement over Zantac 75 in the time decrease heartburn severity. Furthermore, according to Dr. Hu's safety review, Zantac 150 demonstrated a reasonable safety profile.

Limitations of the prevention trial results include the inability of Zantac 150 to demonstrate the following:

1) Completely prevent heartburn prior to a provocative meal and/or beverage
2) Reduce the severity of heartburn during the first 85 minutes after dosing

9.2 Recommendation on Regulatory Action

From a clinical efficacy perspective, this medical officer recommends the approval of OTC Zantac 150™ (Ranitidine 150 mg Tablets) for the over- the-counter treatment of episodic heartburn and the OTC prevention of heartburn [redacted] in adults and pediatric patients over 12 years old.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

From a clinical perspective, this medical officer does not recommend risk management steps for Zantac 150 in the OTC treatment of episodic heartburn and the OTC prevention of heartburn [redacted]

9.3.2 Required Phase 4 Commitments

From a clinical perspective, this medical officer does not recommend phase 4 studies for Zantac 150 in the OTC treatment of episodic heartburn and the OTC prevention of heartburn [redacted]

9.3.3 Other Phase 4 Requests

From a clinical perspective, this medical officer does not recommend additional phase 4 studies for Zantac 150 in the OTC treatment of episodic heartburn and the OTC prevention of heartburn [redacted]

9.4 Labeling Review

The major changes needed in the labeling include the following:

9.5 Comments to Applicant

This medical officer supports the approval of over-the-counter Zantac 150 (Ranitidine 150 mg Tablets) for the treatment of episodic heartburn and for the prevention of heartburn in adults and pediatric patients over 12 years old.

In the treatment trials, a limited number of geriatric patients were enrolled. Limitations of the treatment trial results include the inability of Zantac 150 to demonstrate the following:

1) The complete resolution of episodic heartburn in more than a third of the Zantac 150 treated patients
2) Unequivocal superior efficacy over Zantac 75

Limitations of the prevention trial results include the inability of Zantac 150 to demonstrate the following:

1) Completely prevent heartburn prior to a provocative meal and/or beverage
2) Reduce the severity of heartburn during the first 85 minutes after dosing

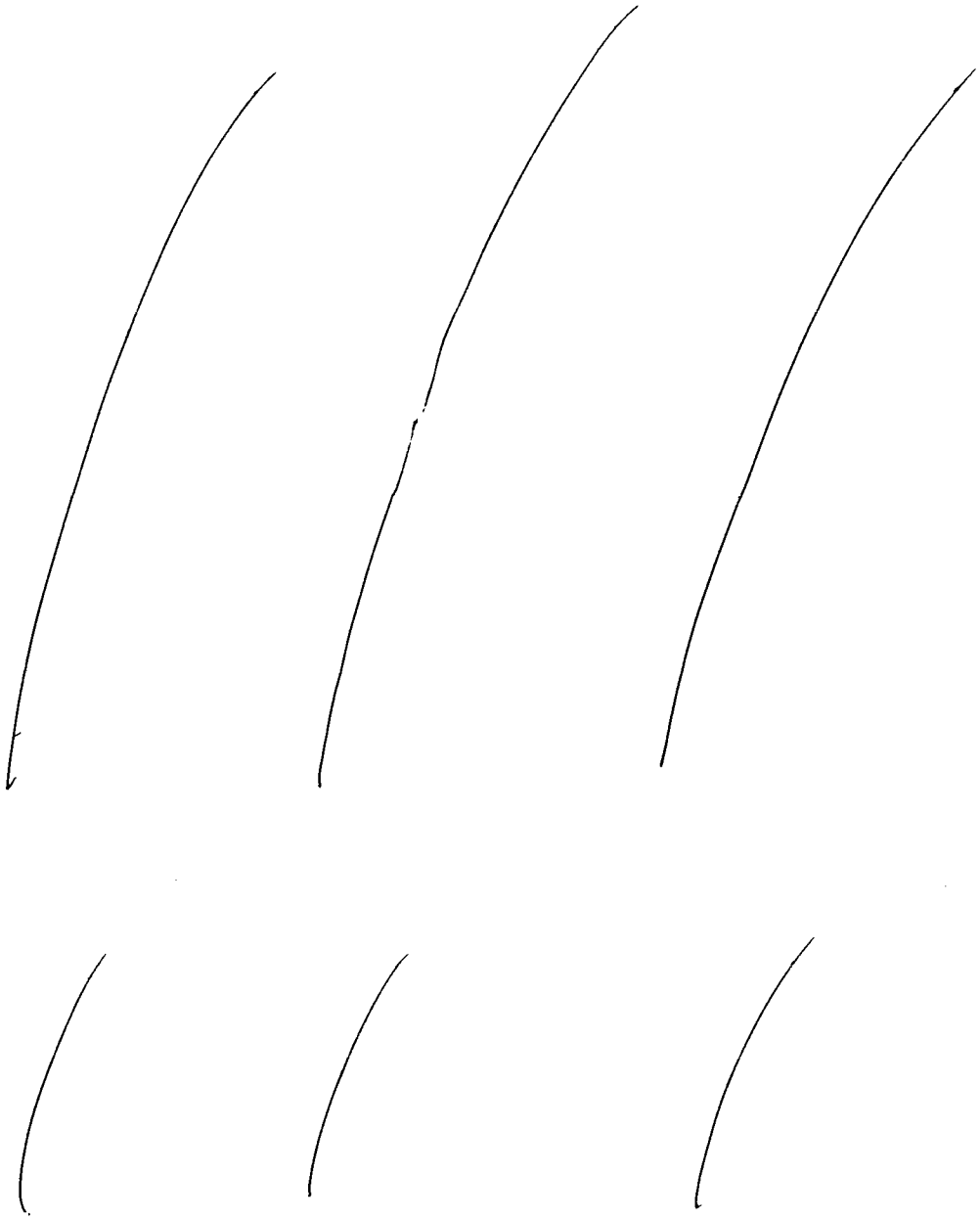
Additionally, this medical officer has important revisions to the sponsor's proposed labeling (see the Labeling Review Section).

10 APPENDICES

10.1 Review of Individual Study Reports

The full reports of all the treatment studies (3013 and 3014) and all the prevention studies (3016, 4006, and 3018) are detailed in sections 6.1 and 6.2, respectively, of this review.

10.2 Line-by-Line Labeling Review

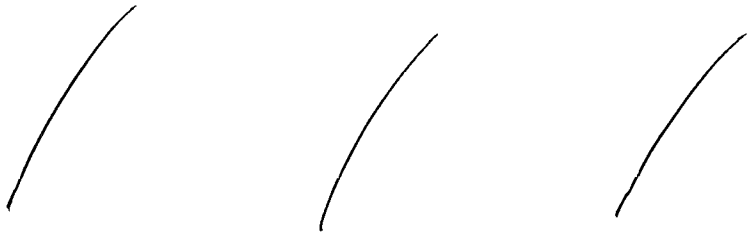


7 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process



10.3 Abbreviations

Please see Table 41 for a list of abbreviations used in this review.

Table 41: List of abbreviations

3013	Trial RANA3013
3014	Trial RANA3014
3016	Trial RANA3016
3018	Trial RANA3018
4006	Trial RANA4006
AEs	adverse drug events
AGIDA	Abdominal Gastric Index of Digestive Annoyances
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BID	two times a day
BMI	body mass index
C_{max}	maximum observed plasma concentration
CYP	cytochrome
DGICDP	Division of Gastrointestinal and Coagulation Drug Products
DOTCDP	Division of Over-The-Counter Drug Products
EE	Erosive esophagitis
EGD	esophagogastroduodenal endoscopic examination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	Gastro-esophageal reflux disease
GSK	GlaxoSmithKline
H_2RAs	histamine-2 receptor antagonists
lbs	pounds
ICH	International Conference on Harmonisation
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety

ITT	Intent-to-treat
LOCF	Last Observation Carried Forward
mg	Milligram
mL	Milliliter
mL•Hr	Millimeters times hours
mm	Millimeters
ng	Nanogram
NSAID	Non-steroidal anti-inflammatory drugs
OTC	Over-the-counter
PD	Pharmacodynamic
Pfizer	Pfizer Inc.
pg/mL	Picograms per milliliter
PK	Pharmacokinetic
PPI	Proton pump inhibitor
q d	Once daily
SAE	Serious adverse event
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
The Division	Division of Gastrointestinal and Coagulation Drug Products
T_{max},	Time to reach the observed maximum plasma concentration
TOTPAR	Total (heartburn) pain relief
VAS	Visual Analog Scale
Z 150	Zantac 150 mg Over-The-Counter (OTC)
Z 75	Zantac 75 mg Over-The-Counter (OTC)

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/s/

Eric Brodsky
8/13/04 03:14:25 PM
MEDICAL OFFICER

Ruyi He
8/13/04 03:47:20 PM
MEDICAL OFFICER
I concur with Dr. Brodsky's evaluation and recommendations. The data submitted in NDA 21,698 support the efficacy results for the proposed indications, the OTC treatment of episodic heartburn and the OTC prevention of heartburn before a provocative meal.

Zantac 150 mg Tablet
OTC Switch

NDA 21-698

Medical Safety Review

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Ranitidine 150 mg tablets have a very good safety record based on extensive post-marketing experience (since 1983 for the US in prescription form and since 1996 for ranitidine 75 mg). OTC approval of the 150 mg tablets would double the available OTC ranitidine dosage, to a total daily dose (TDD) of 300 mg. Review of post-marketing data showed higher reporting rates of serious and fatal AEs for 150 mg tablets than for 75 mg tablets, but the difference may be due to differences between prescription and OTC user populations. A literature report of a large epidemiological study, which used a database including medical records of up to 4 million subjects followed for more than a decade, showed that there is a small added risk of neutropenia with ranitidine at TDD ≥300 mg than at TDD 150 mg (the current OTC dose). The reporting rates of serious and fatal reactions involving ranitidine did not change notably following the OTC switch of ranitidine 75 mg.

Available data are supportive of approval given clear evidence of clinical efficacy superior to ranitidine 75 mg for the heartburn relief and prevention indications, and given sponsor agreement to

B. Recommendation on Phase 4 Studies and/or Risk Management Steps If Approvable

Information reviewed for this application support

This reviewer agrees with the sponsor's proposed kidney disease warning.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The clinical program for this application consisted of the following trials:

- Two treatment trials RANA3013 and RANA3014 to treat severe or very severe heartburn up to twice daily for up to 14 days.
- Three prevention trials RANA3016, RANA3018, RANA4006 where subjects consumed provocative meals and adverse events occurring within 24 hours of eating were recorded in a diary.

B. Efficacy

Please refer to review by HFD-180 by Dr. Eric Brodsky.

C. Safety

The following adverse events have been reported for patients treated with Zantac (see http://www.fda.gov/cder/foi/label/2001/20251s10lbl.pdf). The relationship to therapy with Zantac has been unclear in many cases.

Central Nervous System: Headache, sometimes severe. Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision and reversible involuntary motor disturbances have been reported.

Cardiovascular: Rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: Occasional reports of hepatocellular, cholestatic, or mixed hepatitis, with or without jaundice. These events are usually reversible, but in rare circumstances death has occurred. Rare cases of hepatic failure have also been reported.

Musculoskeletal: Rare reports of arthralgias and myalgias.

