CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-082

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Hilfiker

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-082/N-000

JUL 25 2000

Generic name, dose and formulation:	clemastine fumarate/acetaminophen /pseudoephedrine hydrochloride Tablets
Trade name:	Tavist Allergy/Sinus/Headache
Sponsor:	Novartis Consumer Health, Inc.
Type of submission:	Original NDA, Category 4S
Dates of submission:	10/07/1999, 06/14/2000
Reviewer:	Monique Wakelkamp-Barnes, M.D., Ph.D.

I SYNOPSIS

Tavist Allergy/Sinus/Headache is a triple combination product, consisting of an antihistamine, a nasal decongestant and an analgesic/antipyretic intended for the OTC market and to be used in adults and children 12 years and older. Each tablet contains 0.335 mg clemastine fumarate (0.25 mg clemastine), 30 mg pseudoephedrine hydrochloride and 500 mg acetaminophen. The proposed dosing regimen is 2 tablets every 6 hours. The combination of these three active ingredients has not previously been approved. The dosing regimen for the proposed triple combination product is more frequent (every 6 h) as compared to the currently approved clemastine regimens (every 12 h), although the total daily dose would remain the same.

The comparative bioavailability of the proposed combination product (CTC) vs. the separate administration of clemastine fumarate and a pseudoephedrine/acetaminophen combination was investigated in two studies. The first study (HSC-152) had a four-way cross-over design, comparing 2 CTC tablets, one 0.5 mg clemastine tablet (clinical service formulation), 5 ml Tavist syrup (clemastine fumarate 0.1 mg/ml), and 2 TheraFlu® Sinus tablets (30 mg pseudoephedrine and 500 mg acetaminophen per tablet). It was found that clemastine from the CTC tablet was not bioequivalent to either the clinical service formulation or to Tavist Syrup. However, the CTC tablets were bioequivalent to the TheraFlu Sinus tablets with respect to pseudoephedrine and acetaminophen.

Under the hypothesis that the clemastine dose was too low, relative to the sensitivity of the assay, study HSC-153B was conducted, in which the respective doses were doubled. This study also had a four-way cross-over design comparing 4 CTC tablets, two 0.5 mg clemastine tablets (clinical service formulation), two 0.5 mg clemastine tablets (clinical service formulation) plus 4 TheraFlu Sinus tablets, and one Tavist-1 (1 mg clemastine) tablet. With respect to clemastine, 4 CTC tablets were found to be bioequivalent to two 0.5 mg clemastine tablets, two 0.5 mg clemastine tablets combined with four TheraFlu Sinus tablets, and to one Tavist-1 tablet. The 0.5 mg clemastine tablets also were bioequivalent to 0.5 mg clemastine tablets combined with the TheraFlu Sinus tablets and to Tavist-1. This indicates that there were no significant effects of

formulation, pseudoephedrine or acetaminophen on the bioavailability of clemastine. With respect to pseudoephedrine and acetaminophen, the CTC tablets were bioequivalent to the administration of the 0.5 mg clemastine tablets plus the TheraFlu Sinus tablets, indicating that the CTC formulation does not significantly influence the bioavailability of pseudoephedrine or acetaminophen. The bioequivalence of the CTC tablets to the TheraFlu Sinus tablets with respect to pseudoephedrine and acetaminophen, as observed in study HSC-152 also indicates a lack of kinetic interaction between clemastine and pseudoephedrine/acetaminophen.

Reviewer Comments

1) The dissolution specifications proposed by the sponsor (using water as medium, USP II (paddle), temp 37°C, volume 900 ml, speed 50 rpm) are as follows:
Clemastine fumarate: Q = — at — min
Pseudoephedrine hydrochloride: Q = — at ~min
Acetaminophen: Q = — at — min

Based on the submitted dissolution data for the batch that was used in the comparative BA studies and other submitted stability data, these specifications should be revised to:
Q = — at 30 min for clemastine fumarate, pseudoephedrine and acetaminophen.

II RECOMMENDATION

The Human Pharmacokinetics and Bioavailability section of NDA 21-082 is acceptable to support the BA and BE regulation covered by 21 CFR part 320, provided that comment 1 is adequately addressed. Comment 1 should be conveyed to the sponsor.

Reviewer Date

/S/ 07/25/2000

Monique Wakelkamp-Barnes, M.D., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

Final version signed by Ramana Uppoor, Ph.D., Teamleader

/S/ 07/25/00

cc NDA 21-082/N-000:

	Division File
HFD-870:	Shiew-Mei Huang
HFD-570:	Ramana Uppoor
	Monique Wakelkamp-Barnes
	Charles Lee
	Kevin Swiss
	David Hilfiker
CDR:	Barbara Murphy

III BACKGROUND

Q. What is Tavist Allergy/Sinus/Headache?

Tavist Allergy/Sinus/Headache is a triple combination product, consisting of an antihistamine, a nasal decongestant and an analgesic/antipyretic intended for the OTC market and to be used in adults and children 12 years and older. Each tablet contains 0.335 mg clemastine fumarate (0.25 mg clemastine), 30 mg pseudoephedrine hydrochloride and 500 mg acetaminophen. The proposed dosing regimen is 2 tablets every 6 hours.

Both pseudoephedrine hydrochloride and acetaminophen are currently available as OTC drugs, either single or in combination. Pseudoephedrine is an adrenergic agent with decongestant action, available OTC at a maximum daily dose of 240 mg. Acetaminophen is available OTC at a maximum daily dose of 4000 mg. The tentative final monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Anti-asthmatic Combination Drug Products (53 FR 30522) allows for combination products of pseudoephedrine and acetaminophen, if their respective daily dosage limits are maintained. Pseudoephedrine and acetaminophen may also be combined with a number of antihistamines for OTC use. However, clemastine fumarate is currently not included in the active ingredient list of antihistamines of the applicable OTC monographs. Also, the combination of these three active ingredients has not been previously approved. The present submission is therefore a type 4 NDA (new combination).

