

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020951**

**MEDICAL REVIEW(S)**

CSO / Kacuba

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICE  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 18, 1998

/S/ [Redacted]

FROM: Medical Team Leader  
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Approvability Recommendation: new formulation of cimetidine (TAGAMET HB® 200)  
coal mint-flavored suspension for over-the-counter (OTC) consumption.  
NDA 20-951. Submission of 29 December, 1997.

TO: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

/S/ 9-22-98

TAGAMET® (cimetidine) is a histamine H<sub>2</sub>-receptor antagonist that inhibits both daytime, and nocturnal based gastric acid secretion and gastric secretion stimulated by a variety of agents. The prescription indications for cimetidine include short-term treatment of active duodenal ulcer, active benign gastric ulcer and erosive esophagitis, as well as maintenance therapy for duodenal ulcer patients, prevention of upper gastrointestinal bleeding in critically ill patients and the treatment of pathological hypersecretory conditions. For these prescription indications, the drug is available in several formulations: tablet and liquid form for oral administration, and injection (single- and multi-dose vials, single-dose premixed plastic containers and ADD-Vantage® vials). The safety experience with these cimetidine formulations, especially the tablets for oral administration is vast; it dates from the mid-70s.

The tablet formulation is also approved for non-prescription use, as TAGAMET HB® 200 for the relief and prevention of heartburn, acid indigestion, and sour stomach. Other H<sub>2</sub>, (ranitidine, famotidine and nizatidine) and a number of antacid formulations are also available OTC for this indication. Through the present submission, the sponsor request approval for a new dosage form (oral suspension) for non-prescription cimetidine. The proposed product contains 200 mg of cimetidine per 20 ml and would be indicated for the same approved use as the tablets. The recommended dose is 4 teaspoons or 20 ml (200 mg) that can be taken up to twice daily. SK & B has developed this new dosage form for consumers that have difficulty swallowing tablets or who prefer a liquid form.

From the September 14, 1998 Biopharm. review of the sponsor's submission, it is concluded that under fasting conditions, cimetidine Oral Suspension, 200 mg/ml, is essentially equivalent to one 200 mg cimetidine Tiltab® Tablet (Tagamet HB® 200). Minor PK differences between the tablet and suspension formulation, noted by both the Biopharm. and the MO Review (September 19, 1998) are not clinically relevant.

The MO, Dr. J. Senior, does not recommend approval of this application on grounds of clinical concern about highly probable use of the proposed liquid suspension principally for infants and children. However, in the U.S., infants and young children are customarily treated by physicians. In addition, the already approved OTC formulation is labeled down to 12 years of age, with extrapolation from the adult population to children between 12 and 16 years of age. Therefore, although this reviewer shares some of the medical concern (misuse in infants and children up to 12 years of age), this potential misuse of the drug argument has neither regulatory nor legal basis.

Therefore it is recommended to make this application approvable, pending the following:

1. Resolution of the chemical issue, an unknown material that builds up on storage, pointed out by Dr. M. Ysern, the Chemistry Reviewer.

2. Wording in the labeling indicating that the suspension formulation has not been shown to be safe and effective in children under 12 years of age and limiting its use to children older than 12 years.



/S/

*September 22, 1998*

Hugo Gallo-Torres, M.D.

cc:

NDA 20-951

HFD-180

HFD-180/HGallo-Torres

HFD-181/CSO/AKacuba

F/t by deg: 9/18/98/9/22/98

Memo/Tagamet

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CSJ Folkerdt

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

NDA: 20-951 SEP 17 1998

SPONSOR: SmithKline Beecham Consumer Healthcare  
1500 Littleton Road, Parsippany NJ 07054-3884

DATE OF SUBMISSION: 29 December 1997  
DATE OF RECEIPT: 30 December 1997  
ASSIGNED FOR REVIEW: 7 January 1998

DRUG: Cimetidine (TAGAMET HB<sup>®</sup> 200) cool mint-flavored suspension 10 mg/mL (new formulation) for over-the-counter (OTC) consumption

ROUTE OF ADMINISTRATION: Oral, 20 mL (200 mg) up to twice daily for up to 2 weeks

INDICATIONS: Relief and prevention of heartburn, acid indigestion, sour stomach brought on by consuming food and beverages (reduces production of stomach acid).

MATERIAL REVIEWED: Application, 10 volumes; data from pharmacokinetic and bioequivalence study MD-01010 (#143-09-11255) and reports by clinical pharmacology and chemistry; proposed labeling; pertinent other information and references.

REVIEWER: John R. Senior, M.D./ 15 September 1998

**Brief Overall Review Summary**

The sponsor has requested approval of a new 1% aqueous suspension formulation of cimetidine for OTC sale to consumers, based on bioequivalence to already-approved oral 200 mg OTC cimetidine tablets for such use. The new formulation is sweetened and cool mint-flavored to conceal the bitter taste of cimetidine, to make the preparation more palatable. It is to be labeled, as are the 200 mg tablets, for use to reduce production of stomach acid, to relieve and prevent heartburn, acid indigestion, and sour stomach. Doses of 200 mg are to be recommended up to twice daily for up to two weeks, with use for children under 12 to be guided by having the parent ask a doctor. However, reported experience with the approved *prescription* formulation of cimetidine HCl as a clear, light orange, mint-peach flavored solution containing 300 mg/5 mL has revealed that about [REDACTED] of the prescriptions were for children under 13, and about [REDACTED] of those for infants under a year old, despite lack of safety, efficacy, and dosage data for indications for the use of the drug in those children. Approval is not recommended for the OTC sale and use of this additional formulation of cimetidine, based on lack of data for the consumers in whom it is most likely to be used.