Hematologic: Rare blood count changes (leukopenia, granulocytopenia, and thrombocytopenia). These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and acquired immune hemolytic anemia have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence,

and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases of erythema multiforme. Rare cases of alopecia and vasculitis.

Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

The present reviewer notes that the following rare adverse events were retrieved from the literature and/or post-marketing surveillance reports, but are not listed in the prescription labeling information for famotidine:

interstitial nephritis, aseptic meningitis, rhabdomyolysis, carcinoid tumor

This information will be shared with HFD-180 for further consideration.

D. Dosing

The proposed OTC dosing is as follows. To relieve symptoms of heartburn, take 150 mg, up to twice a day, with a glass of water. To prevent symptoms of heartburn, take 150 mg [redacted]. In either case, do not take more than 300 mg in 24 hours. The product can be used up to 14 days before a physician needs to be consulted.

E. Special Populations

Ranitidine is pregnancy category B. As for OTC ranitidine 75 mg, the proposed labeling for ranitidine 150 mg will direct lactating or pregnant women to ask a doctor before use.

The sponsor proposes to include a label warning "Do not use if you have kidney disease, except under the advice and supervision of your doctor."

Since ranitidine is known to be substantially excreted by the kidney, the labeling for prescription ranitidine 150 mg recommends a dose reduction for patients with impaired renal function. The direction is for the dose to be limited to 150 mg/day for patients with creatinine clearance <50 mL/min. The sponsor proposed to include a label warning for OTC ranitidine 150 mg, saying do not use "if you have kidney disease" except under the advice and supervision of a doctor. The issue is that many consumers who should reduce their dose of ranitidine because of their low GFR may not have a formal diagnosis of kidney disease or may not be aware of their reduced renal function. A recent study (the Kidney Early Evaluation Program; Brown et al. 2003) in a high-risk community population found a prevalence >20% of low estimated GFR (Table 7) in subjects with specific risk factors (age, diabetes, and hypertension).

Clinical Review

I. Introduction and Background

This is a clinical review focused on the safety of ranitidine 150 mg b.i.d. for over-the-counter (OTC) use. The efficacy review is being done by Dr. Eric Brodsky (HFD-180).

A. Drug Name and Indications

This is an OTC switch application for ranitidine 150 mg (Zantac) to relieve heartburn and to prevent meal-induced heartburn

B. OTC Armamentarium

Other H2 blockers available OTC for these relief and prevention indications include cimetidine, famotidine, and nizatidine. Antacids are also available OTC for heartburn. A proton pump inhibitor (omeprazole) has been approved for OTC use to treat frequent heartburn.

C. Important Milestones in Product Development

Zantac (ranitidine hydrochloride) was originally approved by the FDA in June 1983. Glaxo was the original sponsor of ranitidine.

NDA 20-520 was approved on December 19, 1995, for the over-the-counter (OTC) use of Zantac (ranitidine hydrochloride) 75 mg tablets in the relief of episodic heartburn. Supplement 001 was approved June 8, 1998 for prevention of heartburn. Ownership of the Zantac 75 NDA was acquired by Pfizer Consumer Healthcare on January 1, 1999 along with marketing rights to OTC Zantac 75 in USA and Canada.

In October 2000, Pfizer Consumer Healthcare acquired the rights to Zantac (ranitidine hydrochloride) 150 mg tablets from GlaxoSmithKline (GSK). Reference is thereby made to NDA 18-703 maintained by GSK for prescription Zantac 150 mg.

On November 7, 2001, the FDA met with representatives of Pfizer to discuss issues related to the development plans for the over-the-counter use of Zantac 150 mg tablets for the prevention of heartburn. The indication discussed was for prevention only.

On July 17, 2003, the Sponsor met with the Agency to obtain further guidance concerning the Pre-NDA development plans for OTC switch of Zantac 150 mg tablets.

The Agency stated that evidence of a dose response for prevention and treatment of heartburn would be evaluated. For both the treatment and prevention claims, there should be some benefit of taking 150 mg compared to 75 mg.

D. Other Relevant Information

To date Zantac 150 mg has not been approved OTC in Canada. GSK maintains rights to OTC marketing of Zantac 150 mg in the rest of the world.

The Sponsor was asked to provide the following marketing information:

- Tables showing countries where ranitidine 75, 150, 300 mg tablets have been approved, when approved, whether Rx or OTC (distinguish behind the counter vs OTC as in the US), approved indications and labeled duration of use.
- Note if a marketing application was ever withdrawn for safety reasons.
- numbers of prescriptions by year and dose form, numbers of pills sold by year and dose (US and rest of world). Need OTC and prescription marketing data.

Pfizer Consumer Healthcare (PCH) responded that it was unable to provide a complete response (as of March 26, 2004) to this request because:

- PCH markets OTC Zantac 75 mg tablets in the USA and Canada.
- PCH has acquired from GlaxoSmithKline (GSK) the right to market OTC ranitidine 150 mg in the US and Canada, but does not have marketing rights for any ranitidine products outside the USA and Canada.
- Ranitidine 150 mg and 300 mg are currently marketed as prescription products in the US and Canada by GSK

There is a letter of authorization from GSK allowing FDA to reference NDA 18-703. PCH has requested a current list of marketing authorizations for ranitidine worldwide from GSK. However, no response from GSK has been received to date. PCH has never however withdrawn a marketing application for safety reasons in the USA and Canada. PCH has also requested this information from GSK for prescription ranitidine and to date has not received a response from GSK.

E. Important Issues with Pharmacologically Related Agents

The prescription labeling for cimetidine, ranitidine, nizatidine and famotidine (all of which are H2 blockers available OTC) includes directions to reduce the dosing schedule in patients with renal insufficiency. For ranitidine, nizatidine and famotidine, the direction is to adjust the dosage for patients with creatinine clearance <50 mL/min. For cimetidine, the dose should be reduced in patients with 'severely impaired renal function', no specific criterion defined.

A member of the H2 blocker family, oxmetidine, proved to be intrinsically hepatotoxic. Severe liver toxicity has been reported in association with use of two H2 blockers, ebrotidine and niperotidine, which are structurally related to ranitidine and famotidine, but differ in the composition of the side chain. Ebrotidine was withdrawn from marketing in Spain for safety reasons [Micromedex].

References

Andrade RJ, Lucena MI, Martin-Vivaldi R et al: Acute liver injury associated with the use of ebrotidine, a new H2- receptor antagonist. J Hepatol 1999; 31:641-646.

Devuyst O, Acute Cholestatic Hepatitis with Rash and Hperesoinophilia associated with Ranitidine Treatment.Acta Clinica Belgica 48.2 (1993); 109-114

Jimenez-Saenz M, Arguelles-Arias F, Herrerias-Gutierrez JM, Duran-Quintana JA: Acute cholestatic hepatitis in a child treated with famotidine. Am J Gastroenterol 2000;95(12):3665-6.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

See separate efficacy, statistical and chemistry reviews for this application. There were no new toxicology studies submitted with this application.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Data relating to pharmacokinetics and bioavailability of ranitidine were previously submitted in the original NDA

B. Pharmacodynamics

IV. Description of Clinical Data and Sources

A. Overall Data

The following data were used in this review. Safety results were evaluated from 5 clinical trials submitted with NDA (see next section). These were two treatment trials (RANA3013 and RANA3014) and three prevention trials (RANA3016, RANA3018, RANA4006). Worldwide safety surveillance review included

- spontaneous AE reports as compiled by GSK (for the period January, 1994 through March, 2002) and PCH (through September 12, 2003) for ranitidine 150 mg
- World Health Organization international drug monitoring database examined for cases associated with terms Zantac and ranitidine for 1993 through 2002. A total of 13,290 AE reports were received during the period examined.

- Toxic Exposure Surveillance System (TESS) of the American Association of Poison Control Ceners (AAPCC) from 1993 through 2002. There were 23,358 reports of Zantac exposures, of which 16,694 involved Zantac only.

Literature review for safety of ranitidine 150 mg covered the period 1993 through February, 2004 and included searches of MEDLINE, BIOSIS and EMBASE. A total of 801 citations were identified. Of the 801 citations, 645 were found to include reports of clinical experiences with ranitidine (animal toxicity reports were not reviewed) and to be available in full-text English editions.

B. Tables Listing the Clinical Trials

Figure 1 lists the studies that were submitted in this application. The five controlled studies enrolled a total number of 11817 subjects of whom 4504 were randomized into ranitidine 150 mg (1501 subjects), ranitidine 75 (1505 subjects) and placebo groups (1498 subjects), while the remaining 7313 subjects were entered into the nonrandomized population. The Figure also shows the numbers of subjects in each of the three randomized groups who did not complete the study (23 for ranitidine 150 mg, 21 for ranitidine 75 mg, and 27 for placebo). The numbers of subjects who discontinued because of AEs was low, only 2 each for the ranitidine 150 mg and placebo groups, and 3 for the ranitidine 75 mg group (see Table 1).

Two treatment trials RANA3013 and RANA3014 had a common protocol. Following a one week single-blind placebo run-in period, subjects were given double blind study drug and instructed to treat severe or very severe heartburn up to twice daily for up to 14 days. For these studies the safety evaluation consisted of the following. At each visit, the subject was asked two standard questions, and any medical problem elicited by these queries was considered an AE:

- Have you had any (other) medical problems since your last visit/assessment?
- Have you taken any new medicines, other than those given to you in this study, since your last visit/assessment?

The investigator then attempted to make a diagnosis based upon presenting signs and symptoms and reported any adverse events.

Three prevention trials RANA3016, RANA3018, RANA4006 were of similar design. At the Run-In meal visit, subjects consumed a provocative meal and a single blind placebo, after which they rated heartburn over the next 4 hours and 40 minutes. If they reported a sufficient degree of heartburn, they were qualified for randomization. At the Treatment Meal visit, subjects took a double blind study drug and consumed the same provocative meal as before. They were then discharged with a diary and instructed to record any adverse events within 24 hours.

All subjects who took the double blind study drug and who provided follow-up information were included in the safety database. All reported adverse events were recorded. Excluded from the safety analysis were adverse events reported as occurring before administration of the study drug.

Pooled RANA3013/RANA3014/RANA3016/RANA3018/RANA4006:
Summary of Subject Disposition

	Placebo	Total Ranitidine	Ranitidine 75mg	Ranitidine 150mg	Total Randomized
Entered	1498	3006	1505	1501	4504
Completed	1471 (98.2%)	2962 (98.5%)	1484 (98.6%)	1478 (98.5%)	4433 (98.4%)
Withdrawn	27 (1.8%)	44 (1.5%)	21 (1.4%)	23 (1.5%)	71 (1.6%)
Reason for Withdrawal					
Adverse event	2 (0.1%)	5 (0.2%)	3 (0.2%)	2 (0.1%)	7 (0.2%)
Withdrew consent	1 (<0.1%)	0	0	0	1 (<0.1%)
Lost to follow-up	22 (1.5%)	31 (1.0%)	17 (1.1%)	14 (0.9%)	53 (1.2%)
Non-compliance in following protocol [1]	0	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)
Does not meet randomization criteria [2]	0	3 (<0.1%)	0	3 (0.2%)	3 (<0.1%)
Other	2 (0.1%)	4 (0.1%)	1 (<0.1%)	3 (0.2%)	6 (0.1%)

[1] Reason applies to RANA3016, RANA3018, and RANA4006 only.
[2] Reason applies to RANA3013 and RANA3014 only.

