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NDA74374

GENERIC NAME:

FIRM: ASCENT PHARMS

TRINETHOPRIN

1 OF 1

Cover Form

[REDACTED]
[REDACTED]
Reviewing Div: 600

Trade Name:
[REDACTED]
[REDACTED]

Approval Letter: Y

Statistician Review: N

SBA Form: N

Bio/Dissolution Review: Y

Final Printed Labeling: Y

Microbiologist Review: N

Medical Officer Review: N

NAS/NRC Review: N

Chemist Review: Y

Pharmacologist Review: N

Federal Register Notice: N

Completion Date: 07-NOV-95

APPROVAL

LETTER

JUN 23 1995

Ascent Pharmaceuticals, Inc.
Attention: Robert W. Mendes, Ph.D.
9 Linnell Circle
Billerica, MA 01821

Dear Sir:

Reference is made to your new drug application dated June 16, 1993, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Primsol™ (Trimethoprim Hydrochloride Oral Solution), equivalent to 25 mg Trimethoprim per 5 mL.

Reference is made to your letter of amendment dated April 12, 1994, dated May 26, 1994, and dated June 1, 1994.

We have reviewed the data of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The drug can be expected to have the same therapeutic effect as that of the reference listed drug product relied upon by the Agency for the basis of safety and effectiveness.

Under 21 CFR 314.70, certain changes in the conditions described in this application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of the drug.

We request that you submit in duplicate any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FDA-2253 at the time of their initial use.

Sincerely yours,

Michael Williams 6/23/95

Roger L. Williams, M.D.
Associate Director for Science
and Medical Affairs
Center for Drug Evaluation and Research

CC: NDA 74-374
NDA 74-374/Division File
Field Copy
HFD-600/Reading File
HFD-82

Endorsements:

HFD-629/Schaefer/5-17-95
HFD-617/Hopps/5-18-95
HFD-617/Phillips/5-22-95
HFD-629/Schwartz/5-17-95
HFD-613/AMWeikel/CSO/5-16-95
X:\wpfile\majors\weikel\74374.AP
F/T by MM 5-22-95

APPROVAL LETTER

E. L. Schaefer 5/24/95

Amie 5/24/95

R. A. J. J. J.
6/20/95

*Awaiting
Satisfactory
E.L. Schaefer
6/21/95*

LABELING

(trimethoprim hydrochloride oral solution)
• trimethoprim, 25 mg/5 mL

Primsol Solution

NDC 59439-477-02

NDC 59439-477-02

USUAL ADULT DOSAGE:
100 mg (20 mL) every 12 hours or
200 mg (40 mL) every 24 hours

**PrimsolTM
Solution**

Store between 15°-25°C (59°-77°F)

**PrimsolTM
Solution**

(trimethoprim
hydrochloride
oral solution)
trimethoprim, 25 mg/5 mL

(trimethoprim
hydrochloride
oral solution)
trimethoprim, 25 mg/5 mL

Trimethoprim is a synthetic antibiotic that
acts by inhibiting the growth of bacteria.

Trimethoprim is used to treat urinary tract
infections, skin infections, and other bacterial
infections.

Trimethoprim is a synthetic antibiotic that
acts by inhibiting the growth of bacteria.

Trimethoprim is a synthetic antibiotic that
acts by inhibiting the growth of bacteria.

400 mL (13.5 fl oz)

AscentTM

Manufactured by
Ascent Pharmaceuticals, Inc.
Boston, MA 02114

Trimethoprim is a synthetic antibiotic that
acts by inhibiting the growth of bacteria.

Trimethoprim is a synthetic antibiotic that
acts by inhibiting the growth of bacteria.

400 mL (13.5 fl oz)

AscentTM

Manufactured by
Ascent Pharmaceuticals, Inc.
Boston, MA 02114

Trimethoprim is a synthetic antibiotic that
acts by inhibiting the growth of bacteria.

NDC 59439-477-02

PrimsolTM Solution

(trimethoprim
hydrochloride
oral solution)
trimethoprim, 25 mg/5 mL

USUAL ADULT DOSAGE:

100 mg (20 mL) every 12 hours
or 200 mg (40 mL) every 24 hours.