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## I. Introduction

### A. Approach to the review and conventions used

The reviewer has approached this submission first by focusing upon what the sponsor has requested, and what evidence has been submitted in support of that request. The overall structure for the review includes an introduction with a very brief mention of the drug, the sponsor, and diseases for which it was investigated, dates of submission and review, and materials reviewed. Immediately following the title page is a boxed, concise, half-page summary of the review, to provide the reader with a picture of the purpose, context, issues, major findings and conclusions, evaluation and regulatory recommendations. The organization of the review and a road map to its sections in a Table of Contents follows on the second page, and that is immediately followed by this explanation of the process used to approach the information submitted in 10 volumes. Ancillary as well as other pertinent submissions and reviews previously reported also have been considered.

The convention used in the review, to distinguish sponsor's data and interpretations, the reviewer's abstracting, paraphrasing, or summarization of submitted material, and reviewer-generated opinions and discussion, was to use typeface variants:

1. Material summarized by the reviewer from that submitted by the sponsor is shown in plain 12-point CG Times font, with references to Volume and page numbers in the submitted material;
2. Text taken directly from that submitted by the sponsor is shown in quotations, and tables or figures copied from the submitted material were noted "As submitted in Volume \_\_, page \_\_."
3. Material provided by the reviewer in explanation of the approach taken to review, or taken from other sources, whether pertinent literature or other regulatory material, in 11-point font;
4. *Commentary, opinion, discussion by the reviewer about the submitted material or about the literature or other sources (cited, wherever possible) was shown in 12-point italic CG Times font.*

Sections of the review were numbered and paginated as shown in the Table of Contents, which corresponded in general with the "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application," published in July 1988 by the Center for Drug Evaluation and Research of the Food and Drug Administration.

In this particular review, the principal data submitted were pharmacokinetic comparisons of the plasma cimetidine concentrations after 20 mL (200 mg) orally of the new suspension product and a single 200 mg TAGAMET HB® 200 tablet as sold in the OTC market, and chemical-manufacturing data on use of the cimetidine crystalline polymorph B rather than A as used in the prescription tablets and solutions. No clinical efficacy data were submitted, nor were any pharmacodynamic data provided. Of special importance was information obtained by the Division of Pharmacovigilance and Epidemiology on the marketing and use of the approved prescription oral liquid cimetidine product.

**B. Description of Drug (as labeled)**

DRAFT LABELING



The original 100 mg HB tablets for OTC sale approved in 1995 have been supplanted by TAGAMET HB<sup>®</sup> 200 Acid Reducer/Cimetidine Tablets 200 mg that contain inactive ingredients including cellulose, cornstarch, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sodium lauryl sulfate, sodium starch glycolate, titanium dioxide.

The compound was developed as a competitive histamine-H<sub>2</sub>-receptor antagonist that inhibits gastric acid secretion and reduces pepsin output. It was patented in 1974 to G. J. Durant of Smith Kline & French, U.S. patent 3,950,333. The compound inhibits H<sub>2</sub>-receptors of the gastric mucosal parietal cells, but is not an anticholinergic agent. It inhibits both daytime and nocturnal gastric acid secretion, and acid secretion stimulated by food, histamine, pentagastrin, caffeine, and insulin. Cimetidine has no effect on lower esophageal sphincter pressure or the rate of gastric emptying.

After oral administration, cimetidine is rapidly absorbed, reaching peak plasma concentrations in 45 to 90 minutes, and shows a half-time of elimination from plasma of about 2 hours. The drug is extensively metabolized after oral administration, the sulfoxide being the major metabolite. After a single oral dose, about 48% is recovered in the 24-hour urine as the parent compound; about 75% may be so recovered after parenteral administration. Cimetidine at prescription doses has been reported to inhibit in vivo the metabolism of other drugs that are substrates for mainly hepatic cytochrome P450 isozymes (CYP) 1A2 (theophylline, R-warfarin, acetaminophen, caffeine); 2C (phenytoin, S-warfarin, diazepam, tolbutamide, phenylbutazone, sulfapyrazole), 2D6 (propranolol, metoprolol, amitriptyline, codeine, debrisoquine), 2E1 (acetaminophen, ethanol), and 3A (erythromycin, ketoconazole, miconazole, quinidine, cyclosporin A, nifedipine, midazolam, triazolam, diltiazem, lovastatin).

The inhibition of metabolism of those drugs at doses of 200 mg once or twice daily was not extensively studied, but the Gastrointestinal Advisory Committee on 29 July 1994 recommended additional study of effects of cimetidine 200 mg b.i.d. on metabolism of 0.25 mg triazolam and sustained-release theophylline dosing. Results in 23 healthy men showed that cimetidine, compared to placebo, at the OTC dose-regimen increased triazolam plasma maximal concentration (C<sub>max</sub>) by 24% and area-under-the-curve (AUC) of plasma concentration over time by 28%, although there was wide inter-individual variability. Study of 46 healthy men showed that cimetidine produced increases in the mean C<sub>max</sub> and AUC, with reduced clearance, of theophylline. No women were studied. Initially, the medical reviewer (Dr. K. Robie-Suh) recommended on 30 July 1993 against approval of the OTC regimen of 200 mg b.i.d. for up to two weeks. This was based on inadequate evidence for efficacy of cimetidine in relieving heartburn and concerns about drug-drug interactions between the OTC doses of cimetidine and other medications and with alcohol (slight increases in blood alcohol concentrations at lower level of alcohol consumption, and safety of the drug in heartburn associated with pregnancy).