Clemastine fumarate is currently available OTC as a single ingredient product, for example Tavist® Allergy 12 Hour Tablets, formerly called Tavist-1®, containing 1 mg clemastine per tablet and as a combination product, Tavist-D® 12-Hour Relief Tablets or Caplets (1 mg clemastine plus 75 mg extended release phenylpropanolamine hydrochloride). The recommended dose of each of these products is one tablet or caplet every 12 h.

Q. What studies have been submitted to the NDA?

The Human Pharmacokinetic and Bioavailability section of the NDA contained four *in vivo* pharmacokinetic studies (HSC-302, -151, -152 and -153B). The most relevant studies were HSC-152 and HSC-153B, in which the relative bioavailability of clemastine, pseudoephedrine and acetaminophen was investigated after administration of the triple combination tablet ("the CTC formulation"), as compared to administration of a clemastine product only and clemastine plus a pseudoephedrine/acetaminophen combination. The studies also aimed at investigating whether there is a pharmacokinetic interaction between clemastine and pseudoephedrine/acetaminophen.

IV FORMULATION

Q.	*What is the proposed CTC tablet formulation?*

The proposed CTC formulation is a single layer, immediate release, capsule shaped, film-coated tablet, containing 0.335 mg clemastine fumarate (0.25 mg clemastine), 30 mg pseudoephedrine hydrochloride and 500 mg acetaminophen. The composition of the tablet is as follows (Table 1):

Table 1.

Ingredient	mg/tablet
Clemastine Fumarate (USP)	0.335
Pseudoephedrine Hydrochloride (USP)	30.0
Maltodextrin (NF)	
Starch (NF)	
Calcium Sulfate (NF)	
Silicon Dioxide (NF)	
Total	

Ingredient	(mg/tablet)	(mg/tablet)
Acetaminophen		
Starch (NF)		
Silicon Dioxide (NF)		
Glyceryl Behenate (NF)		
Methylparaben (NF)		
Titanium Dioxide (USP)		
Silicon Dioxide (NF)		
Methylcellulose (USP)		
Sodium Lauryl Sulfate (NF)		
Maltodextrin (NF)		
Polyethylene Glycol (NF)		
Total Weight		

In short, the clemastine fumarate/pseudoephedrine hydrochloride and the acetaminophen The proposed CTC formulation is to be manufactured, tested, packaged, labeled and released by Novartis Consumer Health, 10401 Highway 6, Lincoln, Nebraska.

Q.	*Are there any differences between the formulations used in the comparative bioavailability studies and the marketed or to-be-marketed formulations?*

The different drug formulations used through studies HSC-302, -151, -152 and -153B are displayed in Table 2. According to the sponsor, no formulation or manufacturing changes were made to either the clemastine clinical service formulation or the proposed CTC tablet during the

study program. The production scale batch size of the CTC tablet will be [redacted] tablets. The batch size of CTC tablets used in the pivotal bioequivalence studies (HSC-152 and -153) represents 10% of the full size production scale batch.

Table 2.

Study #	Dosage form	Lot/Batch Number	Lot/Batch Size	Formulation
HSC-302	Clemastine 0.5 mg Tablet	Lot 662-1854.37	[redacted]	Clinical Service Formula
	Clemastine 1 mg Tablet	Lot 662-1854.38	[redacted]	Clinical Service Formula
	Tavist-1 Tablet (1 mg)	Lot 30044	[redacted]	Marketed
		Lot 30049	[redacted]	Marketed
HSC-151	Clemastine 0.5 mg Tablet	Batch 651-1890.36	[redacted]	Clinical Service Formula
	Tavist-1 Tablet (1 mg)	Batch 118146	[redacted]	Marketed
HSC-152	CTC Tablet	Batch 690-1999.14	[redacted]	Proposed Market Formula
	Tavist Syrup (0.1 mg/ml)	Batch 18167	[redacted]	Marketed
	TheraFlu Sinus Tablet	Batch 18829	[redacted]	Marketed
	Clemastine 0.5 mg Tablet	Batch 651-1890.36	[redacted]	Clinical Service Formula
HSC-153B	CTC Tablet	Batch 690-1999.14	[redacted]	Proposed Market Formula
	Clemastine 0.5 mg Tablet	Batch 651-1890.36	[redacted]	Clinical Service Formula
	TheraFlu Sinus Tablet	Batch 19940	[redacted]	Marketed
	Tavist-1 (1 mg)	Batch 118163	[redacted]	Marketed

Q. Are the proposed dissolution specifications acceptable?

Clemastine fumarate, pseudoephedrine hydrochloride and acetaminophen dissolution profiles from CTC tablet formulations, using batch nr. 690-1999.14 were studied in 3 different media, namely de-aerated water, citrate buffer, pH 4.0 and simulated intestinal fluid without enzymes (pH ≈ 6.8). The release of pseudoephedrine and acetaminophen from the CTC tablets was also studied in simulated gastric fluid without enzymes (pH ≈ 1.2). The USP II (paddle) method was used, 37 °C, 900 ml volume, paddle speed 50 rpm. Dissolution data for batch 690-1999.14 are displayed in Table 3.

Table 3.