Table 1. Discontinuation of subjects in controlled trials. The proportion of subjects withdrawing because of adverse events was low and was similar for placebo and both formulations of ranitidine.

Pooled RANA3013/RANA3014/RANA3016/RANA3018/RANA4006:
Summary of Extent of Exposure During Treatment Phase

	Placebo (N=1498)	Ranitidine 75mg (N=1505)	Ranitidine 150mg (N=1501)
Number of Study Drug Doses [1]			
0	7 (0.5%)	5 (0.3%)	10 (0.7%)
1	831 (55.5%)	836 (55.5%)	829 (55.2%)
2-5	67 (4.5%)	66 (4.4%)	49 (3.3%)
6-10	151 (10.1%)	163 (10.8%)	151 (10.1%)
11-15	171 (11.4%)	138 (9.2%)	157 (10.5%)
16-20	109 (7.3%)	99 (6.6%)	120 (8.0%)
21-25	56 (3.7%)	66 (4.4%)	67 (4.5%)
>25	84 (5.6%)	116 (7.7%)	101 (6.7%)
Unknown	22 (1.5%)	16 (1.1%)	17 (1.1%)

[1] Based on the number of study drug treated episodes recorded and drug accountability records. If a subject had no episodes and no drug accountability information, then the number of doses is considered unknown.

Table 2. Distributions of study drug doses taken. More than half of randomized subjects only one dose of the study drug (placebo or either formulation of ranitidine). Only 281 subjects took at least 16 doses of ranitidine 75 mg, and only 288 subjects took at least 16 doses of ranitidine 150 mg.

Figure 1. Five Controlled Trials submitted for present application.

Postmarketing Experience

The sponsor provided access to postmarketing data for this review.

C. Literature Review

The sponsor provided a summary of literature for this review.

V. Clinical Review Methods

A. Description of How Review was Conducted

The five controlled trials (**Figure 1**) were reviewed separately for safety by the present reviewer. A literature review was also performed, emphasizing results of large epidemiological studies and selected safety review articles, and including some well-documented case reports. The literature review focused on more severe and clinically significant reactions, including hematological events, hepatic events, pancreatic events, neurological events, cardiac events, hypersensitivity, drug interactions, and renal function.

Post-marketing surveillance reports were evaluated and analyzed.

B. Overview of Materials Consulted in Review

No IND(s) were evaluated for this application. See Section A.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No DSI audits were requested.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Yes.

E. Evaluation of Financial Disclosure

There were no financial disclosures that would cast doubt on the findings.

VI. Integrated Review of Efficacy

Refer to review by Dr. Brodsky, HFD-180.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Ranitidine 150 mg tablets have a good safety record based on extensive post-marketing experience (since 1983 for the US in prescription form and since 1996 for ranitidine 75 mg). OTC approval of the 150 mg tablets would double the available OTC ranitidine dosage, to a total daily dose (TDD) of 300 mg. Review of post-marketing data showed higher reporting rates of serious and fatal AEs for 150 mg tablets than for 75 mg tablets, but the difference may be due to differences between prescription and OTC user populations. A literature report of a large epidemiological study, which used a database including medical records of up to 4 million subjects followed for more than a decade, showed that there is a small added risk of neutropenia with ranitidine at TDD ≥300 mg than at TDD 150 mg (the current OTC dose). The reporting rates of serious and fatal reactions involving ranitidine did not change notably following the OTC switch of ranitidine 75 mg.

B. Description of Patient Exposure

The five controlled trials submitted for this application enrolled 11817 subjects (**Figure 1**). Of these subjects, 4504 received double blind study drug and were randomized as follows: 1498 received placebo, 1505 received ranitidine 75 mg, and 1501 received ranitidine 150 mg. Of the 4504 randomized subjects, there were 71 withdrawn from the studies prematurely. No subjects under the age of 18 were included in the studies. There were only 238 subjects in the randomized group above the age of 65 (including 82 on placebo).

Of some concern is the large proportion of enrolled subjects who were not accepted into the five controlled trials of **Figure 1**, namely, the 7313/11817 = 62% of subjects who were entered into the nonrandomized population because they met one or more of many exclusion criteria (the following is a partial list of the exclusion criteria):

1. under a physician's care for ulcer or diagnosed with an ulcer or Zollinger Ellision syndrome within the past year
2. ever used a proton pump inhibitor for treatment of GERD or heartburn
3. used NSAIDs within the last 3 months (except low dose aspirin for coronary artery disease)
4. diagnosis of erosive esophagitis or symptoms of more serious GERD
5. history of significant GI bleed
6. clinically significant disease not "adequately controlled"
7. inability to comprehend or use correctly the diary card, etc.

These exclusion criteria limit the applicability of the safety results from the five controlled trials because the randomized population did not accurately simulate the OTC consumer population. The randomized population excluded those who had or were being treated for an ulcer, those who had ever used a proton pump inhibitor, those who had a diagnosis of GERD, and those who were chronic users of NSAIDs, all of whom might be OTC users of Zantac 150 mg because the labeling of OTC H_2 blockers does not specifically exclude these populations. The controlled trials therefore included only a limited subset of likely OTC consumers.

There is limited exposure of subjects in the five controlled trials to the study drugs (see **Table 2**). The majority of subjects in all three treatment groups took only one dose. The total number of subjects documented as having received at least one dose of ranitidine 150 mg was only 1474. Only 19% of the subjects given either ranitidine 75 mg or ranitidine 150 mg took more than 15 doses. A total of 288 subjects received at least 15 doses of ranitidine 150 mg. Hence the safety experience from the five controlled trials is of limited value for the safety review both because of the small extent of exposure to ranitidine 150 mg and because the randomized population represented a limited subset of likely OTC consumers.

C. Methods and Specific Findings of Safety Review

There were no deaths and two serious AEs in the five studies. Both serious AEs were evaluated as unrelated to study drug by the investigators and this reviewer concurs.

> Subject R3861/T8058 (Investigator 5912) in RANA3014, a 43-year-old white man with a history of depression, was hospitalized for an exacerbation of depression 18 days after beginning the double-blind treatment period (ranitidine 150 mg). The subject was treated with benztropine, lithium carbonate, thiothixene, and multivitamins and was discharged after six days. Trial drug was not discontinued. The investigator deemed this event to be unrelated to trial drug.
>
> Subject R4408/T8332 (Investigator 2697) in RANA3014, a 27-year-old white man, was involved in a snowmobile accident approximately 16 days after beginning the double-blind treatment period (ranitidine 150 mg). The subject was hospitalized with a fractured lumbar vertebral pedicle, back pain, swelling, tenderness and a hip contusion. The subject also had residual paresthesia in right lower flank. The subject was treated with morphine, meperidine, hydroxyzine, ibuprofen, and codeine and was discharged within 24 hours. Trial drug was not discontinued. The investigator deemed these events to be unrelated to trial drug.

Seven subjects withdrew from treatment because of AEs, of whom two were on placebo. The five subjects given ranitidine were:

> Subject R0955/T6504 (Investigator 46193), a 49-year old white woman in RANA3013, reported swollen, itchy eyes and urticaria while taking ranitidine 75 mg. The subject was withdrawn from the trial and the investigator deemed this adverse event to be unrelated to trial drug.
>
> Subject R5778/T7326 (Investigator 45337), a 38-year old black woman in RANA3013, experienced constipation while taking ranitidine 150 mg. The subject was withdrawn

from the trial and the investigator deemed the adverse event to be possibly related to trial drug.

Subject R3884/T8069 (Investigator 05912), a 39-year old white woman in RANA3014, experienced vomiting while taking ranitidine 150 mg. The subject was withdrawn from the trial and the investigator deemed the adverse event to be related to trial drug.

Subject R4049/T6237 (Investigator 00931), a 31-year old black woman in trial RANA3016, reported headache, dizziness, gastric upset, nausea, vomiting, cramps, and diarrhea beginning approximately 30 minutes after taking ranitidine 75 mg. The headache resolved in 30 minutes and the remaining symptoms resolved within approximately four hours. The investigator deemed these adverse events to be unrelated to trial drug.

Subject 00148/05058 (Investigator 03895), a 34-year old black woman in trial RANA3018, reported diarrhea approximately one hour and 20 minutes after taking ranitidine 75 mg. The diarrhea resolved in 15 minutes. The investigator deemed this adverse event to be probably related to trial drug.

This reviewer feels that urticaria in Subject R0955/T6504 could have been related to the trial drug.

The AEs reported by at least 0.5% of subjects are listed in Table 3. The incidence of all AEs was low and was not significantly different between the two treatment groups nor between either treatment group and placebo.

Adverse Event	Number of Subjects Reporting Event (%)			
	Total Ranitidine (N= 3006)	Ranitidine 150 mg (N= 1501)	Ranitidine 75 mg (N= 1505)	Placebo (N= 1498)
Any Event N(%)	233 (7.8)	121 (8.1)	112 (7.4)	135 (9.0)
Headache	46 (1.5)	21 (1.4)	25 (1.7)	21 (1.4)
Diarrhea	36 (1.2)	15 (1.0)	21 (1.4)	24 (1.6)
Nausea	22 (0.7)	13 (0.9)	9 (0.6)	10 (0.7)
Influenza	16 (0.5)	12 (0.8)	4 (0.3)	6 (0.4)
Upper respiratory tract infection	15 (0.5)	6 (0.4)	9 (0.6)	6 (0.4)
Common cold	12 (0.4)	5 (0.3)	7 (0.5)	9 (0.6)
Vomiting	10 (0.3)	5 (0.3)	5 (0.3)	11 (0.7)

Data Source: Table A.8

Table 3. Adverse events reported by >0.5% of subjects in the five controlled trials.

As shown in Table 4, the overall adverse event incidence for ranitidine 150 mg and 75 mg was comparable to placebo within all studies except RANA3013, where placebo-treated subjects reported an adverse event slightly more frequently than ranitidine-treated subjects.

The overall and gastrointestinal adverse event frequencies (Table 4) among both ranitidine-treated and placebo-treated subjects were higher in RANA3013 and RANA3014 than in RANA3016, RANA3018, and RANA4006. The frequencies of adverse events in the two treatment trials were higher than the corresponding frequencies in the three prevention trials. This may be due to the multiple doses of trial drug taken and the longer surveillance period used in the treatment trials.

There were no subjects under the age of 18 included in the studies. Nine of the 238 subjects in the > 65 age group reported an adverse event. At least one adverse event was reported by 5 (3.2%) ranitidine-treated subjects over 65 years old, and by 4 (4.9%) placebo-treated subjects over 65 years old.

Trial	Trial Drug	N	Any Adverse Event N (%)	Any Adverse GI Event N (%)
RANA3013	Ranitidine 150 mg	338	39 (11.5)	13 (3.8)
	Ranitidine 75 mg	338	39 (11.5)	10 (3.0)
	Placebo	337	60 (17.8)	22 (6.5)
RANA3014	Ranitidine 150 mg	339	56 (16.5)	15 (4.4)
	Ranitidine 75 mg	334	51 (15.3)	15 (4.5)
	Placebo	334	49 (14.7)	17 (5.1)
RANA3016	Ranitidine 150 mg	320	19 (5.9)	10 (3.1)
	Ranitidine 75 mg	320	13 (4.1)	6 (1.9)
	Placebo	322	16 (5.0)	8 (2.5)
RANA4006	Ranitidine 150 mg	198	3 (1.5)	0 (0.0)
	Ranitidine 75 mg	204	4 (2.0)	2 (1.0)
	Placebo	199	4 (2.0)	2 (1.0)
RANA3018	Ranitidine 150 mg	306	4 (1.3)	2 (0.7)
	Ranitidine 75 mg	309	5 (1.6)	2 (0.6)
	Placebo	306	6 (2.0)	6 (2.0)

Data Source: Table A.11

Table 4 Overall Adverse Events and Gastrointestinal (GI) Adverse Events by Trial

D. Adequacy of Safety Testing

The program of safety testing was discussed with the Agency (Section I.C) and is considered adequate, in view of the extensive literature and post-marketing surveillance data available.