### C. Background of previous NDAs approved for cimetidine

Cimetidine (TAGAMET®) was first approved 16 August 1977 (NDA 17-920) as 200 mg tablets for oral ingestion 15 or more minutes before meals and at bedtime, for treatment and prevention of nocturnal heartburn symptoms in patients with gastrointestinal reflux disease (GERD). On the same date, NDA 17-924 for cimetidine HCl oral solution and NDA 17-939 for cimetidine solution for injection were approved. The original IND application for cimetidine capsules was received 1 November 1974, assigned # [REDACTED], and was reviewed by Dr. Thomas Garvey for the indication of healing duodenal ulcers. Cimetidine INDs [REDACTED] for cimetidine HCl solution for injection and [REDACTED] for oral ingestion both were later received on 26 November 1975. Cimetidine was subsequently approved for healing of benign gastric ulcers, for healing erosive esophagitis associated with gastroesophageal reflux disease (GERD), for the treatment of pathological gastric hypersecretory conditions (Zollinger-Ellison syndrome, multiple endocrine adenomas, systemic mastocytosis), for maintenance of healing of duodenal ulcers, and for prevention of upper gastrointestinal bleeding in critically ill patients.



Cimetidine was the first of a new class of drugs that blocked or antagonized the type-2 receptor for histamine, now informally referred to as "H2-blockers" and now including also three other approved drugs: ranitidine, famotidine, and nizatidine. Cimetidine revolutionized the treatment of duodenal ulcer disease, and subsequently the treatment of other acid-peptic diseases such as benign gastric ulcer, erosive esophagitis and GERD, and gastric acid hypersecretory states including Zollinger-Ellison syndrome. The recommended dose of cimetidine, for adults and for youths over 16, is 800 mg h.s., 400 mg b.i.d., or 300 mg q.i.d. for up to 8 weeks, for healing of active duodenal or gastric ulcers. For healing erosive esophagitis, 400 mg q.i.d. or 800 mg b.i.d. for up to 12 weeks is approved. A bedtime dose of 400 mg is approved for maintenance of healing of duodenal ulcer, for up to 5 years (approved before discovery of *Helicobacter pylori*). Doses of 300 to 600 mg q.i.d. are recommended for treatment of Zollinger-Ellison syndrome, for as long as necessary. Prevention of gastrointestinal bleeding by intravenous (IV) administration is accomplished by infusion of 50 mg/hour for up to 7 days, with reduction in the infusion rate of cimetidine to 25 mg/hour if creatinine clearance is less than 30 mL/minute.

The cimetidine patents pertinent to these claims expired 13 April 1993 (U.S. patent 3,950,333) and 17 May 1994 (U.S. patent 4,024,271), before which NDA 20-238 was submitted on 27 November 1991 (not filed, but resubmitted in August 1992) requesting approval of cimetidine 100 mg tablets in dosage of 200 mg up to twice daily *relief* of heartburn, acid indigestion, sour stomach, and upset stomach associated with these conditions for OTC sale and consumption, approved 19 June 1995. Not long after expiration of the patents NDA 20-473 was submitted on 30 November 1994 requesting approval of TAGAMET HB (cimetidine) Tablets 100 mg in doses of 200 mg up to twice daily for *prevention* of meal-induced heartburn, acid indigestion and sour stomach, when taken 30 minutes prior to consuming food or beverages. approved 15 November 1995.

**D. Present cimetidine labeling for OTC TAGAMET HB® 200 Tablets 200 mg**  
(as amended in letter to sponsor of 5 June 1998)

The current cimetidine label states that the OTC uses and directions for cimetidine as TAGAMET HB 200® Acid Reducer/Cimetidine Tablets 200 mg are as follows:

DRAFT LABELING



*Comment: Distinction is made between relieving symptoms of heartburn that already are felt by the person and preventing symptoms that are not yet present but may be expected, based presumably upon the person's previous experience with the type of meal about to be consumed. The labeling therefore should perhaps be stated as "For prevention of symptoms anticipated to be brought on by consuming certain food and beverages...." It is not clear why the labeling covers potential users aged 12 thru 17 if they were not included in studies of safety and efficacy of the prescription tablets. It is also unclear how a doctor could provide advice for use or dosing for children under 12 years of age, without data supporting the safety, efficacy, clear indications, and dosing for such use.*

DRAFT LABELING



The requested labeling for the new suspension (New Liquid Tagamet HB 200<sup>®</sup> Acid Reducer/Cimetidine Suspension 200 mg) is as follows (see Volume 5, page 0026-0028):

., DRAFT LABELING



*Comment: The text proposed for printing on the boxes, which is perhaps all consumers will be likely to see, with respect to Warnings has been much abbreviated to:*