N=12	15 min (% diss) average/max/min	30 min (% diss) average/max/min	45 min (% diss) average/max/min	60 min (% diss) average/max/min
CLEMASTINE				
Water	77.5/	95.1/	98.7/	96.5/
Citrate buffer	62.2/	86.0/	95.3/	97.0/
SIF w/o enzymes	68.4/	85.6/	91.7/	95.9/
Water 24 mo stability	79.6/	91.3/	94.9/	97.1/
PSEUDOEPHEDRINE				
Water	83.4/	100.9/	101.8/	102.1/
Citrate buffer	75.0/	93.0/	99.1/	100.0/
SIF w/o enzymes	76.3/	91.9/	100.6/	103.8/
SGF w/o enzymes	58.9/	94.4/	98.7/	99.1/
Water 24 mo stability	86.5/	99.3/	101.7/	102.2/
ACETAMINOPHEN				
Water	76.8/	98.4/	99.5/	100.0/
Citrate buffer	68.4/	91.3/	98.0/	98.2/
SIF w/o enzymes	72.9/	89.8/	95.2/	98.3/
SGF w/o enzymes	62.0/	91.1/	98.0/	99.2/
Water 24 mo stability	79.6/	91.0/	94.8/	96.5/

Average, maximum and minimum percentage dissolved of clemastine fumarate, pseudoephedrine hydrochloride and acetaminophen from the CTC tablet at different time points, using different dissolution media. USP II (paddle), temp 37 °C, volume 900 ml, speed 50 rpm. Dissolution data were generated after initial release of the batch. Stability data after 24 months of ambient bulk storage, using water as medium, are shown in this table as well.

The dissolution specifications proposed by the sponsor are as follows:
Selected medium: water
Clemastine fumarate: Q = — at — min
Pseudoephedrine hydrochloride Q = — at — min
Acetaminophen: Q = — at — min
The proposed shelf life is — months

Reviewer Comment:
Based on these submitted data and other stability data, the *in vitro* dissolution specifications for the CTC tablet, using the proposed dissolution method, should be revised to Q = — at 30 min for clemastine fumarate, pseudoephedrine and acetaminophen.

V ASSAY METHODOLOGY AND VALIDATION

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VI CLINICAL PHARMACOLOGY

Q.	***What is the comparative bioavailability of the proposed combination tablet vs. the separate administration of the active ingredients? Is there equivalent rate and extent of absorption? Is there reason to suspect a pharmacokinetic interaction?***

The comparative bioavailability of the CTC tablets vs. the separate administration of clemastine fumarate and pseudoephedrine/acetaminophen was investigated in studies HSC-152 and HSC-153B. Since the pseudoephedrine/acetaminophen combination was already approved, the separate administration of these active ingredients was not needed.

Study HSC-152 had a randomized, open-label, four-way cross-over design and included 32 healthy subjects, age 19-50 years, 50% were male. Twenty-nine subjects could be evaluated for bioequivalence. The subjects were given, under fasting conditions, a single administration of one of 4 cross-over dose regimens with at least a 7-day washout between the 4 treatments: 2 CTC tablets, one 0.5 mg clemastine tablet (clinical service formulation), 5 ml Tavist syrup (0.1 mg/ml), and 2 TheraFlu® Sinus tablets (30 mg pseudoephedrine and 500 mg acetaminophen per tablet). Blood samples for determination of plasma levels of clemastine, pseudoephedrine and acetaminophen were taken pre-dose and at 20 min and 40 min, 1 h, 1.5, 2, 3, 4, 5, 6, 9, 12, 16, 24, 36, 48 and 72 hours after dosing. Pharmacokinetic parameters obtained are displayed in Table 6.

Table 6.

	CTC tablets	0.5 mg tablet	TheraFlu Sinus	Tavist Syrup
CLEMASTINE				
C_{max} (pg/ml)	593 (176)	650 (176)	-	601 (167)
T_{max} (h)	4.93 (0.84)	4.76 (1.09)	-	4.55 (1.02)
$AUC_{(0-t)}$ (pg·h/ml)	8447 (5241)	10270 (7299)	-	9695 (7883)
$AUC_{(0-\infty)}$ (pg·h/ml)	11721 (7950)	15529 (19869)	-	16282 (26750)
$t_{½}$ (h)	14.71 (9.89)	17.28 (18.63)		19.89 (23.76)
PSEUDOEPHEDRINE				
C_{max} (ng/ml)	215.9 (49.2)	-	223.7 (52.5)	-
T_{max} (h)	2.64 (1.05)	-	2.32 (1.03)	-
$AUC_{(0-t)}$ (ng·h/ml)	2319 (624)	-	2344 (632)	-
$AUC_{(0-\infty)}$ (ng·h/ml)	2466 (649)	-	2500 (664)	-
$t_{½}$ (h)	5.84 (1.28)		5.74 (1.17)	
ACETAMINOPHEN				
C_{max} (µg/ml)	15.30 (5.69)	-	15.85 (5.38)	-
T_{max} (h)	1.13 (0.76)	-	0.96 (0.69)	-
$AUC_{(0-t)}$ (µg·h/ml)	64.66 (23.13)	-	63.75 (23.15)	-
$AUC_{(0-\infty)}$ (µg·h/ml)	65.95 (23.47)	-	64.79 (23.37)	-
$t_{½}$ (h)	4.32 (0.87)		4.43 (0.92)	

Pharmacokinetic parameters (arithmetic mean and SD) of clemastine fumarate, pseudoephedrine and acetaminophen after the administration of CTC tablets, the clemastine clinical service formulation, TheraFlu Sinus tablets and Tavist Syrup.

For the evaluation of bioequivalence, an ANOVA model was used that included the factors sequence, subject within sequence, period and treatment. Ninety percent confidence intervals were calculated for the ratio of the geometric means of C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ (Table 7). It was found that clemastine from the CTC tablet was not bioequivalent to either the clinical service formulation or to Tavist Syrup. However, the CTC tablets were bioequivalent to the TheraFlu Sinus tablets with respect to pseudoephedrine and acetaminophen.

Table 7.