Trimethoprim Hydrochloride
Oral Solution

400 mL (13.5 fl oz)

Ascent Laboratories, Inc. (25 mg/5 mL) 10/14

Ascent

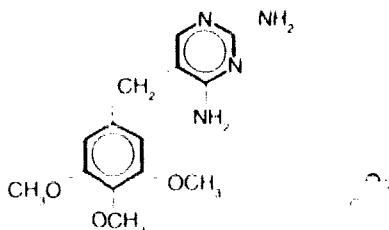
Primsol™ Solution

(trimethoprim hydrochloride oral solution)

Dye-free, alcohol-free, flavored solution,
25 mg trimethoprim per 5 mL

DESCRIPTION

Primsol (trimethoprim hydrochloride oral solution) is a solution of the synthetic antibacterial trimethoprim in water prepared with the aid of hydrochloric acid. Each 5 mL for oral administration contains trimethoprim hydrochloride equivalent to 25 mg trimethoprim and the inactive ingredients bubble gum flavor, methylparaben, propylparaben, propylene glycol, saccharin sodium, sucrose, water and hydrochloric acid to adjust pH to a range of 3.0 - 5.0. Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine. Trimethoprim is a white to cream-colored, odorless, bitter compound with a molecular formula of $C_{14}H_{18}N_4O_3$ and a molecular weight of 290.32 and the following structural formula:



CLINICAL PHARMACOLOGY

Trimethoprim is rapidly absorbed following oral administration. It exists in the blood as unbound, protein-bound and metabolized forms. Ten to twenty percent of trimethoprim is metabolized, primarily in the liver; the remainder is excreted unchanged in the urine. The principal metabolites of trimethoprim are the 1- and 3-oxides and the 3'- and 4'-hydroxy derivatives. The free form is considered to be the therapeutically active form. Approximately 44% of trimethoprim is bound to plasma proteins.

Mean peak plasma concentrations of approximately 1 mcg/mL occur 1 to 4 hours after oral administration of a single 100 mg dose. A single 200 mg dose will result in plasma concentrations approximately twice as high. The mean half-life of trimethoprim is approximately 9 hours. However, patients with severely impaired renal function exhibit an increase in the half-life of trimethoprim, which requires either dosage regimen adjustment or not using the drug in such patients (see DOSAGE AND ADMINISTRATION section). During a 13-week study of trimethoprim tablets administered at a dosage of 50 mg *q i d.*, the mean minimum steady-state concentration of the drug was 1.1 mcg/mL. Steady-state concentrations were achieved within two to three days of chronic administration and were maintained throughout the experimental period.

Excretion of trimethoprim is primarily by the kidneys through glomerular filtration and tubular secretion. Urine concentrations of trimethoprim are considerably higher than are the concentrations in the blood. After a single oral dose of 100 mg, urine concentrations of trimethoprim ranged from 30 to 160 mcg/mL during the 0- to 4-hour period and declined to approximately 18 to 91 mcg/mL during the 8- to 24-hour period. A 200 mg single oral dose will result in trimethoprim urine concentrations approximately twice as high. After oral administration, 50% to 60% of trimethoprim is excreted in the urine within 24 hours, approximately 80% of this being unmetabolized trimethoprim.

Since normal vaginal and fecal flora are the source of most pathogens causing urinary tract infections, it is relevant to consider the distribution of trimethoprim into these sites. Concentrations of trimethoprim in vaginal secretions are consistently greater than those found simultaneously in the serum, being typically 1.6 times the concentrations of simultaneously obtained serum samples. Sufficient trimethoprim is excreted in the feces to markedly reduce or eliminate trimethoprim-susceptible organisms

from the fecal flora. The dominant non-*Enterobacteriaceae* fecal organisms, *Bacteroides* spp. and *Lactobacillus* spp., are not susceptible to trimethoprim concentrations obtained with the recommended dosage.

Trimethoprim also passes the placental barrier and is excreted in breast milk.

Microbiology: Primsol blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. This binding is very much stronger for the bacterial enzyme than for the corresponding mammalian enzyme. Thus, Primsol selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

In vitro serial dilution tests have shown that the spectrum of antibacterial activity of Primsol includes the common urinary tract pathogens with the exception of *Pseudomonas aeruginosa*.