E. Published Literature

The medical literature reviewed by the sponsor covers the time period from 1993 through February, 2004 and includes searches of the MEDLINE, BIOSIS and EMBASE databases. Eight hundred and one citations were provided and reviewed by the sponsor for this application. The present literature review will not attempt to be comprehensive, but will focus on more severe and clinically significant reactions, emphasizing results of large epidemiological studies and selected safety review articles, and including some well-documented case reports. The following topics will be discussed: hematological events, hepatic events, pancreatic events, neurological events, cardiac events, hypersensitivity, drug interactions, and renal function.

Hematologic Adverse Events

Granulocytopenia, thrombocytopenia, and neutropenia have been reported in association with ranitidine use (Micromedex). Gafter et al. 1987 reported a case of thrombocytopenia, purpura and eosinophilia in a 57 year old man with mild renal failure and laboratory findings suggestive of cell-mediated hypersensitivity, in which the blood disorders resolved after ranitidine 300 mg/d was discontinued. Gafter et al. noted two other cases involving thrombocytopenia that were already reported. Andreu et al. 1996 reported a case of eosinophilic pneumonia in a 54 year old man, which resolved after ranitidine 300 mg/day was discontinued and prednisone was administered, also suggesting a hypersensitivity mechanism. Andreu et al. noted additional reports involving ranitidine and leukocytosis (Gelwan et al. 1986) and ranitidine and agranulocytosis (Shields et al. 1986).

Serious hematologic reactions to ranitidine are rare. Choo et al. 1994 studied the incidence of autoimmune hemolytic anemia diagnoses or abnormal Coombs' test results associated with ranitidine use in a large Health Maintenance Organization population. No occurrences of hemolytic anemia were observed in 12054 persons with 38686 prescriptions for ranitidine, yielding a 95% CI upper bound of 3.1 cases/10,000 exposed persons. One abnormal direct Coombs' test with mild anemia was found, but without hemolysis, and association with ranitidine could not be confirmed.

One very large case-control, epidemiologic study using the UK General Practice Research Database (GPRD) has reported a dose-dependent increased risk of neutropenia for ranitidine (Table 5). The GPRD follows approximately 6% of the total registered population in the national health care systems of England and Wales. Using the GPRD over the period 1987-1999, van Staa et al. 2003 identified 3224 patients with neutropenia including 50 with agranulocytosis. There was an increased odds ratio [OR] of 1.6 (1.2 to 2.1, 95% CI) for ranitidine at a total daily dose ≥300 mg, contrasting with an OR of 1.0 (0.6 to 1.6, 95% CI) for ranitidine at 150 mg per day. Given the methodology and study size, this increased OR for neutropenia at ranitidine ≥300 mg/day is evaluated as a robust result. However, the additional SAE risk is still very low. It

should be noted that the duration of ranitidine use was not discussed and that > 300 mg/day is higher than the maximum OTC dose would be if Zantac 150 mg bid were approved.

TABLE V. Risk of Neutropenia for Individual Drugs Stratified by Daily Dose

Drug	Daily dose	No. of cases	No. of controls	Adjusted OR (95% CI)
Amoxicillin	250–750 mg	156	221	2.1 (1.7–2.4)
	≥1,000 mg	38	66	1.6 (1.2–2.2)
Ibuprofen	400–900 mg	17	15	2.9 (1.5–5.3)
	1,200 mg	43	106	1.1 (0.8–1.4)
	≥1,600 mg	23	29	2.5 (1.6–3.9)
Dosulepin/dothiepin	25–75 mg	43	69	1.7 (1.3–2.3)
	≥100 mg	5	13	0.8 (0.4–1.8)
Ranitidine	150 mg	10	30	1.0 (0.6–1.6)
	≥300 mg	55	81	1.6 (1.2–2.1)
Carbamazepine	100–300 mg	16	12	3.3 (1.7–6.3)
	≥400 mg	21	15	3.5 (1.9–6.3)
Sulfasalazine	500–1,500 mg	20	9	5.1 (2.4–10.7)
	≥2,000 mg	54	8	18.3 (8.5–39.4)
Carbimazole	5–15 mg	15	2	17.3 (4.2–72.2)
	≥20 mg	24	2	32.9 (8.0–135.7)

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Table 5. Risk of neutropenia [from van Staa et al., 2003]

References

Andreu V, Bataller R, Caballeria J, Rodes, J 1996. J Clin Gastroent 23: 160-2.

Choo PW, Goldberg J and Platt R. 1994. Ranitidine-associated autoimmune hemolytic anemia in a Health Maintenance Organization population, J Clin Epidemiol, 47, 1175-1179

Gafter U, Komlos, L, Weinstein, T, Zevin D, Levi J, 1987 Thrombocytopenia eosinophilia and ranitidine. Ann Int Med 106: 477.

Gelwan J, Schmitz R, Pelicchia C. 1986 Ranitidine and leukocytosis. Am J Gastroent 81: 685-7

Shields L, Files J, Doll D, Greenberg B. 1986. Ranitidine and agranulocytosis. Ann Int Med 104:128.

Van Staa TP, Boulton F, Cooper C, HagenbeekA, Inskip H, Leufkens H. 2003. Neutropenia and agranulocytosis in England and Wales: incidence and risk factors; Am J Hematol 72:248-54.

Hepatic Adverse Events

The GPRD was also used in a large, epidemiological survey of drug-induced acute hepatic injury. In a nested case control retrospective study, Garcia Rodriguez et al. (1997a) used the General Practitioners Research Database (GPRD) in the UK, studying 108,981 persons who received 746,670 prescriptions during the study period 1990-1993 for cimetidine, ranitidine omeprazole or famotidine. There were an average of 6.9 prescriptions per user over the three

year period. Of these subjects, 55,988 subjects received 377,974 prescriptions for ranitidine. There were a total of 33 cases identified of idiopathic acute liver injury with no fatalities, five in ranitidine users. The relative risk [RR] of acute liver injury for use versus non-use of ranitidine was 1.7 (0.5-5.8 at 95% CI), that is, *not* significantly elevated. The incidence of acute liver injury with use of ranitidine is about 1 per 11,000 users (Garcia Rodriguez et al. 1997b): incidence rate 8.9 (3.8-20.9, 95% CI) per 100,000.

A case report of fatal hepatitis associated with ranitidine was reviewed (Ribeiro et al. 2000) and assessed as of probable causality. Two other case reports of non-fatal hepatotoxicity from ranitidine, assessed as highly probable, involved liver biopsy and positive re-challenges with ranitidine (Hiesse et al. 1985; Souza Lima, 1984).

References

Garcia Rodriguez LA, Ruigomez A., Jick H. 1997a. A review of epidemiologic research on drug-induced acute liver injury using the General Practice Research Database in the United Kingdom. Pharmacotherapy, 17:721-728.

Garcia Rodriguez LA, Wallander M, Stricker B. 1997b. The risk of acute liver injury associated with cimetidine and other acid-suppressing anti-ulcer drugs. Br. J Clin Pharmacol 43: 183-188

Ribeiro J, Lucas M, Baptista A, victorino R. 2000. Fatal hepatitis associated with ranitidine. AJG, 96:559-560.

Hiesse C, Cantarovich M, et al. 1985. Ranitidine hepatotoxicity in a renal transplant patient. Lancet 1:1280

Souza Lima MA. 1984. Hepatitis associated with ranitidine. Ann Int Med. 100:207-8

Cardiac Adverse Events

There are case reports of bradycardia and cardiac arrest associated with administration of IV ranitidine. However, the cardiac arrest report (Hart 1989) involved a 47 year old man with no predisposing conditions or suspect concomitant drugs. At least two reports of ranitidine induced bradycardia (Camarri et al. 1982; Johnson and Miller 1988) involved positive re-challenges and are evaluated as of highly probable causality. A similar report of a ranitidine-induced bradycardia with a positive rechallenge involved oral ranitidine (Shah 1982). This occurred in an elderly woman who had preexisting cardiac disease. The bradycardia resolved spontaneously once ranitidine was discontinued.

References

Camarri E., Chirone E, Fanteria G, Zocchi M, 1982. Ranitidine induced bradycardia. Lancet i:160.

Hart A. 1989 Cardiac arrest associated with ranitidine. Br Med J 299:519.

Johnson W, Miller D. 1988. Ranitidine and bradycardia. Ann Intern Med, 108:493

Shah RR, 1982. Symptomatic bradycardia in association with H_2 receptor antagonists. Lancet ii:1108.

Pancreatic Adverse Events

A case report of pancreatitis associated with ranitidine (Herrman et al. 1990) involved a positive re-challenge and was assessed as highly probable. Another case-control, epidemiologic study (Lancashire et al., 2003) used the UK GPRD to investigate drug-induced acute pancreatitis.

A total of 3673 cases of acute pancreatitis were identified in the GPRD over the period 1989-1998, of which 522 cases were observed in ranitidine users. The odds ratio [OR] of use versus non-use of ranitidine were markedly elevated (see Table 6), indicating that ranitidine-associated acute pancreatitis was clearly detected above background. It is noteworthy in Table 6 that the OR depended strongly on whether the prescription was *recent* (the OR was 11.9 if the prescription was within 90 days of the adverse event, but 3.9 or 3.4 if the prescription was not within the past 90 days or continuing through the previous year). This strongly elevated OR for recent, as opposed to not recent, prescription was most prominent for subjects with no previous ulcer diagnosis [Lancashire et al. 2003]. It is also noteworthy that similar elevated OR was observed not only for ranitidine but also for cimetidine and for all proton pump inhibitors. Hence the induction of acute pancreatitis is not specific to a particular acid-suppressing drug or mechanism of action, and may be explained as confounding by indication [Lancashire et al, 2003].

	Recent prescription within past 90 days		**Prescription between 90 days and 360 days prior**		**Prescription continued over both periods**	
	OR	95% CI	OR	95% CI	OR	95% CI
Ranitidine	11.9	8.5 to 16.6	3.9	3.1 to 4.9	3.4	2.7 to 4.1
Cimetidine	13.6	9.3 to 20.1	3.2	2.6 to 4.1	2.3	1.7 to 3.0
All proton pump inhibitors	9.8	7.2 to 13.4	4.0	3.1 to 5.3	5.0	4.0 to 6.3

Table 6. Odds ratio of pancreatitis with acid-suppressing drugs [Lancashire et al. 2003]

References

Herrmann R, Shaw R, Fone D. 1990. Ranitidine associated acute pancreatitis. Aust NZ J Med, 20:243-4

Lancashire R, Cheng K, Langman J. 2003. Discrepancies between population-based data and adverse reaction reports in assessing drugs as common causes of acute pancreatitis. Aliment Pharmacol Ther 17:887-893.