		CTC tablets	0.5 mg tablet	Theraflu Sinus	Tavist Syrup
CLEMASTINE					
CTC tablets	C_{max} (pg/ml)	-	84.9% - 96.6%	-	91.4% - 104.0%
	$AUC_{(0-t)}$ (pg·h/ml)	-	71.2% - 94.6%	-	76.1% - 101.0%
	$AUC_{(0-inf)}$ (pg·h/ml)	-	71.6% - 93.8%	-	73.8% - 97.3%
0.5 mg tablets	C_{max} (pg/ml)	-	-	-	87.0% - 99.1%
	$AUC_{(0-t)}$ (pg·h/ml)	-	-	-	81.2% - 107.9%
	$AUC_{(0-inf)}$ (pg·h/ml)	-	-	-	84.4% - 110.8%
PSEUDOEPHEDRINE					
CTC tablets	C_{max} (ng/ml)	-	-	93.6% - 99.8%	-
	$AUC_{(0-t)}$ (ng·h/ml)	-	-	94.3% - 104.1%	-
	$AUC_{(0-inf)}$ (ng·h/ml)	-	-	94.4% - 103.2%	-
ACETAMINOPHEN					
CTC tablets	C_{max} (µg/ml)	-	-	88.7% - 103.3%	-
	$AUC_{(0-t)}$ (µg·h/ml)	-	-	98.9% - 104.9%	-
	$AUC_{(0-inf)}$ (µg·h/ml)	-	-	99.2% - 105.2%	-

90% confidence intervals for the ratio of the geometric means of C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of clemastine fumarate, pseudoephedrine and acetaminophen.

Reviewer Comment:
Bioequivalence criteria for clemastine comparison between the CTC tablet and the two other clemastine formulations were met for C_{max}, but not for $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$. It was postulated by the sponsor that this result may be due to a too low clemastine dose, relative to the sensitivity of the assay. This may indeed play a role, since the extrapolated part of the AUC constituted 27.9% (CTC tablets), 33.9% (clinical service formulation) and 40.5% (Tavist Syrup), respectively, of the total AUC (Table 6). However, it should also be noted that the clinical service formulation of clemastine was found to be bioequivalent to Tavist Syrup, with respect to C_{max}, as well as $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$. The findings of study HSC-152 led to the design of new study, HSC-153B, in which the respective doses were doubled.

Study HSC-153B also had a randomized, open-label, four-way cross-over design and included 32 healthy male subjects, age 19-49 years. Thirty-one subjects completed the study. Under fasting conditions, the subjects were given a single administration of one of 4 cross-over dose regimens with at least a 7-day washout between the treatments: 4 CTC tablets, two 0.5 mg clemastine tablets (clinical service formulation), two 0.5 mg clemastine tablets (clinical service formulation) plus 4 TheraFlu Sinus tablets, and one Tavist-1 (1 mg clemastine) tablet. Blood samples for determination of plasma levels of clemastine, pseudoephedrine and acetaminophen were taken pre-dose and at 30 min, 1 h, 1.5, 2, 3, 4, 5, 6, 9, 12, 16, 24, 30, 36, 48, 60 and 72 hours after dosing.

Reviewer Comment:
Five subjects had quantifiable pre-dose clemastine concentrations during study HSC-153B: subject 2 during treatment periods 1 and 2; subject 9 during periods 1, 2 and 3; subject 15 during period 3; subject 18 during period 2 and subject 21 during period 1. Also, one subject had a quantifiable pre-dose concentration for pseudoephedrine, as well as for acetaminophen (subject 15, period 3) (Table 8). For these subjects and periods, the observed concentrations were adjusted for baseline by subtracting for each one value equal to $C_0 * \exp^{(-kel*t)}$. Bioequivalence calculations were performed using baseline adjusted concentrations. Considering that most values were close to the LLOQ, this approach seems acceptable.

Table 8.

Subject no.	*clemastine* CTC tablets	*clemastine* 0.5 mg tablets	*clemastine* 0.5 mg tablets + TheraFlu Sinus	*clemastine* Tavist-1	*pseudoephedrine* CTC tablets	*acetaminophen* CTC tablets
2						
9						
15						
18						
21						

Observed pre-dose concentrations of clemastine fumarate, pseudoephedrine and acetaminophen during study HSC-153B.

Pharmacokinetic parameters obtained are displayed in Table 9. Mean (SD) (baseline-adjusted) clemastine fumarate, pseudoephedrine and acetaminophen concentration vs. time profiles are depicted in Figure 1.1, 2.1 and 3.1, respectively. Please note that certain treatment profiles were shifted to the right for visual clarity.

Table 9.

	CTC tablets	0.5 mg tablets	0.5 mg tablets + TheraFlu Sinus	Tavist-1
CLEMASTINE				
C_{max} (pg/ml)	1031 (246.4)	1010 (241.8)	1114 (272.1)	969.2 (254.2)
T_{max} (h)	5.32 (1.30)	6.03 (5.80)	4.47 (1.57)	4.64 (1.95)
$AUC_{(0-t)}$ (pg·h/ml)	19990 (7154)	21740 (9167)	21980 (7449)	19610 (6764)
$AUC_{(0-\infty)}$ (pg·h/ml)	24560 (8637)	26230 (8909)	27710 (11520)	23820 (7320)
$t_{½}$ (h)	22.24 (7.65)	23.94 (7.17)	23.33 (13.16)	20.40 (8.00)
PSEUDOEPHEDRINE				
C_{max} (ng/ml)	399.8 (51.2)	-	403.0 (52.7)	-
T_{max} (h)	2.74 (0.96)	-	2.59 (1.12)	-
$AUC_{(0-t)}$ (ng·h/ml)	4719 (972.5)	-	4725 (1302)	-
$AUC_{(0-\infty)}$ (ng·h/ml)	4854 (981.2)	-	4883 (1334)	-
$t_{½}$ (h)	6.26 (0.97)	-	6.18 (1.09)	-
ACETAMINOPHEN				
C_{max} (µg/ml)	23.1 (4.8)	-	24.9 (4.9)	-
T_{max} (h)	1.27 (0.58)	-	0.97 (0.59)	-
$AUC_{(0-t)}$ (µg·h/ml)	116.0 (25.6)	-	118.3 (25.9)	-
$AUC_{(0-\infty)}$ (µg·h/ml)	117.3 (25.7)	-	119.6 (25.9)	-
$t_{½}$ (h)	5.56 (0.86)	-	5.59 (0.88)	-

Pharmacokinetic parameters (arithmetic mean and SD) of clemastine fumarate, pseudoephedrine and acetaminophen after the administration of CTC tablets, the clemastine clinical service formulation, the clemastine clinical service formulation plus TheraFlu Sinus tablets and a Tavist-1 tablet.