Representative Minimum Inhibitory Concentrations for Trimethoprim-Susceptible Organisms

Bacteria	Trimethoprim MIC — mcg/mL (Range)
<i>Escherichia coli</i>	0.05 - 1.5
<i>Proteus mirabilis</i>	0.5 - 1.5
<i>Klebsiella pneumoniae</i>	0.5 - 5
<i>Enterobacter</i> species	0.5 - 5
<i>Staphylococcus</i> species (coagulase-negative)	0.15 - 5

The recommended quantitative disc susceptibility method^{1,2} may be used for estimating the susceptibility of bacteria to Primsol. With this procedure, reports from the laboratory giving results using the 5 mcg trimethoprim disc should be interpreted according to the following criteria: Organisms producing zones of 16 mm or greater are classified as susceptible, whereas those producing zones of 11 to 15 mm are classified as having intermediate susceptibility. A report from the laboratory of "Susceptible to trimethoprim" or "Intermediate susceptibility to trimethoprim" indicates that the infection is likely to respond when, as in uncomplicated urinary tract infections, effective therapy is dependent upon the urine concentration of trimethoprim. Organisms producing zones of 10 mm or less are reported as resistant, indicating that other therapy should be selected.

Dilution methods for determining susceptibility are also used, and results are reported as the minimum drug concentration inhibiting microbial growth (MIC).³ If the MIC is 8 mcg per mL or less, the microorganism is considered "susceptible". If the MIC is 16 mcg per mL or greater, the microorganism is considered "resistant".

INDICATIONS AND USAGE

For the treatment of initial episodes of uncomplicated urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Enterobacter* species and coagulase-negative *Staphylococcus* species, including *S. saprophyticus*.

Cultures and susceptibility tests should be performed to determine the susceptibility of the bacteria to trimethoprim. Therapy may be initiated prior to obtaining the results of these tests.

CONTRAINDICATIONS

Primsol is contraindicated in individuals hypersensitive to trimethoprim and in those with documented megaloblastic anemia due to folate deficiency.

WARNINGS

Experience with trimethoprim alone is limited, but it has been reported rarely to interfere with hematopoiesis, especially when administered in large doses and/or for prolonged periods.

The presence of clinical signs such as sore throat, fever, pallor or purpura may be early indications of serious blood disorders.

PRECAUTIONS

General: Trimethoprim should be given with caution to patients with possible folate deficiency. Folate may be administered concomitantly without interfering with the antibacterial action of trimethoprim. Trimethoprim should also be given with caution to patients with impaired renal or hepatic function. If any clinical signs of a blood disorder are noted in a patient receiving trimethoprim, a complete blood count should be obtained and the drug discontinued if a significant reduction in the count of any formed blood element is found.

Drug Interactions: Primisol may inhibit the hepatic metabolism of phenytoin. Trimethoprim, given at a common clinical dosage, increased the phenytoin half-life by 51% and decreased the phenytoin metabolic clearance rate by 30%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Drug/Laboratory Test Interactions: Trimethoprim can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay (RIA).

The presence of trimethoprim may also interfere with the Jaffe alkaline picrate reaction assay for creatinine resulting in overestimations of about 10% in the range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential have not been conducted with trimethoprim.

Mutagenesis: Trimethoprim was demonstrated to be non-mutagenic in the Ames assay. No chromosomal damage was observed in human leukocytes cultured *in vitro* with trimethoprim; the concentration used exceeded blood levels following therapy with Primisol.

Impairment of Fertility: No adverse effects on fertility or general reproductive performance were observed in rats given trimethoprim in oral dosages as high as 70 mg/kg/day for males and 14 mg/kg/day for females.

Pregnancy:

Teratogenic Effects: Pregnancy Category C. Trimethoprim has been shown to be teratogenic in the rat when given in doses 40 times the human dose. In some rabbit studies, the overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with doses 6 times the human therapeutic dose.

While there are no large well-controlled studies on the use of trimethoprim in pregnant women, Brumfitt and Pursell,* in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or trimethoprim in combination with sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim plus sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received trimethoprim plus sulfamethoxazole at the time of conception or shortly thereafter.

Because trimethoprim may interfere with folic acid metabolism, Primisol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: The oral administration of trimethoprim to rats at a dose of 70 mg/kg/day commencing with the last third of gestation and continuing through parturition and lactation caused no deleterious effects on gestation or pup growth and survival.

Nursing Mothers: Trimethoprim is excreted in human milk. Because trimethoprim may interfere with folic acid metabolism, caution should be exercised when Primisol is administered to a nursing woman.