Hypersensitivity

Gielen and Goossens (2001) reported a large survey of occupational allergic contact dermatitis from drugs in healthcare workers, covering a period 1978-2001. In 14689 patients with suspected contact allergies, there were 33 patients with diagnoses of drug-induced dermatitis, confirmed by positive patch test. Of these, 7/61 positive patch tests were for ranitidine, mainly in nurses. This reaction is not of concern for OTC marketing.

References

Gielen K and Goossens A. 2001. Occupational allergic contact dermatitis from drugs in healthcare workers. Contact Dermatitis, 45, 273-279.

Pregnancy

Ruigomez A et al. 1999 studied pregnancy outcomes in women who used cimetidine, omeprazole or ranitidine. In 224 pregnant women exposed to ranitidine, no increase over background was observed for rates of infants born malformed, preterm, or small for gestation age. Ranitidine is pregnancy category B and this study reaffirms that ranitidine exposure is not likely to be a risk to the fetus.

References

Ruigomez A et al. 1999. Use of cimetidine, omeprazole and ranitidine in pregnant women and pregnancy outcomes. Am J Epidemiol 150, 476-481.

Drug Interactions

Ranitidine is metabolized in the liver to at least three distinct metabolites, but 70% of ranitidine is excreted unchanged in the urine. Reported drug interactions associated with ranitidine (Lipsy et al. 1990) include notably procainamide and theophylline. Metabolism of procainamide is decreased by ranitidine, and clearance of theophylline is reduced. Ranitidine may exacerbate renal dysfunction when given with cyclosporine (Katz 1997). Ranitidine like other acid-suppressing drugs reduces absorption of ketoconazole (Clinical Pharmacology Monograph). A case of interaction with phenytoin has been reported (Tse et al. 1994). Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin (Zantac prescription label). However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg/day, no interaction occurred; ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg/day has not been investigated (Zantac prescription label).

In a ranitidine-triazolam interaction study (Zantac prescription label), triazolam plasma concentrations were higher during b.i.d. dosing of ranitidine than with triazolam given alone. The mean area under the triazolam concentration-time curve (AUC) values in 18- to 60-year-old subjects were 10% and 28% higher following administration of 75-mg and 150-mg ranitidine tablets, respectively, than with triazolam given alone. In subjects older than 60 years of age, the mean AUC values were approximately 30% higher following administration of 75-mg and 150-mg ranitidine tablets. It appears that pharmacokinetics and elimination of triazolam and (alpha)-hydroxytriazolam, a major metabolite, did not change. Reduced gastric acidity due to ranitidine may have increased the availability of triazolam (Zantac prescription label).

References

Hinrichsen H Clinical aspects of cardiovascular effects of H_2 receptor antagaonists. 1995. Eur J Clin Invest 24, Suppl 1, 47-56.

Katz HI 1997. Potential drug interactions with cyclosporine. 36, Suppl. 1, 18-24.

Lipsy, R, Fennerty B, Fagan C. 1990. Clinical review of Histamine2 receptor antagonists. Arch Int Med 150, 745-51.

Tse CS Ted, et al. 1994. "Phenytoin and Ranitidine Interaction" Annals of Int Med.120, 892-893.

Porphyria

There are rare reports in the literature of porphyria associated with use of ranitidine (e.g., Pratap et al., 1988; Bhadoria et al. 1988). It is recommended in the prescription label that patients with a history of acute porphyria should avoid use of ranitidine (Zantac prescription label).

References

Pratap D, Agrawal N, Arya T: Can ranitidine induce porphyria. Journal of the Association of Physicians of India 1988;36(3):237-238.

Bhadoria DP et al Ranitidine and acute intermittent porphyria. Journal of the Association of Physicians of India 1988; 36(4): 295-296.

Acute Renal Failure

The UK GPRD was used to assess the renal safety of acid-suppressing drugs (Garcia Rodriguez et al. 1997). This cohort study followed 178,889 healthy patients between Jan 1991 and March 1995, who had at least one prescription for cimetidine, ranitidine, omeprazole, nizatidine, or famotidine, to evaluate the risk of acute renal failure and/or nephrotic syndrome. Two cases occurred during current use of ranitidine: 1 case of acute renal failure and one case of nephrotic syndrome; no cases were found with users of the other four acid-suppressing drugs. Three cases occurred during non-exposure. The incidence of idiopathic renal disease is about 1 per 100,000 person years. The RR with use of acid-suppressing drugs is 1.8 (0.3 to 10.7), which is not significantly elevated above background (Garcia Rodriguez et al. 1997). A published case report described interstitial nephritis attributable to administration of ranitidine (Karra 1994).

References

Garcia Rodriguez LA , Wallander M, Johanson S, Bjorck S. 1997 Pharmacoepi and drug safety, 6:247-251

Karras DJ, Severe Low Back Pain Secondary to Acute Interstitial Nephritis Following Administration of Ranitidine, Am J Emerg Med, Jan 1994; 12:67-68.

Neurologic Reactions

Central nervous system reactions include confusion, delirium, disorientation, hallucinations, and obtundation. A case has been reported of ranitidine-induced aseptic meningitis in a 30 year old man with two rechallenges in which the reaction was demonstrated (Durand and Suchet 1996).

References

Durand, JM and Suchet L. 1996. Ranitidine and aseptic meningitis. BMJ, 312:886.

Marik PE.1999. Stress Ulcer Prophylaxis: A Practical Approach. J of Intensive Care Med, 14: 1-8.

Dose Reduction for Renal Dysfunction

Ben-Joseph et al. (1993) demonstrated that the failure to reduce the dose of H2 blockers in patients with renal dysfunction doubled the likelihood of the patients experiencing an adverse

drug reaction, in an epidemiological study of 1200 patients in 40 hospitals, each of whom enrolled 30 consecutive subjects receiving an intravenous H_2 receptor antagonist. The prescription labeling for ranitidine recommends that the dose be reduced in patients with impaired renal function, to 150 mg/day for creatinine clearance <50 mL/min. The sponsor proposed to include a label warning, not to use "if you have kidney disease" except under the advice and supervision of a doctor. The issue is that renal function normally declines with age, even without kidney disease. Many elderly people may have sufficiently reduced renal function as to require a ranitidine dose reduction even though they may not be aware of their reduced renal function and may not have had any diagnosis of "kidney disease". The literature was reviewed to evaluate the prevalence of the condition creatinine clearance <50 mL/min in various populations versus age.

The normal values of glomerular filtration rate (GFR) are shown in Figure 2 for men and women versus age. At age 65 in men and women, the mean GFR remains above 100 ml/min/1.73 m^2 and a GFR of 80 ml/min/1.73 m^2 would be one s.d. below the mean. Approximately 16% of normal men and women would have GFR of <80 ml/min/1.73 m^2 at age 65. By age 85, about 16% of normal men (but not women) would have GFR low enough that the dose of ranitidine should be reduced.

Age Groups in High-Risk Population			
	46-60 yr	61-75 yr	>75 yr
EGFR<60 ml/min/1.73 m^2	N (%)	N (%)	N (%)
Men	60 (9.5%)	120 (24.3%)	62 (45.6%)
women	156 (11.5%)	280 (29.9%)	121 (45%)

Table 7. Prevalence of low estimated GFR in a pre-screened population [Brown et al. 2003]. For example, 9.5% (60/632) of men aged 46-60 had low EGFR.

Brown et al. (2003) performed a survey (the Kidney Early Evaluation Program, KEEP) in which 6071 persons were screened during the period August 2000 through December 2001 to determine the prevalence of selected risk factors for chronic kidney disease and to evaluate the effectiveness of a simple pre-sreening procedure to identify high-risk individuals. Participants were enrolled if they had a first degree relative with diabetes, hypertension, or kidney disease, or if they had a personal history of diabetes or hypertension. In this population, a significant proportion of subjects had an estimated GFR <60 ml/min/1.73 m^2 as shown in Table 7 (GFR was estimated from an algorithm using serum creatinine, age, race, and sex; Levey et al. 1999).

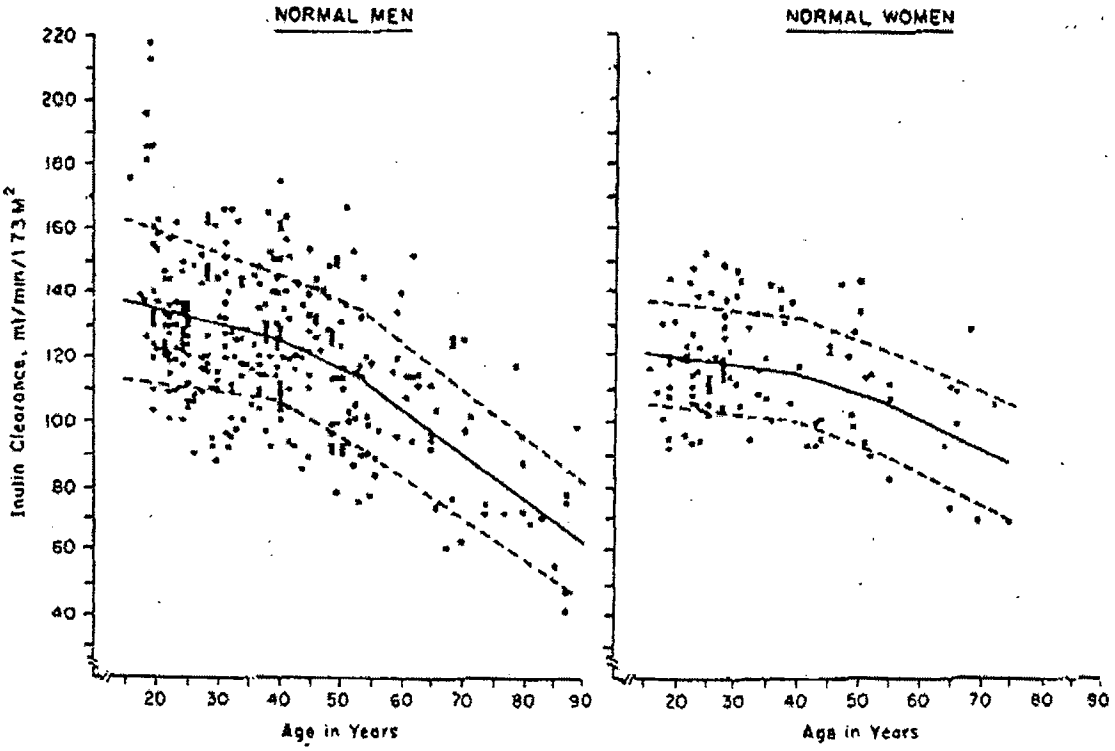

Figure 2. Means and standard deviations for glomerular filtration rate [Wesson 1969]

References

Ben-Joseph, R., Segal R and Russell W 1993. Risk for adverse events among patients receiving intravenous H2 receptor antagonists. Ann Pharmacol 27:1532-7

Brown, W et al. 2003. Early detection of kidney disease in community settings:the Kidney Early Evaluation Program (KEEP). Am J Kidney Diseases, 42:22-35

Levey A et al. 1999. More accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Int Med 130:461-470.

Lindeman RD and Goldman R 1986. Anatominc and physiologic age changes in the kidney. Exp Geront. 21:379-406.

Wesson LG ed. 1969. Physiology Of The Human Kidney. New York, Grune and Stratton.