DRAFT LABELING



*Comment: The proposed text for "Professional Labeling" (see Volume 5, page 0023) for PHARMACOKINETIC INTERACTIONS is the same as for the 200 mg HB tablet formulation, but is not clear exactly for whom it is intended. Is this the information to be provided in case a consumer does actually ask a doctor? What is otherwise a "health professional"? The information is not suitable for reading and interpretation by lay readers, whether consumers or sellers in the OTC markets. It is again unclear what data support the statement to Ask a Doctor if use in children under 12 years of age is desired by consumers. What is the doctor to say? The dose for children has not been established, nor have the indications, by data that prove this new preparation, or the previous 200-mg HB tablets, safe and effective in children of what age and size for what indication at what doses.*

*It is also noted on the proposed labeling for the boxes in which the 12 fluid ounce bottles of new liquid suspension are to be sold that six pairs of bar graphs labeled Study A to Study F are shown, with titles for relieving and preventing heartburn symptoms by Tagamet HB 200 significantly better than placebo. (See also the text on page 0029, Volume 5.) These are the same as were shown for the 200-mg HB tablets, although printing them on the box for the liquid suspension implies that these studies were done with the drug material in the bottles inside those boxes. If those are tablet data, from studies using the HB tablets, the figures should not be reused for the new liquid suspension without stating that the clinical data were obtained using another preparation. The new labeling refers to "Tagamet HB 200" without specifying whether tablets or suspension. Even if the suspension is bioequivalent, or approximately so, perhaps the bar charts should indicate that the studies were done on the 200-mg HB tablets.*