Pediatric Use: The safety of trimethoprim in infants under two months of age has not been demonstrated. The effectiveness of trimethoprim has not been established in pediatric patients under 12 years of age.

ADVERSE REACTIONS

The adverse effects encountered most often with trimethoprim were rash and pruritus. Other adverse effects reported involved the gastrointestinal and hematopoietic systems.

Dermatologic reactions: Rash, pruritus and exfoliative dermatitis. At the recommended dosage regimens of 100 mg b.i.d., or 200 mg q.d., each for 10 days, the incidence of rash is 2.9% to 6.7%. In clinical studies which employed high doses of trimethoprim, an elevated incidence of rash was noted. These rashes were maculopapular, morbilliform, pruritic and generally mild to moderate, appearing 7 to 14 days after the initiation of therapy.

Gastrointestinal reactions: Epigastric distress, nausea, vomiting and glossitis.

Hematologic reactions: Thrombocytopenia, leukopenia, neutropenia, megaloblastic anemia and methemoglobinemia.

Miscellaneous reactions: Fever, elevation of serum transaminase and bilirubin, and increases in BUN and serum creatinine levels.

OVERDOSAGE

Acute: Signs of acute overdosage with trimethoprim may appear following ingestion of 1 gram or more of the drug and include nausea, vomiting, dizziness, headaches, mental depression, confusion and bone marrow depression (see CHRONIC OVERDOSAGE).

Treatment consists of gastric lavage and general supportive measures. Acidification of the urine will increase renal elimination of trimethoprim. Peritoneal dialysis is not effective and hemodialysis only moderately effective in eliminating the drug.

Chronic: Use of trimethoprim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anemia. If signs of bone marrow depression occur, trimethoprim should be discontinued and the patient should be given leucovorin, 3 to 6 mg intramuscularly daily for three days, or as required to restore normal hematopoiesis.

DOSAGE AND ADMINISTRATION

The usual oral adult dosage is 100 mg (20 mL) every 12 hours or 200 mg (40 mL) every 24 hours, each for 10 days. The use of trimethoprim in patients with a creatinine clearance of less than 15 mL/min is not recommended. For patients with a creatinine clearance of 15 to 30 mL/min, the dose should be 50 mg (10 mL) every 12 hours.

The effectiveness of trimethoprim has not been established in pediatric patients under 12 years of age.

HOW SUPPLIED

Primisol (trimethoprim hydrochloride oral solution), dye-free, alcohol-free, bubble gum flavored, containing trimethoprim hydrochloride equivalent to 25 mg of trimethoprim in each 5 mL bottle of 400 mL (13.5 fl oz). NDC 59439-477-02. Store between 15°-25°C (59°-77°F). Dispense in tight, light-resistant glass or PET plastic containers as defined in USP. Dispense with enclosed dose cup. Do not dispense if tamper-evident neck seal is broken prior to initial use.

Caution: Federal law prohibits dispensing without prescription.

REFERENCES

1. Bauer AW, Kirby WMM, Sherris JC, Tenckhoff M: Antibiotic Susceptibility Testing by Standardized Single Disk Method. *Am J Clin Pathol* 45:493-496, 1966.
2. Approved Standard ASM 2 Performance Standards for Antimicrobial Disk Susceptibility Test. National Committee for Clinical Laboratory Standards, 771 East Lancaster Avenue, Villanova, Pennsylvania 19085.
3. Ericsson HM, Sherris JC: Antibiotic Sensitivity Testing: Report of an International Collaborative Study. *Acta Pathol Microbiol Scand (B)* (suppl 217):1-90, 1971.
4. Brumfitt W, Pursell H: Trimethoprim/Sulfamethoxazole in the Treatment of Bacteremia in Women. *J Infect Dis* 128 (suppl): S657-S663, 1973.
- Revised February 8, 1995.
5. Manufactured for Ascent Pharmaceuticals, Inc., Billerica, MA 01821 by Lyle Laboratories, Inc., Stoughton, MA 02072.
- U.S. Patent pending; serial number 07/772,926.