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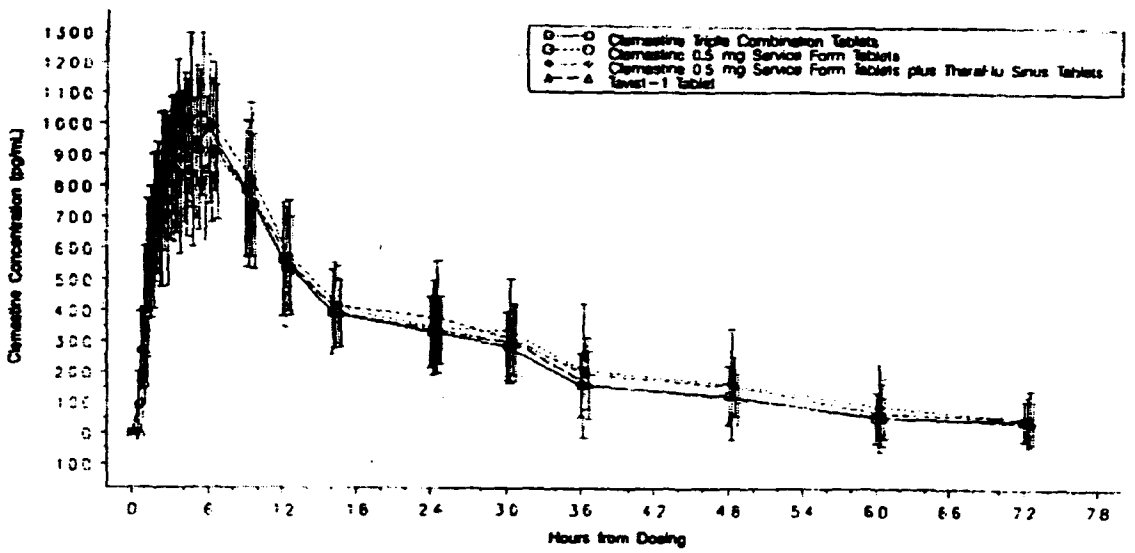
Figure 1.1

Mean (S.D.) Baseline – Adjusted Clemastine Concentrations Versus Time

Linear Scale



Treatments B, C, and D are shifted to the right for ease of reading

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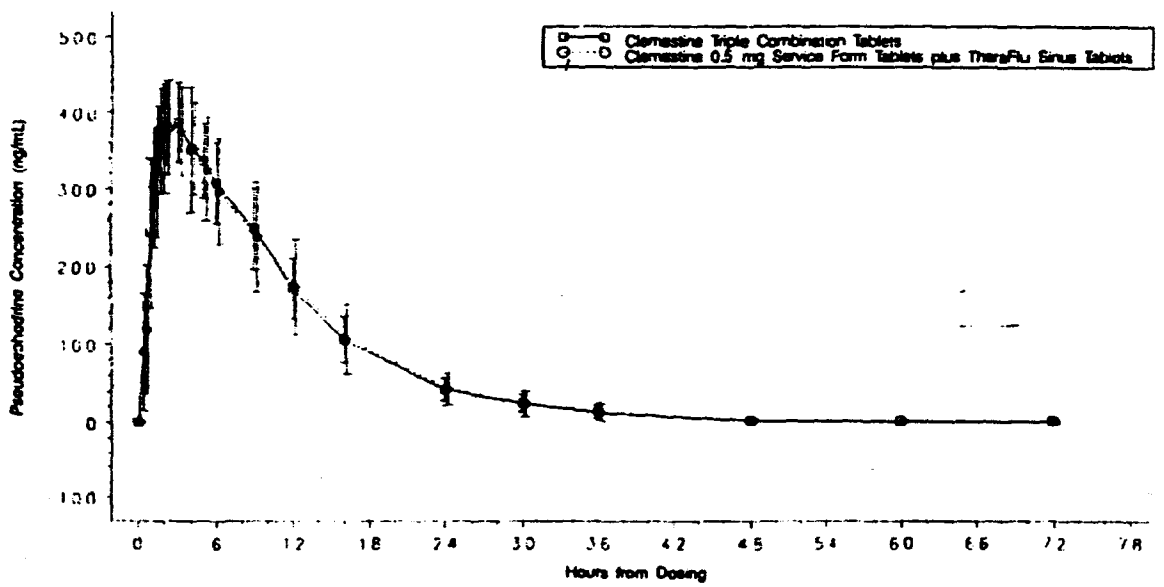
Protocol No HSC-1538