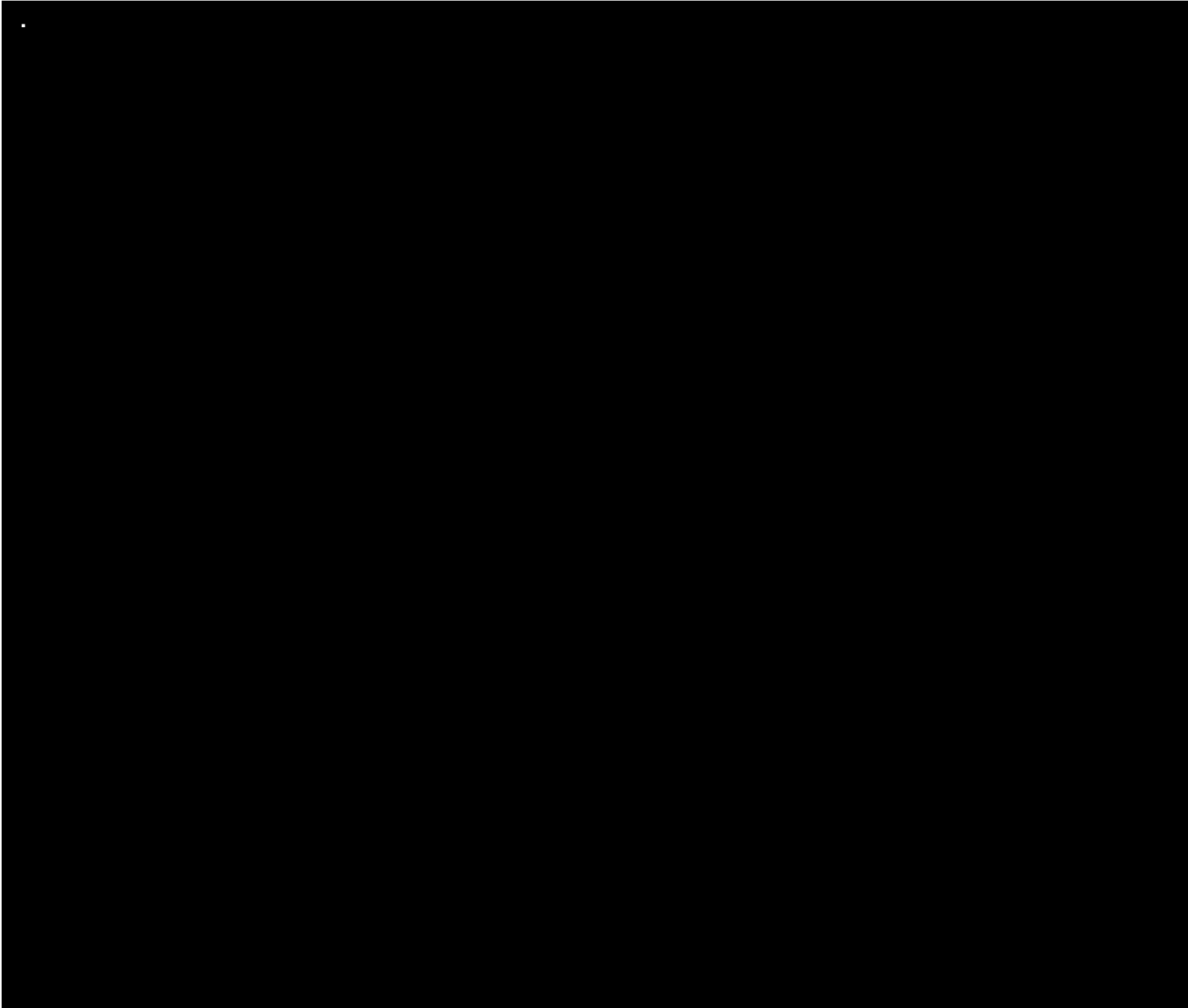
#### **E. Marketing of cimetidine**

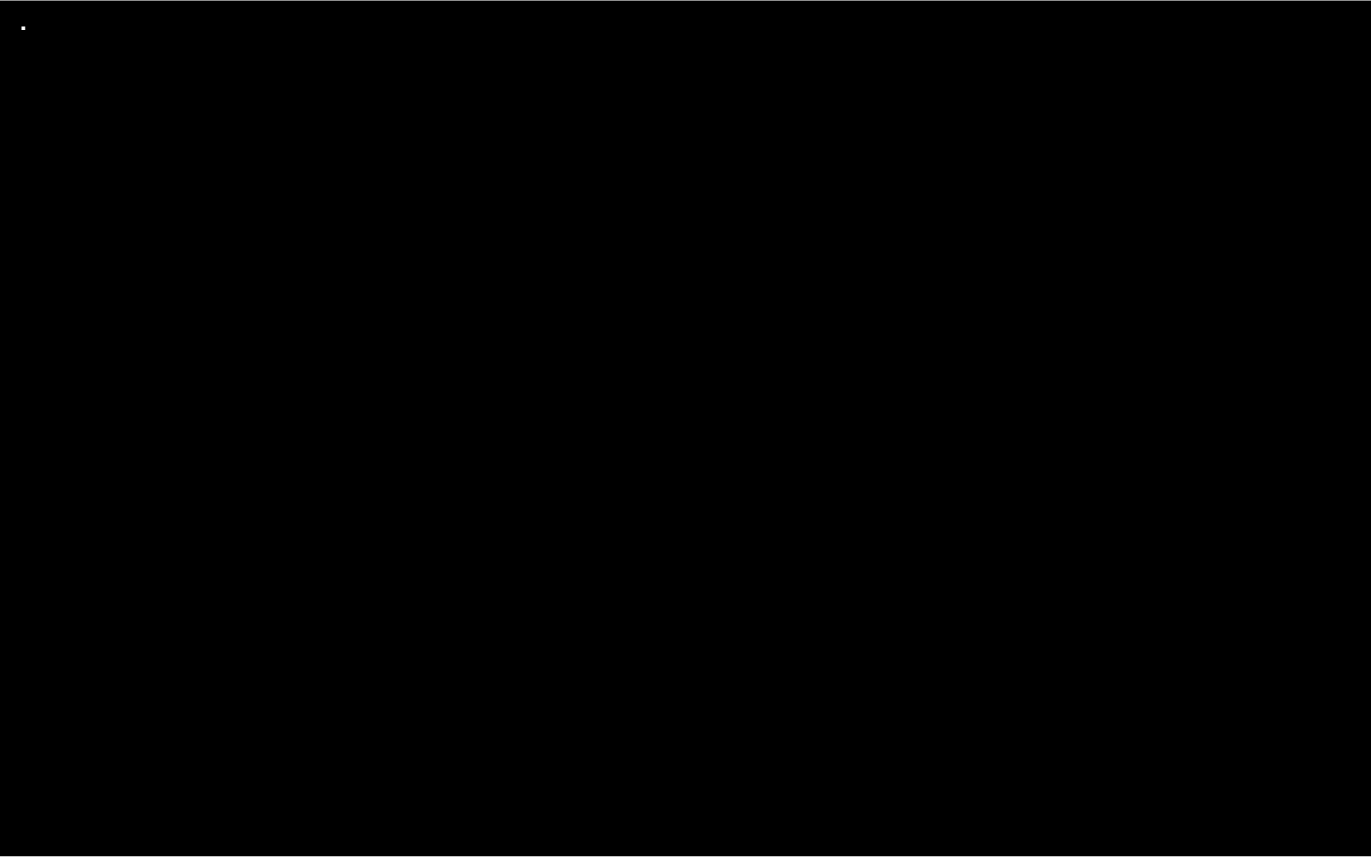
The sponsor states (Volume 1, page 0102) that only in the United Kingdom are suspension formulations of cimetidine approved and marketed (since May 1995), as a dual action liquid containing cimetidine 200 mg as crystalline polymorph A and sodium alginate 500 mg per 10 mL (also available by prescription for treatment of GERD), and a suspension of cimetidine only in a strength of 200 mg/5 mL for healing of duodenal and benign gastric ulcers.

Information on the marketing of cimetidine products in the United States was not provided, nor data on the worldwide use of the various cimetidine products, although a statement on the cartons for Tagamet HB 200 tablets states that "The active ingredient in Tagamet HB 200 is the same medicine doctors have prescribed over 200 million times."

## II. Summary Description of New Formulation

As summarized briefly in Volume 1, pages 108-38, the new liquid suspension of cimetidine uses a [REDACTED] as its principal active constituent. [REDACTED] differs slightly from [REDACTED] that occurs as well developed [REDACTED] and was used in formulating the tablets of Tagamet because of its superior [REDACTED] characteristics. [REDACTED] are obtained as fine [REDACTED] with [REDACTED], respectively. The hydrochloride salt of cimetidine used to make the oral solution and intravenous solution is not [REDACTED] as are the cimetidine [REDACTED]. However, [REDACTED] although quite stable in the [REDACTED] especially in aqueous suspension, even at constant temperature, the transition leading to formation of [REDACTED], and suspensions of inferior appearance. By preparing [REDACTED] as the starting material, from pure [REDACTED] cimetidine base, [REDACTED] can be accomplished, and the [REDACTED] confirmed by [REDACTED]





The sponsor has amended the original application to include the stability data, and has reported this new and unknown peak on [REDACTED]. It has been stated that they are investigating the unknown material by [REDACTED] but results are not yet available. The data to be obtained will be critical to establishing the expiration date for the product.