CHEMIST'S REVIEW

1. CHEMISTRY REVIEW NO 5
2. ANDA 74-374
3. NAME AND ADDRESS OF APPLICANT

Ascent Pharmaceuticals, Inc.
Attention: Robert W. Mendes
9 Linnell Circle
Billerica, MA 01821

4. LEGAL BASIS FOR SUBMISSION

The most similar listed drug is trimethoprim oral tablets, 100 and 200 mg (Trimpex™, Roche), NDA 17-952. The reference listed drug is not entitled to a period of marketing exclusivity.

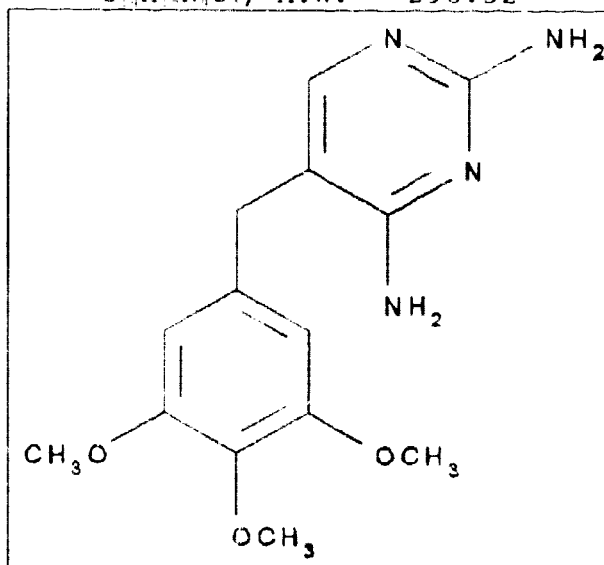
The ANDA is being reviewed under Section 505(b)(2) of the FD&C Act.

5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME Primsol™ Oral Solution
In the original submission, the proprietary name was Primstat™ Syrup.
7. NONPROPRIETARY NAME Trimethoprim Hydrochloride
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:

06/16/93 Original ANDA.
11/12/93 First NA letter.
12/23/93 Response to NA letter.
11/10/94 Second NA letter.
12/02/94 Minor amendment.
01/17/95 Methods validation was requested from FDA laboratory (WEAC).
01/30/95 Third NA letter.
02/28/95 Methods validation report was sent from WEAC to review chemist.
03/08/95 Minor amendment.
04/06/95 Fourth NA letter.
04/12/95 Minor amendment.

10. PHARMACOLOGICAL CATEGORY
Synthetic antibacterial for the treatment of uncomplicated urinary tract infections in patients 12 years of age and older.
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM
Oral Solution
14. POTENCY
25 mg of trimethoprim per 5 mL
15. CHEMICAL NAME AND STRUCTURE

Trimethoprim USP
 $C_{14}H_{14}N_4O_3$; M.W. = 290.32



2,4-Pyrimidinediamine, 5-[(3,4,5-trimethoxyphenyl)methyl]-;
2,4-Diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine.
CAS-738-70-5

16. RECORDS AND REPORTS

N/A

17. COMMENTS

The following Point **has not been completed** for ANDA 74-374,
as of 4/21/95:

33. Establishment Inspection

18. CONCLUSIONS AND RECOMMENDATIONS

The Office of Compliance has issued an **UNACCEPTABLE** status
for the manufacturer of the drug
substance . Otherwise, ANDA 74-374
CAN BE APPROVED.

19. REVIEWER:DATE COMPLETED:

Eugene L. Schaefer, Ph.D.

4/21/95

Endorsed by P.Schwartz, Ph.D.

4/24/95

BIO/DISSOLUTION

REVIEW

DEC 27 1993

Trimethoprim (Primstat)
5mg/mL Syrup
ANDA # 74-374
Reviewer: Man M. Kochhar
A.74374S.693

Ascent Pharmaceuticals, Inc.
Billerica, MA
Submission Date:
June 16, 1993

REVIEW OF A BIOEQUIVALENCE STUDY

The purpose of this study was to determine the relative bioequivalency of the oral solution to the reference product Trimplex (100 mg trimethoprim tablet, Roche), in fasting healthy adult male volunteers. The protocol was designed for a two-way crossover, single dose bioequivalence study.

BACKGROUND:

Trimethoprim is a synthetic antibacterial available as 100 mg tablets (Roche). Trimethoprim is rapidly absorbed and has been shown to be roughly 90 to 100% bioavailable following oral administration. Peak plasma concentrations are expected between 1 to 4 hours with a half-life of 8 to 10 hours.