Figure 2.1

Mean (S.D.) Baseline – Adjusted Pseudoephedrine Concentrations Versus Time

Linear Scale

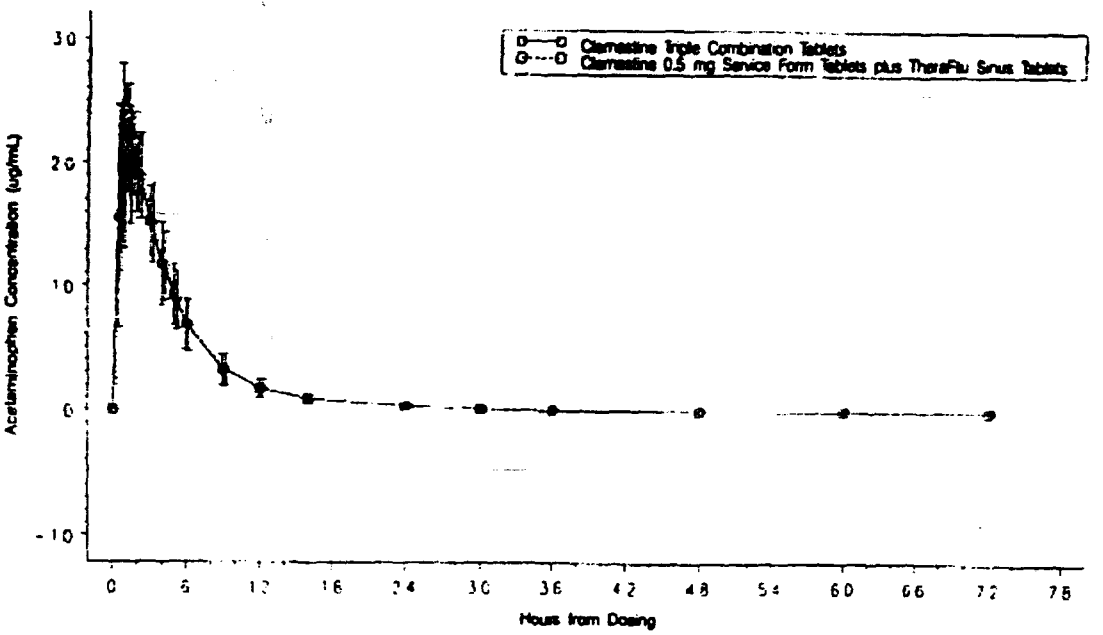


Treatment B is shifted to the right for ease of reading

Figure 3.1

Mean (S.D.) Baseline-Adjusted Acetaminophen Concentrations Versus Time

Linear Scale



Treatment B is shifted to the right for ease of reading

Differences between treatments were compared, using an analysis of variance model that incorporated the following factors: sequence, subject within sequence, period, treatment and, additionally, previous treatment (carry-over). The "previous treatment" term was removed from the model, if it was not statistically significant at the 0.05 level. Since no carry-over effects were found, the "previous treatment" term was removed from the final ANOVA analyses. Ninety percent confidence intervals were calculated for the ratio of the geometric means of C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ (Table 10). With respect to clemastine, 4 CTC tablets were found to be bioequivalent to two 0.5 mg clemastine tablets, two 0.5 mg clemastine tablets combined with four TheraFlu Sinus tablets, and to one Tavist-1 tablet. The 0.5 mg clemastine tablets also were bioequivalent to 0.5 mg clemastine tablets combined with the TheraFlu Sinus tablets and to Tavist-1. This indicates that there were no significant effects of formulation, pseudoephedrine or acetaminophen on the bioavailability of clemastine. With respect to pseudoephedrine and acetaminophen, the CTC tablets were bioequivalent to the administration of the 0.5 mg clemastine tablets plus the TheraFlu Sinus tablets, indicating that the CTC formulation does not significantly influence the bioavailability of pseudoephedrine or acetaminophen. The bioequivalence of the CTC tablets to the TheraFlu Sinus tablets with respect to pseudoephedrine and acetaminophen, as observed in study HSC-152 also indicates a lack of kinetic interaction between clemastine and pseudoephedrine/acetaminophen.

Reviewer Comment:
Since no clemastine, pseudoephedrine or acetaminophen metabolites were measured during any of the studies, the presence or absence of a possible pharmacokinetic interaction at the metabolite level could not be thoroughly evaluated. The enzymes involved in clemastine metabolism have not been well characterised.

Table 10.

		CTC tablets	0.5 mg tablets	0.5 mg tablets + Theraflu Sinus	Tavist-1
CLEMASTINE					
CTC tablets	C_{max} (pg/ml)	-	96.5% - 107.4%	87.8% - 97.8%	101.2% - 112.6%
	$AUC_{(0-t)}$ (pg·h/ml)	-	84.9% - 102.3 %	82.6% - 99.5%	93.1% - 112.1%
	$AUC_{(0-\infty)}$ (pg·h/ml)	-	83.5% – 100.3%	83.9% - 100.7%	93.2% - 111.7%
0.5 mg tablets	C_{max} (pg/ml)	-	-	86.3% - 96.0%	99.4% - 110.7%
	$AUC_{(0-t)}$ (pg·h/ml)	-	-	88.7% - 106.8%	99.8% - 120.3%
	$AUC_{(0-\infty)}$ (pg·h/ml)	-	-	91.6% - 110.2%	101.7% - 122.2%
PSEUDOEPHEDRINE					
CTC tablets	C_{max} (ng/ml)	-	-	97.4% - 100.7%	-
	$AUC_{(0-t)}$ (ng·h/ml)	-	-	95.5% - 107.6%	-
	$AUC_{(0-\infty)}$ (ng·h/ml)	-	-	95.1% - 107.2%	-
ACETAMINOPHEN					
CTC tablets	C_{max} (µg/ml)	-	-	86.3% - 99.0%	-
	$AUC_{(0-t)}$ (µg·h/ml)	-	-	96.1% - 99.9%	-
	$AUC_{(0-\infty)}$ (µg·h/ml)	-	-	96.1% - 99.8%	-

90% confidence intervals for the ratio of the geometric means of C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of clemastine fumarate, pseudoephedrine and acetaminophen.