*Comment: Although this is a chemistry issue, clinical concern may be expressed about approving a formulation whose composition is still imperfectly characterized. The unknown peak appears to be increasing with time in storage, may not be related to cimetidine, and could or could not be a harmless product of one of the inactive other components of the new formulation. There is no rush or urgent need for this drug product, anyway, since an approved oral solution of the cimetidine hydrochloride is available for anyone who needs cimetidine but cannot swallow tablet preparations, prescription or OTC. Perhaps the new suspension should be compared with the oral solution already approved, and not just to the OTC tablet formulation. The unknown substance needs to be identified, its structure and source determined, and consideration may have to be made to reformulate to eliminate the source of the degradation substance unless is proved to be entirely harmless and not to affect the quality of the product over time.*

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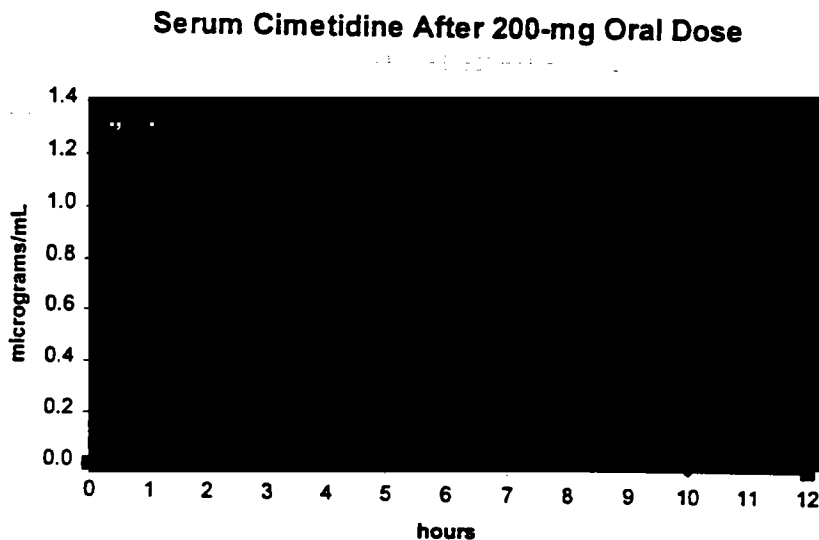
### III. Clinical Pharmacology, Bioequivalence

Study #143-09-11255 (SmithKline Beecham protocol MD-01010) was carried out by a contract facility, [REDACTED] to compare the serum cimetidine levels after oral administration of 200 mg of cimetidine as the HB tablets and the new liquid suspension. For the study, 14 women and 12 men of mean age 35 years were recruited for the study in June-July 1997. Single doses of 200 mg of cimetidine were administered orally with 240 mL water either as the tablet or suspension in random order, with a week of intervening washout, to fasted healthy adults. The participants were kept erect for 4 hours after dosing, not allowed to smoke from an hour before until at least 4 hours after dosing; they were fasted for 10 hours before and for 5 hours after dosing. Serial blood 10 mL-samples were collected before dosing, and then at 15, 30, 45, 60, 75, 90, 105, 120, 140, 160, 180, 210 minutes and at 4, 5, 6, 7, 8, 10, and 12 hours afterward (total about 200 mL of blood). Blood samples were allowed to clot, centrifuged, and serum frozen at  $-20^{\circ}\text{C}$  for later analysis. (Please see report by Dr. C. Cronenberg, Clinical Pharmacology & Biopharmaceutics, dated 27 August 1998).

Two subjects did not complete the second study: #5, [REDACTED] a 41-year-old, black woman, was taken out of the study because her urine tested positive for cannabinoids before her second study; #11, [REDACTED] a 39-year-old, white man, failed to show for the second test for "personal reasons." There were therefore 24 participants, 13 women and 11 men, who completed both studies and had paired data for analyses. While the two formulations produced almost exactly the same total uptake of drug into the blood, as measured by the areas-under-the serum concentration curves (AUCs), the suspension produced a significantly ( $p=0.0071$ ) faster uptake as shown by a shorter time to the maximum serum concentration ( $T_{\text{max}}$ ) of  $1.007 \pm 0.623$  vs  $1.643 \pm 0.948$  hours a shortening of about 39%, and a significantly ( $p=0.0076$ ) greater maximum serum concentration ( $C_{\text{max}}$ ) of  $1.436 \pm 0.396$  vs  $1.241 \pm 0.347$   $\mu\text{g/mL}$ . The almost identical AUCs were produced by the more rapid decline of the serum concentrations after 2 hours than for the tablets. The 90% confidence intervals were within the acceptable limits of 80% to 125% for bioequivalence for  $\text{AUC}_{0 \rightarrow 24}$  (96-104%) and  $\text{AUC}_{0 \rightarrow \infty}$  (96-105%) but slightly high for the  $C_{\text{max}}$  (106-126%).