This application is based on a ANDA-Suitability Petition filed in accordance with the provisions of Section 505(j)(2)(C) and 21 CFR 314.93 (b). The petition was filed on December 21, 1992 and was approved on May 20, 1993.

In-Vivo Study:

The objective of this study was to determine the relative bioequivalency of the oral solution to the reference product Trimplex (100 mg trimethoprim tablet, Roche)

The study was conducted by
under the supervision of

STUDY DESIGN:

The study was designed as a randomized, two-way crossover, single dose bioequivalence study in 21 healthy volunteers under fasting conditions.

Subjects:

The study employed twenty-one (21) healthy male volunteers between 19 and 45 years of age and within $\pm 15\%$ of the ideal body weight for their height and body frame (Metropolitan Insurance Company Bulletin, 1983). Volunteers without history of asthma, nasal polyps, or serious cardiovascular, hepatic, renal, hematopoietic, peptic ulcer or gastrointestinal disease, alcohol or drug abuse were employed.

Good health was ascertained from medical history, physical

examination and routine laboratory tests (blood chemistry, hematology, urinalysis, etc.). The volunteers were not allowed to take any prescription medications and/or OTC preparations for at least 72 hours prior to the start and until the end of the study. The volunteers should be non smokers. The volunteers were not allowed to drink alcoholic beverages or caffeine-containing products for 48 hours prior to dosing and until study completion.

The subjects were housed in the live-in facility from 12 hours before until 48 hours after the drug administration.

Methods:

The products and dosage employed in this study were as follows:

A: Regimen A: 1 x 20 mL oral syrup (trimethoprim, test drug, Ascent), lot # 3EX01A2 with 250 mL of water.

Batch Size: Expiration date: 6-1-94,
Content Uniformity: 98.1%

B. Regimen B: One 100 mg tablet of Trimplex (trimethoprim, Roche) lot # 0433 with 250 mL of water. Expiry date: 11-94
Content Uniformity: 98.7%

The subjects fasted for 8 hours prior to and 4 hours after the drug administration. Water ad lib was allowed except within 2 hours of drug administration.

Ten (10) mL of venous blood were drawn in Vacutainers with Heparin at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours. The plasma was separated and promptly frozen for analysis.

Urine was collected pre-dose, and from 0-4, 4-8, 8-12, 12-24, and 24-48 hours post-dose. Samples were analyzed for trimethoprim concentrations.

WASHOUT PERIOD: 7 DAYS

ANALYTICAL METHODOLOGY:

Plasma trimethoprim was measured by a specific HPLC method developed by

ASSAY VALIDATION

1. Linearity: Trimethoprim 0.1 to 4 mcg/mL
2. Sensitivity: 0.1 mcg/mL. Any sample below this concentration was reported as zero.
3. Specificity: Blank plasma sample from the subjects in the study indicated no interference with trimethoprim

and/or internal standard.

4. Accuracy & Precision

Interday (N=36)

Actual (mcg/mL)	0.150	0.8	3.0
Observed (mcg/mL)	0.141	0.848	3.28
Accuracy %	94.0	106.0	109.33
CV %	7.2	4.1	3.9

Intraday (N=6)

Actual (mcg/mL)	0.150	0.8	3.0
Observed (mcg/mL)	0.133	0.839	3.25
Accuracy %	88.67	104.88	108.33
CV %	6.1	2.4	1.4

5. The assay was validated by analyzing three single standard curve sets with three sets of high (4.0 mcg/mL), medium (0.5 mcg/mL) and low (0.1 mcg/mL) QC samples for a total of three days. The standard curve concentrations ranged from 0.05 to 4.0 mcg/mL. The assay was documented to be reproducible. For standards, the intra-day precision was 11% or better for each of the three days, and the inter-day precision was 9% or better. The mean accuracy was within the range of 89% to 109%

6. The recovery of trimethoprim and internal standard were calculated by direct comparison of peak height of extracted standards to unextracted test solutions prepared in an interference free matrix at the same concentrations. The mean recovery was 65.2%.