F. Worldwide Post-Marketing Surveillance

Extensive safety data are available from post-marketing surveillance of ranitidine. For the present review, safety update reports were obtained from the spontaneous report database maintained by the prescription ranitidine sponsor GSK; the safety database kept by the World Health Oragnization (WHO) ; and the FDA spontaneous report databases SRS and AERS (AERS superceded SRS in 1997). These data were supplemented by marketing data from the sponsor and from IMS Health Inc.

GSK Database

The GSK database maintains records of spontaneous adverse event (AE) reports. Examined for the present application were all reports received by GSK world-wide from Jan 1, 1994 to March 30, 2002 in association with oral or unknown ranitidine formulations. Reports were received from health care practitioners or patients, or they were identified from literature review. There were a total of 8354 reports in the GSK database. The vast majority of these reports involved ranitidine for prescription use. The majority of reports (57%) originated from the USA and the UK, while France supplied 8%, and Japan and Germany each supplied 6% of the reports. No other country provided more than 5% of the reports.

The time to onset of the AE was provided in 99% of the reports. The reported time to onset of the AE was <24 hours in 64% of reports, within 1 week in 78% of reports, and within 2 weeks in 84% of reports. The time-to-onset distribution of spontaneous reports may be biased relative to the true distribution in favor of adverse events with rapid onset, as a closer temporal association between taking a drug and observing an AE may induce a higher probability of generating a report.

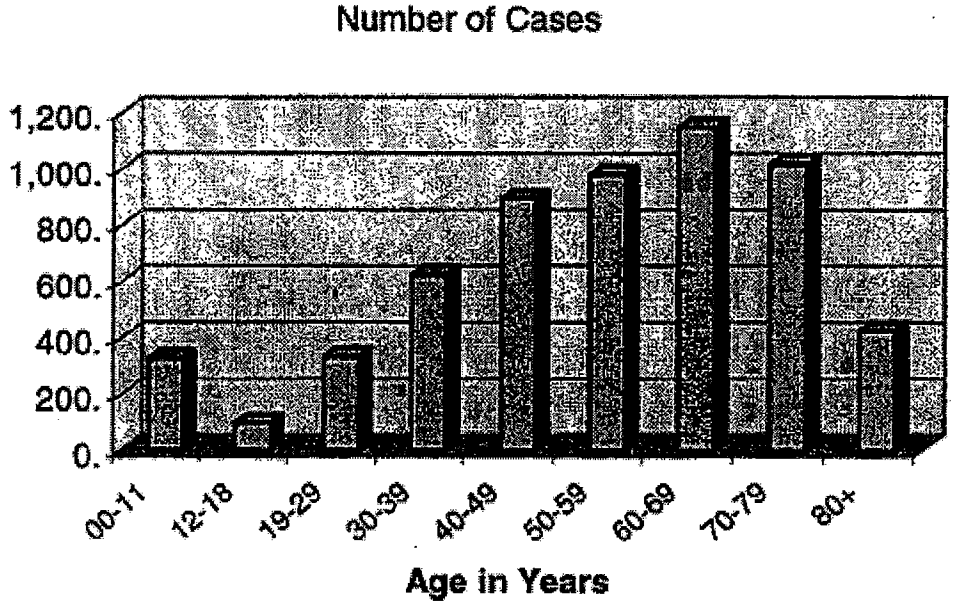

Figure 3. The age distribution, spontaneous AE reports, from GSK database.

There were fatal outcomes in 2% of the GSK reports (177/8354 reports). It is noted that causality is usually difficult to assess in spontaneous reports, and that outcomes are often confounded by pre-existing or co-morbid conditions and/or concomitant medications. Poor documentation prevents assessment of causality in many cases.

The GSK safety database reveals significant differences in the safety profiles between the users of ranitidine 150 mg and ranitidine 75 mg, although these differences may be explained by use patterns: the former are prescription users whereas the latter are mostly OTC users with some prescription users. The age distribution of the spontaneous reports is shown in **Figure 3**, which displays one peak of pediatric users under 12 years of age and another peak of elderly users. A separate table supplied by the sponsor showed that subjects aged >65 years accounted for 32.5% of spontaneous reports.

The age distributions for the GSK safety reports were significantly different between those for ranitidine 150 and those for ranitidine 75 (see Table 8, $p<<10^{-4}$ by chi-squared test, 4x2 table). The most noteworthy difference was a much higher proportion of reports from young subjects (17 years or younger) among ranitidine 150 users. Even with adolescent users excluded, the age distributions (18 to 65 years vs > 65 years) were different between the 150 mg and 75 mg users: $p = 0.0076$ by chi-squared test for 2x2 table), because of a higher proportion of elderly users > 65 years of age among the reports for ranitidine 150. Another significant demographic difference between spontaneous reports for ranitidine 150 users vs ranitidine 75 users was that a higher fraction of ranitidine 75 users was female (3089/5028 =61% female) vs the fraction of female users for ranitidine 150 (4259/8967 = 47% female).

Because of the demographic differences between users of ranitidine 150 mg and ranitidine 75 mg, differences in reporting rates of adverse events may not indicate differences in safety. For example, a higher rate of reporting for ranitidine 150 may result in part from a higher proportion of elderly users or a higher proportion of users with more serious medical conditions since ranitidine 150 mg is a prescription dose.

Subject age	Number of spontaneous reports with 150 mg	Number of spontaneous reports with 75 mg
< 12 years	459	103
12 – 17 years	88	43
18 – 65 years	3685	2884
> 65 years	2059	1439

Table 8. Age distributions of ranitidine spontaneous reports: a much higher proportion of reports from children and adolescents, and a higher proportion of reports from elderly users, for ranitidine 150

There is a notable difference in the safety profiles between users of ranitidine 150 mg versus ranitidine 75 mg. Namely, for users of ranitidine 150 mg, a much greater proportion of spontaneous reports involved serious or fatal outcomes, compared with users of ranitidine 75. As shown in Table 9, there were 20% serious and death outcomes in the spontaneous reports for ranitidine 150, whereas there were only 0.9% serious and death outcomes for ranitidine 75

reports (these differences were statistically significant by chi squared test at $p << 10^{-4}$). Also, there were 2.4% deaths among the ranitidine 150 reports, but only 0.1% deaths among the ranitidine 75. These differences most likely came about because of the differences between prescription use for 150 mg tablets versus OTC use for the 75 mg tablets and the differences between the patient populations using these two products.

Outcome	Number of spontaneous reports with 150 mg	Number of spontaneous reports with 75 mg
Nonserious	7443	4983
Serious without death	1344	40
Death	180	5

Table 9. Serious and death outcomes in spontaneous reports for ranitidine 150 mg and 75 mg

The different safety profile for ranitidine 150 mg versus ranitidine 75 mg is also demonstrated by the distinct distributions of MEDRA System Organ Classification (SOC) terms for the serious reports and the deaths. Again, these differences may be explained at least in part by the demographic and other differences in the user populations (such as underlying medical conditions).

Comparison of

Table 10 with Table 11 shows that none of the three most common SOC terms involved in the serious AEs for ranitidine 150 ('inv' which most often meant liver function abnormalities, 'skin', and 'blood') even appeared among the top four SOC terms for ranitidine 75 serious AEs (which were 'general', 'nervous system', 'immune system', and 'respiratory system').

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MedDRA SOC Abbr	Serious	Non Serious	Death	Overall Total
Inv	856	1000	107	1963
Skin	505	2299	38	2842
Blood	446	302	86	834
Gastr	415	2371	71	2857
Genrl	407	1727	161	2295
Nerv	352	1651	48	2051
Hepat	287	262	55	604
Psych	267	1192	25	1484
Resp	210	515	32	757
Musc	151	731	12	894
Card	145	207	73	425
Renal	112	225	28	365
Vasc	111	169	21	301
Immun	98	159	6	263
Inj&P	97	209	15	321
Infec	92	84	34	210
Eye	90	406	3	499
Metab	89	170	25	284
Neopl	58	15	22	95
Repro	31	769	2	802
Cong	25	9	0	34
Endo	16	32	0	48
Ear&La	14	101	1	116
Preg	11	145	1	157
SocCi	9	13	0	22
Surg	9	8	0	17
Inj&P	0	1	0	1
Total Terms	4903	14772	866	20541
Total Cases	1344	7443	180	8967

Table 10 Ranitidine 150 AE reports: distribution of SOC terms

MedDRA SOC Abbr.	Serious	Non Serious	Death	Overall
Genrl	16	1769	2	1787
Nerv	15	878	0	893
Immun	14	19	0	33
Resp	13	230	2	245
Skin	13	734	0	747
Gastr	8	2038	1	2047
Inv	5	239	1	245
Eye	4	103	0	107
Hepat	4	10	0	14
Inj&P	4	129	0	133
Psych	3	315	0	318
Vasc	3	52	2	57
Infec	2	27	0	29
Metab	2	29	0	31
Neopl	2	0	0	2
Renal	2	97	0	99
Repro	2	31	0	33
Blood	1	8	1	10
Card	1	72	1	74
Musc	1	147	0	148
Cong	0	1	0	1
Ear&La	0	56	0	56
Preg	0	1	0	1
Surg	0	3	0	3
Total terms	115	6988	10	7113
Total Cases	40	4983	5	5028

Table 11. Ranitidine 75 AE reports: distribution of SOC terms

It is concluded that the safety profile for ranitidine 150, primarily from prescription use, was distinctly different from that for ranitidine 75 which was for OTC use. Most notably, ranitidine 150 use was associated with higher rates of serious AE reports and death, as well as different different types of reactions in terms of body systems affected. These differences may largely reflect differences in the user populations. The sponsor also analysed the spontaneous report data by total daily dose (TDD), and there were more serious and death reports for TDD 300 mg (primarily from users of ranitidine 150 mg) than for TDD 150 mg.

The reviewer examined case summaries of GSK spontaneous reports of deaths from the period 1992 to 2003. A total of 180 fatal cases were assessed for causality by the reviewer and three of the deaths were evaluated as probably caused by ranitidine. One probable case B0047574A was that of hepatitis related to ranitidine, occuring in a previously healthy 66 year old female who was hospitalized with a one week history of jaundice (Ribeiro et al. 1997). Another

was a case of anaphylactic shock in a 52 year old hospitalized after an auto accident (B0112423A). Case B0047509A involved an 89 year old female with a history of MI 2 months earlier who developed a positive lymphocyte skin test after three days of ranitidine treatment and who died of hepatic failure and disseminated intravascular coagulation. Sixty-six cases were assessed as possible for causality. Most of these cases were confounded by medical conditions and concomitant medications, while others provided insufficient information for a more definitive assessment.

Reference

Ribeiro L.M. et al. Iatrogenic hepatitis with fulminant hepatic insufficiency. Portuguese Journal of Gastroenterology,Issn No. 0872-8178. Ano IV-Vol4. No.2 April/May/June 1997 - Supplement.

WHO Safety Surveillance Database

The sponsor provided safety data from the WHO database covering the period 1993 through 2002, which comprised a total of 13,290 AE reports, including 2207 reports of serious AEs or deaths. The proportion of death and serious reports, out of the total number of reports, was 2207/13290 = 17%, which is similar to the proportion (1524/8967 = 17%) shown in Table 9 for ranitidine 150 mg, supports the consistency of the data provided. The sponsor provided an update to the serious and death reports through February, 2004, bringing the total serious (including death) reports in the WHO database to 2330. Of these, there are 676, none from the US, evaluated as being of possible or probable causality by the reporter. Causality was not assessed for any of the US reports. The majority of WHO spontaneous reports originated from seven countries as shown in Table 12. These seven countries accounted for 88% of all WHO reports, where the USA accounted for 34% of reports.