*Comment: As stated in the report, faster absorption of the suspension was not surprising, for it did not need time for dissolution and could be presented to the absorbing surface more rapidly, and it is well known that liquids tend to be emptied faster from the stomach than solids and could thus reach the absorbing surface of the proximal small intestine faster. The significantly faster absorption after oral administration of a suspension dose is clinically to be expected, and the very slight excess  $C_{\text{max}}$  beyond the defined bioequivalence boundaries has no clinical significance, in light of the fairly wide range of approved dosing for adults for the several indications, and the general safety of cimetidine. However, for children and particularly for infants, the suspension effects and differences from adults are unknown, especially since studies to define dosing in them have not been done.*

The difference between the serum concentration curves shown graphically (data taken from Table 2 of Dr. Cronenberger's biopharmaceutics review) shows at a glance the more rapid rise of the drug in the blood, and its more rapid decline, after subjects took the suspension, compared to the tablets. The areas between the two curves, more for the suspension in the first two hours, and less after two hours, are approximately equal, so the total AUCs of the two preparations are almost the same. The tablets simply take a little longer to dissolve and reach the absorbing surface of the proximal intestine, on average (mean values for the 24 subjects are shown). The standard deviations for the T<sub>max</sub> values are relatively large compared to the mean values [REDACTED], indicating a wide inter-subject variability. The more rapid absorption of the suspension, despite the variations between different people, is generally consistent, and statistically significant (p=0.007).



*Comment: It is clear from the data that the suspension is not exactly bioequivalent to the tablets, being significantly faster absorbed, reaching a higher C<sub>max</sub> in the serum at a mean of about 1 hour, compared to the lower, broader, and later peak after oral dosing with the tablets. The two preparations are, however, bioequivalent in the sense that equal total amounts of drug are absorbed after equal 200-mg oral doses. No data on pharmacodynamic effects were submitted, so the implications of the pharmacokinetic differences on suppression of secretion of gastric acid may not be inferred. Again individual variations in secretory responses to given blood levels of cimetidine are to be expected. Even more pertinent to the proposed OTC use of the suspension is what might be the differences in clinical effects on heartburn or other symptoms, and the major issues of dosing in children for whom a suspension product would be an attractive option.*

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#### **IV. Integrated Summary of Effectiveness**

No clinical data were submitted.

#### **V. Integrated Summary of Safety**

##### **A. Extent of exposure in these submitted studies**

Only 26 participants were enrolled in the only study submitted, of whom 2 had only the first dose, and the other 24 had only two single doses of 200 mg of cimetidine. Compared to the vast experience with cimetidine at much higher doses for up to many years in duration, this newly reported exposure is minor, and does not contribute materially to the safety database.

##### **B. Adverse clinical and laboratory events in these studies**

No serious adverse events were observed in the pharmacokinetic study of the 26 healthy men and women given the single 200-mg doses of cimetidine. Subject #17 (a 35-year-old black woman) reported feeling lightheaded at 4 hours after a dose of the suspension in Period I, and Subject #19 (a 24-year-old black woman) reported stomach ache 2.5 hours after a tablet in Period II. Both events were mild, resolved spontaneously, and could have been drug-induced.

##### **C. Serious adverse events in these studies**

There were no serious adverse events in this study.

##### **D. Drug-drug interactions in these studies**

No other drugs were allowed in this study.

##### **E. Comparisons with post-marketing safety experience**

It is difficult to compare the minimal exposure in such a small number of healthy subjects to the very extensive exposure at much higher doses for long periods of time in millions of sick patients who have been prescribed one or another of the approved preparations of cimetidine over almost 20 years in this country. With respect to safety data on the OTC Tagamet HB 200 mg tablets, no information has been provided.

## F. Use data on the approved and marketed oral solution of cimetidine

An oral solution of cimetidine hydrochloride, sweetened and flavored to mask its bitter taste, has been available for prescription use for many years. It is not labeled for use in children, and its reason for existence is nominally to provide an alternative formulation for those people who need cimetidine, in the opinion of their physicians, but either cannot swallow tablets or prefer a liquid preparation. The oral liquid product contains 300 mg of cimetidine per 5 mL, 2.8% alcohol (140 mg ethanol/5 mL), is sweetened with saccharin and sorbitol, mint-peach flavored, and contains inactive solution stabilizers and preservatives.

The proposed OTC suspension is very likely to be used for infants and children by their parents who buy the formulation with no guidance except the advertising on the box or elsewhere, unless they ask a doctor about it. Because of concerns about possible or probable off-label use of the suspension, an inquiry into use of the oral solution by prescription was initiated soon after receipt of this application. Data from the National Disease and Therapeutic Index (NDTI) database of IMS America were obtained. For the three-year period from 1995 through 1997, Tagamet Liquid was mentioned [REDACTED] and for children less than age 13, [REDACTED]. For oral tablets, both prescription and OTC, only [REDACTED] were used in children. Further, when the category of children 0-12 was broken down to ages 1 to 12 and infants <1 year old, the numbers were [REDACTED] respectively. Thus, of all use of the oral liquid solution of cimetidine over that recent three-year period, 60% was in infants, 24% in children 1 to 12 years of age, 2.5% in adolescents, 3.7% in adults 21-65 years old, and 8.5% in elderly adults >65 years old, with 1.3% unspecified (data from consultation report to HFD-180 by Dr. D. Wysowski, Epidemiology Branch, Division of Pharmacovigilance and Epidemiology, 9 February 1998). The reported clinical use of the oral liquid cimetidine in the infants was principally for esophageal reflux (62%), with some for post-inflammatory pulmonary fibrosis (7%), anomalies of the digestive system (5%), unspecified gastritis and gastroduodenitis (4%), nausea and vomiting (3%), and other (19%).