7. The stability of trimethoprim at three different concentrations in plasma was evaluated over three freeze-thaw cycles. The three sets of controls included high (3.0 mcg/mL), medium (0.8 mcg/mL) and low (0.15 mcg/mL). These samples were subjected to three freeze and thaw cycles before analyzing. The results show that the mean change for trimethoprim was +1.14%, +1.04%, and -0.96%. The samples were stable for at least 4 weeks at -20°C. The in process stability was performed at 3 different concentrations (0.15 mcg/mL, 0.8 mcg/mL and 3.0 mcg/mL). These samples were prepared and allowed to sit next to HPLC for 24 hours at room temperature prior to analysis. The results show that trimethoprim was stable during the maximum time required for sample processing at room temperature.

DATA ANALYSIS:

Individual analysis of variance (ANOVA with factors including

drug, phase, and sequence) were carried out to compare plasma levels at each sampling time, AUC (0-t), AUC (inf.), Cmax, Tmax, t1/2 and Kel. All ANOVAs were performed with SAS General Linear Models Procedures (GLM). 90% confidence intervals (two one-sided t-test) were calculated for trimethoprim pharmacokinetic parameters.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

All of the 21 subjects enrolled in the study completed the crossover. The plasma samples from 21 subjects were assayed for trimethoprim as per protocol. The study was completed with no major protocol violations. The results of the study comparing the bioavailability of trimethoprim are given in Table 1, and 2. The mean plasma trimethoprim concentrations are given in Figure 1 and 2.

TABLE 1

Mean (CV%) Plasma Concentration of Trimethoprim (N=21)

Time (hours)	Ascent's Trimethoprim (Primstat) Lot # 3EX01A2 mcg/mL	Roche's Trimper Lot # 0433 mcg/mL
0	0 (-)	0 (-)
0.5	0.83 (32.5)	0.41 (65.8)
1.0	0.94 (17.0)	0.83 (26.5)
1.5	0.95 (13.7)	0.90 (20.0)
2.0	0.92 (13.0)	0.92 (17.4)
3.0	0.87 (14.9)	0.91 (16.6)
4.0	0.81 (14.8)	0.85 (17.6)
6.0	0.66 (16.7)	0.69 (15.9)
8.0	0.59 (13.6)	0.63 (17.5)
12.0	0.42 (16.7)	0.44 (20.5)
24.0	0.17 (35.3)	0.18 (33.3)
36.0	0.05 (100)	0.05 (100)
48.0	0.01 (200)	0.01 (200)

Table 2**A Summary of Pharmacokinetic Parameters for 21 subjects
TRIMETHOPRIM**

Parameters	Ascent's Trimethoprim Mean (CV%)	Roche's Trimpex Mean (CV%)	% Diff	90% Confidence Interval
AUC_{0-t} mcg.hr/mL	12.67 (22.2)	12.97 (22.8)	2.31	94; 101
AUC_{inf} mcg.hr/mL	13.89 (20.6)	14.17 (22.1)	1.98	95; 101
C_{max} mcg/mL	1.02 (15.7)	0.97 (13.4)	5.15	101; 110
T_{max} (hours)	1.19 (53.8)	1.83 (32.8)	34.97	
K_{el} 1/hr	0.0799 (18.0)	0.0809 (18.0)	1.24	
$t_{1/2}$ hours	8.94 (17.3)	8.82 (17.4)	1.36	
$\ln AUC_{0-t}$ mcg.hr/mL	2.52	2.54		94; 102
$\ln AUC_{inf}$ mcg.hr/mL	2.61	2.63		95; 102
$\ln C_{max}$ mcg/mL	0.011	-0.040		101; 110

The trimethoprim AUC_{0-t} and AUC_{inf} produced by Ascent's formulation were 2.3% lower and 1.98% lower respectively than the values for the reference drug. The C_{max} for the test drug was 5.15% higher than reference product. T_{max} was 35% lower for the test drug. ANOVA performed on the plasma trimethoprim concentration data at each of the twelve sampling times detected no statistically significant differences between the two formulations except at 0.5 hour. The 90% confidence intervals for untransformed parameters were 94 to 101 for AUC_{0-t} , 95 to 101 for AUC_{inf} , and 101 to 110 for C_{max} . The 90% confidence intervals for $\ln AUC_{0-t}$ was 94 to 102, for $\ln AUC_{inf}$ was 95 to 102 and for $\ln C_{max}$ was 101 to 110.

The results of the study comparing the amounts of trimethoprim

excreted in the urine are presented in Table 3 and 4. The urine trimethoprim concentrations are given in Figure 3 and 4.