Q. ***The proposed dosing regimen for the CTC tablet with regard to clemastine is very different from that of previously approved clemastine fumarate products, namely 2x0.25 mg clemastine every 6 h vs. 1 mg clemastine every 12 h. How do these dosing regimen compare after multiple dosing?***

No comparative studies were performed using multiple dosing of the CTC tablet. However, study HSC-151 was a randomized two-way cross-over study aimed at investigating the bioavailability at steady-state of 0.5 mg clemastine tablets (a clinical service formulation), administered every 6 h for a total of 26 doses, vs. the administration of Tavist-1, given every 12 h for a total of 13 doses. The study included 22 healthy male subjects, age 19-49 years. Blood samples for determination of clemastine fumarate levels were taken pre-dose on days 1, 4, 5 and 6, followed by a 12-hour pharmacokinetic profile after the morning dose on day 7. On day 8, subjects crossed over to the other dosing regimen and trough levels were measured on days 11, 12 and 13, followed by a 72- hour profile after the morning dose on day 14. Steady-state was determined via regression analysis of 4 trough concentrations at –72, -48, -24 and 0 h prior to the last BID dose or next to last QID dose. The mean slope was compared against a nominal value of zero. It was found that linear regression of trough values at time points –48, -24 and 0 h yielded an estimated

slope of zero. Pharmacokinetic parameters obtained are displayed in Table 11. Plasma clemastine fumarate concentrations vs. time profiles are shown in Figure 4.

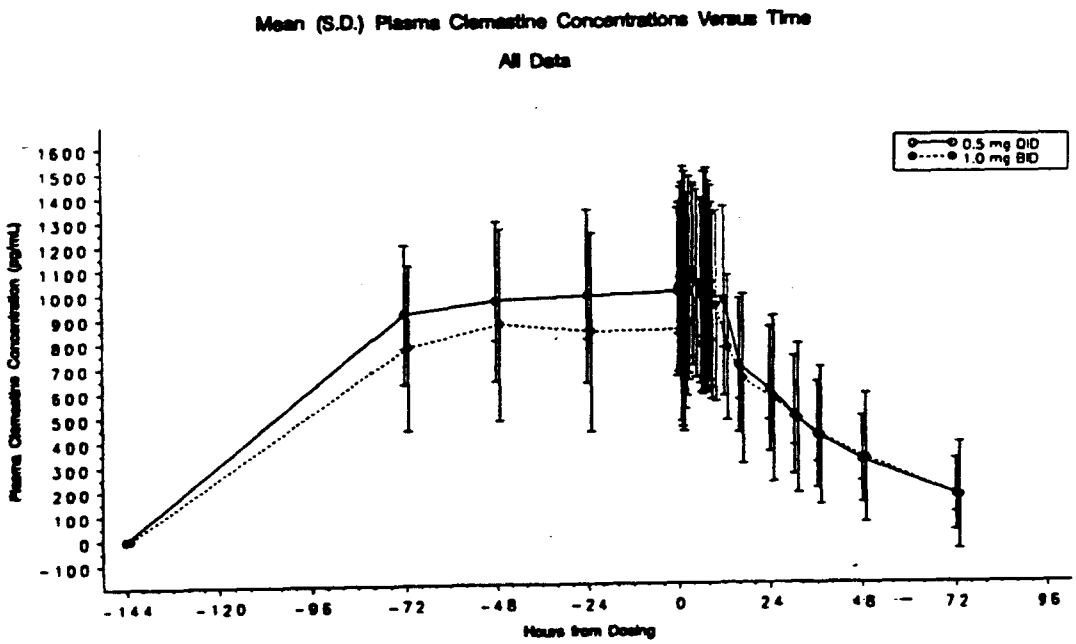
Table 11.

	0.5 mg tablet	Tavist-1 tablet	90% CI
CLEMASTINE			
C_{max} (pg/ml)	1170 (399)	1171 (437)	93.8% - 107.3%
T_{max} (h)	1.92 (0.94)	4.54 (2.02)	-
C_{avg} (pg/ml)	1013 (374)	958 (372)	102.1% - 110.2%
C_{min} (pg/ml)	875 (372)	744 (297)	109.6% - 123.5%
$AUC_{(0-12h)}$ (pg·h/ml)	12153 (4487)	11498 (4467)	102.1% - 110.2%
$t_{½}$ (h)*	25.94 (7.03)	27.15 (12.30)	-

Basic pharmacokinetic parameters and 90% confidence intervals for the ratio of the geometric means of C_{max}, C_{avg}, C_{min} and $AUC_{(0-12h)}$ after the administration of clemastine fumarate as a clinical service formulation, 0.5 mg clemastine QID for a total of 26 doses and Tavist-1 BID for a total of 13 doses, respectively. *: Estimated for study period 2 only.

Figure 4.

Sandoz Pharmaceutical Corporation
Clemastine Study No. HSC-151



Plasma clemastine fumarate concentrations vs. time after the administration of the clinical service formulation, 0.5 mg clemastine QID for a total of 26 doses and Tavist-1 BID for a total of 13 doses, respectively.

The treatments were compared, using an analysis of variance model that incorporated the following factors: sequence, subject within sequence, period and treatment. It was found that QID dosing of a 0.5 mg clemastine clinical service formulation is bioequivalent to BID dosing of Tavist-1 with respect to C_{max}, C_{min}, C_{avg} and $AUC_{(0-12h)}$.

Reviewer comment:
The study results seem to indicate that the two dosing regimen may be comparable from a safety and efficacy perspective. However, it should be noted that this study was not optimally conducted, since there was no adequate wash-out period between the two treatments. Although no statistically significant sequence effect could be detected for any of the above-mentioned variables, absence of an adequate wash-out could have influenced the study results. This influence is expected to be minimal, considering that the second pharmacokinetic profile was obtained several days after the cross-over.

Reviewer Comment:
Study HSC-302 was found to be less informative with regard to evaluating the comparative bioavailability of the proposed CTC formulation and the presence of a pharmacokinetic interaction. Therefore, this study is not discussed in great length in this review. Study HSC-302 had a two-way cross-over design aimed at investigating the dose proportionality of single doses of 0.5 mg and 1.0 mg clemastine, administered to healthy male volunteers. However, for the 1 mg dose, half of the subjects received 1 mg clemastine clinical service formulation (during period 1) and the other half received 1 mg of Tavist-1 (during period 2), rendering this study difficult to evaluate. It should be noted that the 1 mg clemastine clinical service formulation was not bioequivalent to Tavist-1. Also, dose proportionality was not demonstrated between the 0.5 mg and 1 mg doses. However, when comparing C_{max} and AUC values of clemastine fumarate between studies HSC-152 and HSC-153B, it appears that clemastine displays dose-proportional kinetics in the 0.5-1 mg range.