Country of origin	Number of Serious and Death Reports, Total = 2330
United States	787
United Kingdom	350
Australia	335
France	219
Spain	154
Germany	148
Canada	54

Table 12. WHO Safety Surveillance Reports, Country of Origin

As shown in Figure 4, the total numbers of reports per year have been roughly constant, aside from a peak in 1994 and a weaker maximum in 2000. No reports were received in 2004. Two additional curves are given in the figure, showing the numbers of reports evaluated as of possible or probable causality, and showing the numbers of reports from the US only. These two peaks in 1994 and in 2000 are prominent in the numbers of US reports, but not in the numbers of possibly or probably related reports (none of which are US reports, because those were not rated for causality). The earlier peak predates the OTC approval in the USA, in December 1995, but

the later peak in 2000 closely follows the 1999 acquisition of ranitidine OTC 75 marketing rights in the US and Canada by Pfizer Consumer Healthcare.

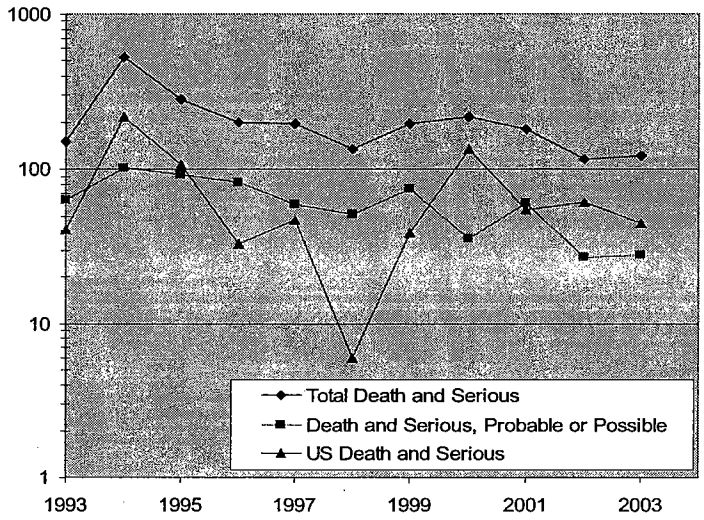


Figure 4 WHO Safety Surveillance Reports (all possible or probable are non-US reports)

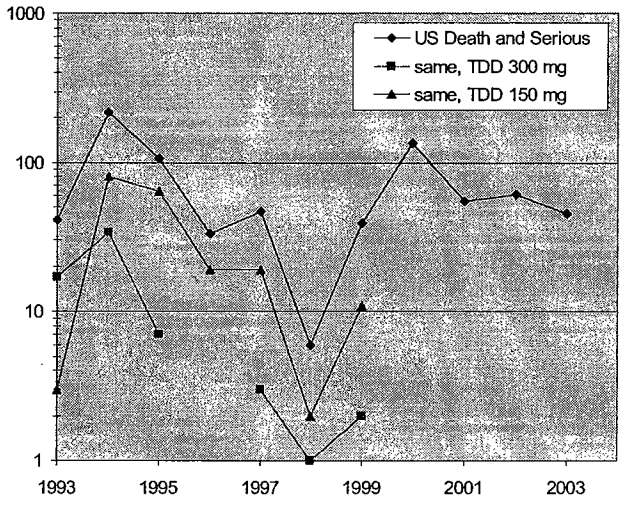


Figure 5. Death and Serious WHO Reports from US vs TDD. The proportions of serious and death reports did not change after OTC approval in December, 1995.

The numbers of serious AE and death reports from the US were plotted by year for TDD of 150 mg and TDD of 300 mg, to search for any indication of dose dependence. Figure 5 shows the total death and serious reports from US (same data as in Figure 4) but now compared to numbers of reports by year for TDD of 150 mg and TDD of 300 mg. It is seen that all three curves track each other closely on a logarithmic scale, with consistently greater death and serious reports for TDD 300 than for TDD 150 (excepting the one year 1993). Missing points in Figure 5

indicate zero reports received for those TDD values. No US reports for TDD of 150 mg or for TDD of 300 mg were received after 1999 in the data submitted.

The WHO safety surveillance reports show there are fewer reports at a total daily dose of 300 mg than for 150 mg after 1994. Reporting rates did not change notably as a result of the OTC switch of ranitidine 75 mg in December 1995 (so 1996 is the first full year of OTC marketing).

Distribution Data for Ranitidine

The sponsor provided IMS data on the numbers of prescriptions written by year from 1998 through 2003 for ranitidine in the US, in Canada, and in the rest of the world. Data are plotted in Figure 6 showing the numbers of prescriptions written (not necessarily dispensed) by office-based physicians. These data do not account for refills or include detailed information on the quantity of drug prescribed or the directions for use.

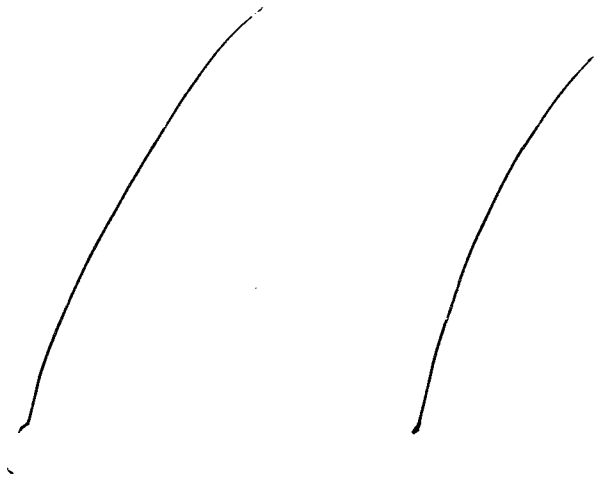


Figure 6 Number of written prescriptions for ranitidine by year,

For the US, both the total number of ranitidine prescriptions and the number of prescriptions for the OTC 75 mg dose are shown in Figure 6. The US total includes the latter. The Canada total also includes prescriptions for the OTC dose. The worldwide total prescriptions per year as shown in Figure 6 per year. At an average of prescriptions per year, the US accounts for , of worldwide prescriptions, and

Also provided by the sponsor at the request of the Agency were data from 1996 through 2003 for US sales of Zantac 75 mg tablets (OTC). The Agency also obtained from NDA 18-703 (with the sponsor's permission for right of reference) the yearly sales data for Zantac 150mg tablets and 300 mg tablets (both prescription) from 1985 through 2002. The numbers for the reporting period beginning June 1997 were missing. These data were merged in Figure 7. It is noted that 1996 was the first year of OTC marketing of Zantac 75. These data do not include generic ranitidine distribution figures.

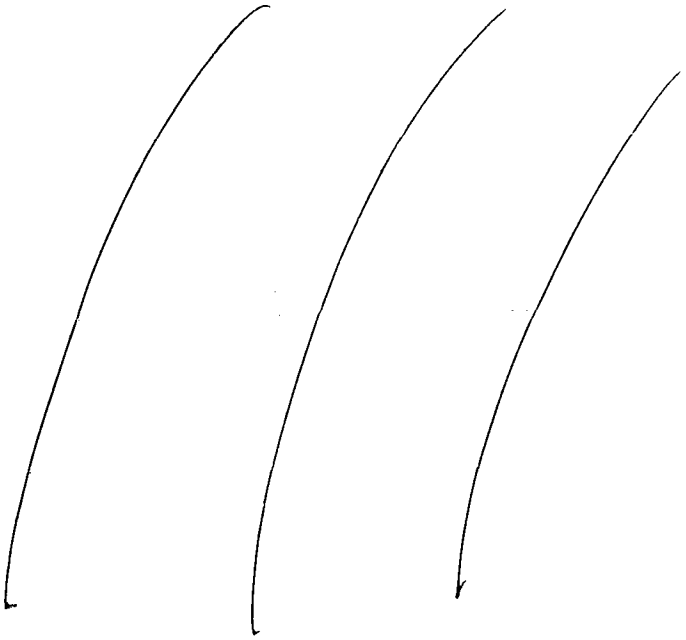
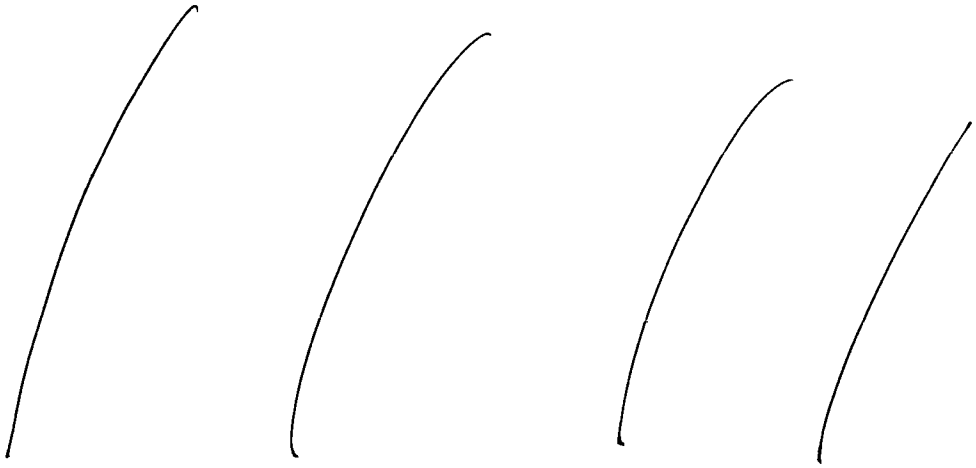


Figure 7. Sales of Zantac tablets by year. Date shown is the year at the start of the annual reporting period, which begins mid-year.



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FDA Safety Surveillance: SRS and AERS

Information was retrieved from the FDA postmarketing safety surveillance databases, SRS and AERS. SRS was the system used to archive spontaneous reports prior to 1997, so the SRS reports received before January 1996 involve AEs from prescription ranitidine only. The FDA converted to AERS in 1997, and AERS reports cover only the period of time after OTC marketing of 75 mg ranitidine tablets. The sponsor retrieved serious event and death reports involving ranitidine from SRS since 1982 through 1997, and from AERS since 1997 through March 2003. This database was used to perform an analysis to determine the numbers of reports of serious events, not including deaths, and number of reports of deaths, versus total daily dose [TDD] 75 mg, 150 mg, 300 mg, and >300 mg, and to compare these reporting rates before and after OTC 75 mg marketing approval.

However, a complication is that AERS reports document dose form (e.g., ranitidine 150 mg tablets versus 75 mg or 300 mg tablets) but not TDD. The SRS reporting format, on the other hand, documents TDD but not dose form. Hence these data can be usefully compared only given additional information on use patterns or, as in this case, prescribing patterns. Such information was available (Table 13). Results of the FDA comparisons of SRS and AERS reporting rates are shown in Table 14, where the numbers of death and serious (not including death) AE reports are shown for AERS versus dose form, and these numbers are shown for SRS from Jun 1990 to Jan 1996 (prior to the OTC ranitidine 75 mg switch) versus TDD.