*Comment: This information raised serious concerns about allowing a suspension formulation, sweetened and flavored to be very attractive to children, to be used OTC, with uncertain medical supervision if any. If physicians, presumably mostly pediatricians and family physicians, were prescribing cimetidine for infants and children, with very little information on appropriate indications, dosing, efficacy, and safety, then how could mothers evaluate the use of this potent drug in their children? The pediatric use prescription labeling states:*

**Pediatric Use:** Clinical experience in children is limited. Therefore, Tagamet therapy cannot be recommended for children under 16, unless, in the judgment of the physician, anticipated benefits outweigh the potential risks. In very limited experience, doses of 20 to 40 mg/kg per day have been used.

*For the OTC use of Tagamet HB 200 mg tablets, the age for seeking medical advice was changed from the disclaimer for use in children <16 to "ask a doctor" for children <12 years of age. Ask a doctor what? There are almost no data for doctors to rely upon in giving advice. This submission does not provide any reassurance on the issues of unapproved, inappropriate, off-label use of cimetidine in children, and especially in infants who scarcely complain of heartburn for which the OTC tablets are labeled.*

## VI. Summary of Benefits, Risks of the Proposed Suspension Formulation

There simply are insufficient data to assess clinical benefits or risks of the use of the proposed new liquid suspension for infants and children for whom the bulk of the new product is very likely to be used. It has been shown that labeling does not even control adequately the behavior of the prescribing physicians, and it is even more likely that the vast preponderance of OTC use of a new liquid suspension would be for infants and children.

A request was sent to the sponsor on 31 July 1998, asking for any available information concerning clinical safety/efficacy, pharmacokinetic/pharmacodynamic data on cimetidine use for children and infants. No response has been received as yet.

There does not appear to be any apparent need of consumers for this new suspension product. There is already an adequate liquid solution product approved and available to meet the needs of those with real indications for cimetidine who cannot swallow tablets. That oral solution could be considered for OTC use, if its preponderant use in children and infants could be justified.

The application to introduce a new liquid suspension based simply on bioequivalence is not clinically appropriate at this time. Studies are needed of the pharmacokinetics, pharmacodynamics, clinical efficacy and safety, and establishment of the appropriate doses for defined indications in children and infants. Denial of the request for approval of the suspension product cannot be considered "interference with the practice of medicine," since consumers will simply be able to buy as much of the suspension as they wish, use it for whatever they want to in their children, ask or not ask doctors for advice (and the doctors have little or no clinical evidence upon which to base such advice, even if asked).

This submission has three main problems, but the greatest is the lack of information about potential use of the product for infants and children. The unknown material that builds up on storage can be corrected perhaps by identifying it, determining its source, and perhaps substituting another compound for it in the formulation. The minor lack of bioequivalence of Cmax and Tmax are not clinical differences of any concern; it would be expected that the suspension would be absorbed a little faster than tablets. However, the concerns about use of the proposed suspension in children and infants raise serious medical and clinical concerns. The sponsor has not addressed these concerns.

Labeling simply does not control adequately what people do, even well informed physicians. For consumers who are not trained or educated to carry out adequate assessments of risks versus possible benefits, it may be very difficult to interpret and evaluate the labeling on a box of OTC product called an "acid reducer," to know the appropriate dose and regimen for their child, and for what problems it should be used. Only by doing appropriate studies to define clear indications for cimetidine use for infants and children, showing efficacy and safety for those indications, and establishing appropriate dosing in them, can a suspension product be made available safely to consumers for OTC purchase, in the opinion of this reviewer.

## VII. Regulatory Recommendations

On grounds of clinical concern about highly probable use of the proposed liquid suspension principally for infants and children, and grossly inadequate information about such use, approval of this product for OTC sale is not medically recommended.

There may well be valid indications for use of cimetidine for infants and children; if so data to support such indications should be submitted, clearly establishing appropriate dosing and regimens. Both pharmacokinetic data on blood levels, and pharmacodynamic data on gastric acid suppression should also be obtained for infants and young children. The approval of cimetidine tablets for adult heartburn does not extend automatically to use for infants and young children who do not complain of heartburn nor can they adequately express their relief of heartburn. If they are being given cimetidine to prevent gastroesophageal reflux and possible aspiration pneumonitis, then let that new indication be established. If there are other indications for use of cimetidine in children, then let them also be proved.

/s/ [REDACTED]

15 September 1998

John R. Senior, M.D., Medical Officer  
Division of Gastrointestinal & Coagulation Drug Products

date

cc:

NDA 20-951  
HFD-180  
HFD-180/LTalarico  
HFD-180/HGallo-Torres  
HFD-180/JSenior  
HFD-180/JChoudary  
HFD-180/MYsern  
HFD-870/CCronenberger  
HFD-181/CSO  
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September 16, 1998

*N. Ad. I do not concur.  
See separate memorandum.*

/s/ [REDACTED]

*Medical Officer's Review (Dr. Senior) and  
recommendations noted - Pending  
issues of characterization of preparation  
impurities must be addressed -  
labeling revision will be discussed  
with OTC to minimize the risk of  
pediatric use of the cimetidine suspension -*

/s/ [REDACTED]

APPEARS THIS WAY ON ORIGINAL

9-17-98