VII LABELING

The labeling of Tavist Allergy/Sinus/Headache will be evaluated by the Division of Over-The-Counter Drug Products, in collaboration with the Division of Pulmonary and Allergy Drug Products.

Hilfiker
DEC 23 1999

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing Memorandum

NDA:	21-082	**Sponsor:**	Novartis
IND:			
Brand Name:	? (pending)	**Priority Classification:**	3S
Generic Name:	Clemastine 0.25 mg Pseudoephedrine 30mg Acetominophen 500 mg	**Indication(s):**	Temporary relief of sneezing, runny nose, itching, nasal and sinus decongestion, minor headache, and fever
Drug Class:	Antihistaminic, Decongestant, Analgesic/Antipyretic	**Date of Submission:**	10/07/99
Dosage Form:	Tri-Combo Tablet	**Route of Admin.:**	Oral
Dosing Regimen:	2 tablets QID	**Due Date of Agency's Review:**	08/07/2000
Division:	HFD-870	**Medical Division:**	HFD-570
Reviewer:	Tien-Mien Chen	**Team Leader:**	Ramana Uppoor

Items included in NDA (CTD)	*Yes*	*No*	*Request*
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		
Labeling	X		
Reference Bioanalytical and Analytical Methods	X		
Bioavailability and Bioequivalence Studies	X		
Mass Balance Study		X	
BA Studies		X	
Absolute BA		X	
Relative BA		X	
BE Studies	X		
Average BE	X		
Population BE		X	
Individual BE		X	
Food-Drug Interaction		X	
Dissolution Tests (In Vitro-In Vivo Comparison Studies)	X		No IVIVC
Studies Using Human Biomaterials		X	
Plasma Protein Binding Studies		X	
Blood/Plasma Ratio		X	
Metabolism Studies Using Hepatocytes, Microsomes,etc		X	
In Vitro Drug Interaction Studies		X	
Human Pharmacokinetics Studies	X		
PK, and Initial Safety and Tolerability in Healthy Volunteers	X		
Single Dose	X		
Multiple Dose	X		
PK, and Initial Safety and Tolerability in Patient Volunteers		X	
Single Dose		X	

Multiple Dose		X	
Dose Proportionality	X		
Single Dose	X		
Multiple Dose		X	
PK in Population Subsets to Evaluate Effects of Intrinsic Factors		X	
Ethnicity		X	
Gender		X	
Pediatrics		X	
Geriatrics		X	
Renal Impairment		X	
Hepatic Impairment		X	
PK to Evaluate Effects of Extrinsic Factors	X		
Drug-Drug Interaction: Effects on Primary Drug	X		
Drug-Drug Interaction: Effects of Primary Drug	X		
Population PK studies		X	
Summary Table of PK/PD Studies		X	
PK/PD studies in Volunteers		X	
PK/PD studies in patients		X	
Individual Datasets for all PK and PK/PD studies in electronic format		X	To be requested
Other		X	
Genotype/Phenotype Studies		X	
Chronopharmacokinetics		X	

Summary of Submission:

Clemastine is a sedating antihistamine that has previously been approved as BID dosing. Pseudoephedrine and acetominophen are OTC drugs currently marketed as single and/or combination products. The new triple combination product will be administered QID. The total daily dose of each of the active moieties is still within the approved dosing range.

Four human PK/Bio studies were conducted: (*: pivotal)

1. *Single-dose, 4X4 crossover for **1)** 4 Tri-combo tablets vs. **2)** 2 clemastine 0.5 mg tablets vs. **3)** 2 clemastine 0.5 mg tablets plus currently marketed 2 TheraFlu Sinus tablets (pseudoephedrine 30mg+acetominophen 500 mg) or **4)** 1 Tavist-1 tablet in healthy male adults.

2. *Single-dose, 4X4 crossover for **1)** 2 Tri-combo tablets vs. **2)** 1 clemastine 0.5 mg tablet vs. **3)** currently marketed 2 TheraFlu Sinus tablets (pseudoephedrine 30mg+acetominophen 500 mg) or **4)** 5 ml Tavist syrup (0.5 mg) in healthy male & female adults.

3. *Multiple-dose, 2X2 crossover for **1)** 1 clemastine 0.5 mg tablet qid vs. **2)** 1 Tavist-1 tablet bid in healthy male adults.

4. Single-dose, 2X2 crossover for **1)** 1 clemastine 0.5 mg tablet vs. **2)** 1 clemastine 1 mg tablet or 1 Tavist-1 tablet in healthy male adults.

The to-be-marketed triple combination tablet formulation was used in the studies. No individual datasets were provided in electronic format.

This application is__X__ is not___ filable.
(if not filable, discuss reasons why below:)

QBR questions: (Key Issues to be Considered)

Is the systemic exposure from Tavist triple combination product greater than that of the individual marketed products given alone or concurrently? (**Note**: Will be updated later after thorough review)

APPEARS THIS WAY
ON ORIGINAL

Information Request (Needs to be sent to the sponsor)

1. Individual datasets in electronic format (e.g., Excel spreadsheet or SAS transport file).

Requests/Comments are _X__ are not ___ to be sent to firm.

Signature /S/ 12/23/99
Primary Reviewer

/S/ 12/23/99
Secondary Reviewer

CC: NDA 21-082, HFD-850 (Electronic Entry or P. Lee), HFD-570 (Hilfiker), HFD-870 (R. Uppoor, T.M. Chen, S.M. Huang), CDR (B. Murphy)

APPEARS THIS WAY
ON ORIGINAL