After OTC 75 mg approval			Before OTC 75 approval		
AERS August 1997 to Mar 2003	AERS Deaths	AERS Serious	SRS Jun 1990 to Jan 1996	SRS Deaths	SRS Serious
total	102	616	total	209	654
			TDD>300	1	23
300 mg	19	88	TDD300	29	216
150 mg	25	239	TDD150	25	224
75 mg	7	44	TDD75	0	11

Table 14. AERS and SRS ranitidine reports; serious (not including deaths) and deaths. Equal time spans are shown before and after OTC 75 mg approval. Total exceeds sum of entries because of cases in which dose (AERS) or TDD (SRS) were not reported.

The SRS data of Table 14 show that there were similar numbers of serious and death reports for TDD=300 mg and for TDD=150 mg, [redacted], according to the IMS drug appearances survey data of Table 13. However, the numbers are low, and in many cases the TDD was not reported. In any case, the SRS data do not suggest that there is an increased rate of serious adverse events from the higher daily dose. For the AERS data in Table 14, it is noted that there were more serious and death reports for the 150 mg tablet than for the 300 mg tablet, by factors of 25/19 for deaths and 239/88 for serious reports. However, Table 13 shows that there [redacted]

(Table 13). Hence, AERS and SRS do not indicate an increased risk at the higher TDD=300 mg versus TDD=150 mg in prescription use.

The numbers of serious and death reports to SRS and AERS are plotted by year in Figure 9, which shows that the reporting rates have been remarkably stable throughout the period analysed. The picture that emerges from the post-marketing surveillance is therefore that OTC approval of ranitidine 75 mg did not produce any notable change in the overall reporting rates of serious and fatal AEs, . In any case, the prescription marketing experience has not yielded evidence suggesting a dose dependent, increased risk associated with TDD=300 mg versus TDD=150 mg.

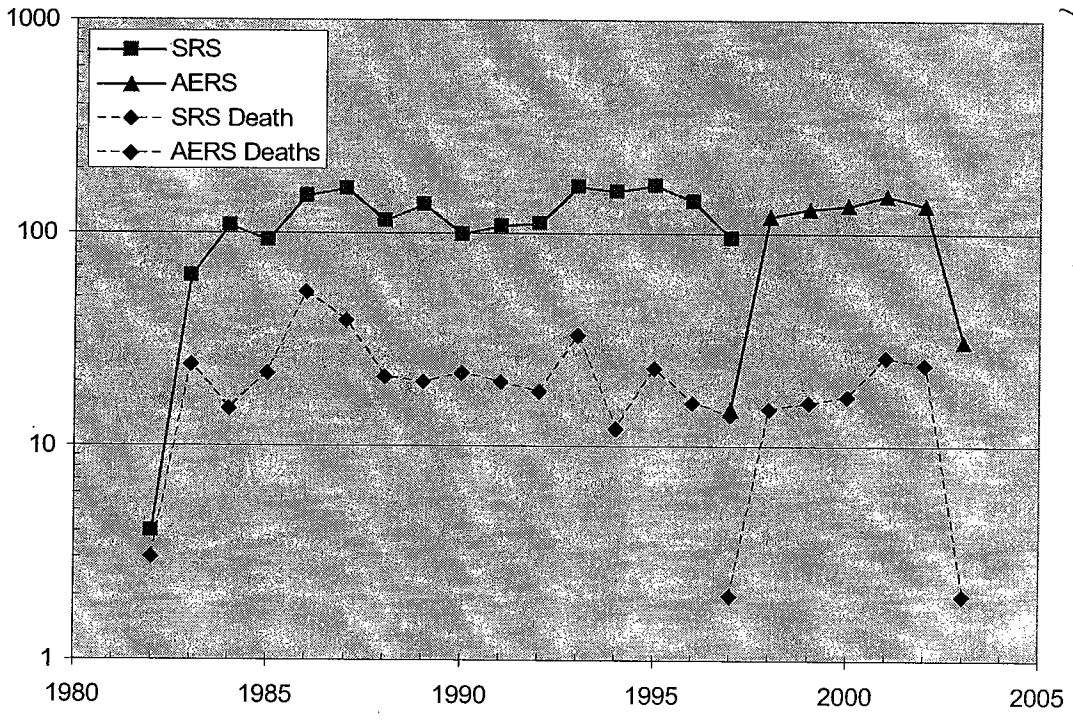


Figure 9. Serious and Death Reports to SRS and AERS by year; upper curves are serious and death reports combined, while lower curves are death reports only

VIII. Dosing, Regimen, and Administration Issues

See section IX for dose reduction in patients with impaired renal function, and for discussion of use in elderly patients.

IX. Use in Special Populations

A. Use in Pregnancy

Ranitidine is pregnancy category B. The sponsor proposed labeling for ranitidine 150 mg that will direct lactating or pregnant women to ask a doctor before use. The present review supports this label warning on the grounds that only limited safety data are available for use in pregnancy. One study (Ruigomez et al.) has reported exposures to ranitidine of 224 pregnant women. No increase over background was observed for rates of infants born malformed, preterm, or small for gestation age. This study suggests that ranitidine exposure is not a teratogenic risk, but the number of pregnant women exposed was small.

Ranitidine is secreted in breast milk (Lipsy et al. 1990).

Ruigomez A et al. 1999. Use of cimetidine, omeprazole and ranitidine in pregnant women and pregnancy outcomes. Am J Epidemiol 150, 476-481.

Lipsy, R, Fennerty B, Fagan C. 1990. Clinical review of Histamine2 receptor antagonists. Arch Int Med 150, 745-51.

B. Evaluate Pediatric Program

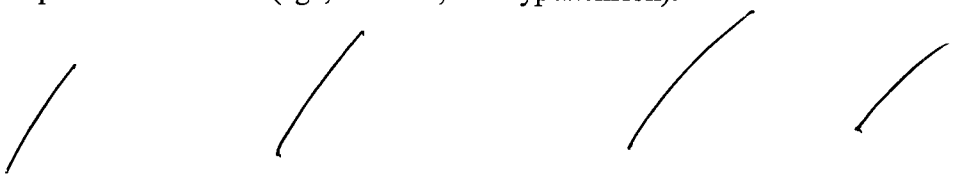
The safety and effectiveness of Zantac have been established in children aged 1 month to 16 years for prescription indications of duodenal and gastric ulcers, gastroesophageal reflux disease and erosive esophagitis, and the maintenance of healed duodenal and gastric ulcer (prescription label). For the present application, there was no pediatric program, but the sponsor provided an update of the safety experience from post-marketing surveillance. From the GSK safety database covering the period Jan 1 1994 to Mar 30 2002, there were 8354 AE reports of which 329 occurred in children under the age of 12, and 97 occurred in adolescents from 12 to 18 years old. There were 9 deaths of subjects under 12 and 5 deaths of subjects 12-18 years of age. The numbers of deaths in these age groups is approximately in accord with the overall age distribution of reports (Figure 3) and the total number of fatal reports (180), so there does not appear to be any excess of fatalities in pediatric use. Among the AE reports in children under 12, there is a high proportion of overdosing from medication error. As these are errors in use of prescription ranitidine, most often in liquid suspension formulations, there does not appear to be any issue for OTC ranitidine tablet formulations.

The package insert states that the recommended oral dose for the treatment of active duodenal and gastric ulcers is 2 to 4 mg/kg per day twice daily to a maximum of 300 mg/day.

This recommendation is derived from adult clinical studies and pharmacokinetic data in pediatric patients. In addition, the package insert states that published literature supports a dosage of 5 to 10 mg/kg per day for GERD and erosive esophagitis, usually given as two divided doses. Children aged 12 under the 25th percentile for weight would be given greater than 4 mg/kg if administered a single dose of 150 mg of ranitidine.

C. Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy

Since ranitidine is known to be substantially excreted by the kidney, the labeling for prescription ranitidine 150 mg recommends a dose reduction for patients with impaired renal function. The direction is for the dose to be limited to 150 mg/day for patients with creatinine clearance <50 mL/min. The sponsor proposed to include a label warning for OTC ranitidine 150 mg, saying do not use "if you have kidney disease" except under the advice and supervision of a doctor. The issue is that many consumers who should reduce their dose of ranitidine because of their low GFR may not have a diagnosis of kidney disease or may not be aware of their reduced renal function. A recent study (the Kidney Early Evaluation Program; Brown et al. 2003) in a high-risk community population found a prevalence >20% of low estimated GFR (Table 7) in subjects with specific risk factors (age, diabetes, and hypertension).



X. Conclusions and Recommendations

A. Conclusions

Safety results were evaluated from 5 clinical trials submitted with the NDA. These were two treatment trials (RANA3013 and RANA3014) and three prevention trials (RANA3016, RANA3018, RANA4006). While there were no serious AEs that were probably or possibly drug-related, these trials provided only a limited extent of patient exposure and were insufficient to reveal uncommon AEs of incidence <1%. Only 288 subjects took 16 or more doses of the ranitidine 150 mg tablets. No actual use trial was performed (none was requested by the Agency).

Approval of the present application should be based upon a risk-benefit analysis, showing that improved efficacy of the higher 150 mg dose versus the 75 mg dose already available OTC outweighs any additional risk of adverse events from making the higher total daily dose of 300 mg available OTC. Since efficacy was not evaluated in this review, risk versus benefit will not be addressed.

The safety profile of ranitidine has been studied extensively in the literature. Recent, large-scale epidemiological databases, such as the UK GPRB which followed 3 to 4 million people for more than a decade (see section VII E), have provided valuable, quantitative

information on the incidence rates of rare but serious adverse events involving ranitidine. There is an added risk of neutropenia with higher TDD (van Staa 2003), indicated by an increased odds ratio [OR] of 1.6 (1.2 to 2.1, 95% CI) for ranitidine at a total daily dose ≥300 mg, versus an OR of 1.0 (0.6 to 1.6, 95% CI) for ranitidine at 150 mg per day. The data do not address the duration of drug exposure. Still, the risk of hemolytic anemia is very low with ranitidine use, <3.1 cases per 10,000 exposed persons (Choo et al. 1994). The incidence of acute liver injury with ranitidine use is is about 1 per 11,000 users (Garcia Rodriguez et al. 1997b), but this incidence rate is not significantly elevated above background. There is a strikingly elevated OR for use versus non-use of ranitidine in cases of acute pancreatitis, but such was also observed for cimetidine and for proton-pump inhibitors and is not necessarily attributable to any of these drugs (Lancashire et al. 2003). There are also well-documented reports of serious cardiac events, hypersensitivity, and drug interactions discussed in Section VII E, which are rare and most of which resolved. Hence, the literature review has revealed an added risk of neutropenia from the increased TDD of 300 mg versus 150 mg, and this risk is still very low.

Overall, ranitidine has a very good safety profile, based on extensive post-marketing experience (since 1982 for the US in prescription form and since 1996 for ranitidine 75 mg). The Sponsor estimates that over 200 million patient courses have been dispensed worldwide. The review of US post-marketing data did not reveal evidence for increased reporting rates of serious and fatal AEs depending on TDD. Moreover, the reporting rates of serious and fatal reactions did not change notably following the OTC switch of ranitidine 75 mg.

B. Recommendations

Available data are supportive of approval given clear evidence of clinical efficacy superior to ranitidine 75 mg for the heartburn relief and prevention indications, and given sponsor agreement [redacted] This reviewer agrees with the sponsor's proposed kidney disease warning.

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