Table 3

Mean Urine Concentration of Trimethoprim (N=21)

Time (hours)	Ascent's Trimethoprim (Primstat) Lot # 3EX01A2 mg (CV%)	Roche's Trimpex Lot # 0433 mg (CV%)
0 to 4	9.0 (42.2)	9.6 (79.2)
4 to 8	8.2 (34.1)	8.7 (33.3)
8 to 12	7.8 (26.9)	7.5 (28.0)
12 to 24	16.6 (23.5)	15.1 (26.5)
24 to 48	2.7 (40.7)	3.2 (34.4)

Table 4

Mean Urine Trimethoprim Excretion Rate (N=21)

Time (Hours)	Ascent's Trimethoprim (Primstat) mg/hr (CV%)	Roche's Trimpex mg/hr (CV%)
0	0.0	0.0
2	2.3 (39.1)	2.4 (79.2)
6	2.1 (33.3)	2.2 (31.8)
10	2.0 (25.0)	1.9 (26.3)
18	1.4 (21.4)	1.3 (23.1)
26	0.7 (42.9)	0.8 (37.5)
Max. Rate	2.6 (30.8)	2.7 (66.7)
Tmax Rate	6.0 (73.0)	5.0 (60.8)

There were no significant differences in the excretion rate of test and reference drugs.

There were no serious adverse effects which required dropping any subject from the study or required therapeutic medical intervention.

On the basis of fasting in vivo bioavailability data it is determined that Ascent's trimethoprim syrup, 100 mg (25 mg/5 mL) is bioavailable to the extent of Roche's Trimpex tablets, 100 mg.

COMMENTS:

1. This application is based on a ANDA-Suitability Petition filed in accordance with the provisions of # 505(j)(2)(C) of the Act and 21CFR 314.93(b). The petition was approved on May 20, 1993.

2. The study was conducted in 21 healthy volunteers comparing the plasma concentrations from Ascent's trimethoprim syrup 25 mg/mL to those of reference Trimplex tablets 100 mg manufactured by Roche. The trimethoprim AUC_{0-t} , AUC_{inf} , and C_{max} of the Ascent's formulation were 2.3% lower, 1.98%, and 5.15% higher respectively than the corresponding Roche's reference values. ANOVA performed on the plasma trimethoprim concentration data detected no statistically significant differences between two formulations.

3. Analysis of variance indicated no statistical significant treatment differences for AUC and C_{max} for trimethoprim. The 90% confidence intervals were 93 to 102 for $\ln AUC_{0-t}$, 95 to 102 for $\ln AUC_{inf}$ and 101 to 110 for $\ln C_{max}$. These parameters were well within the range acceptable to the Division of Bioequivalence.

4. The urinary excretion rates detected no significant differences between test and reference products.

5. The validation studies conducted by the sponsor for trimethoprim are acceptable to the Division of Bioequivalence.

6. No serious adverse event or clinical abnormality was reported by any subject.

7. The in vivo fasting bioequivalence study is acceptable.

These results indicate that the test drug is bioavailable to the extent as reference product under fasting conditions.

DEFICIENCY: None

RECOMMENDATIONS:

1. The fasting bioequivalence study conducted by Ascent on its Trimethoprim (Primstat) syrup, 25 mg/5 mL lot # 3EX01A28, comparing it to Trimplex Tablets 100 mg, lot # 0433 manufactured by Roche have been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions the Ascent's Trimethoprim Syrup 25 mg/5mL is bioavailable to the extent of Trimplex Tablets, 100 mg (Reference Product), manufactured by Roche.

2. From the bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence study, and therefore, the application is approvable.

The firm should be informed of the recommendations.

Man M. Kochhar

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

Man M. Kochhar *for RMM* *12/9/93*

Concur:

R. N. Patnaik
Rabindra N. Patnaik, Ph.D.
Acting, Director
Division of Bioequivalence

Date: *12/27/93*

MMKochhar/mmk/10-15-93; 11-24-93; A:74374 BIO

cc: ANDA # 74-374 original, HFD-630, HFD-604 (Hare), HFD-130
(Jallen), HFD-344 (CViswanathan), HFD-658 (Mhatre, Kochhar), Drug
File, Division File.

FIGURE 1
MEAN (S.D.) OF ALL VOLUNTEERS

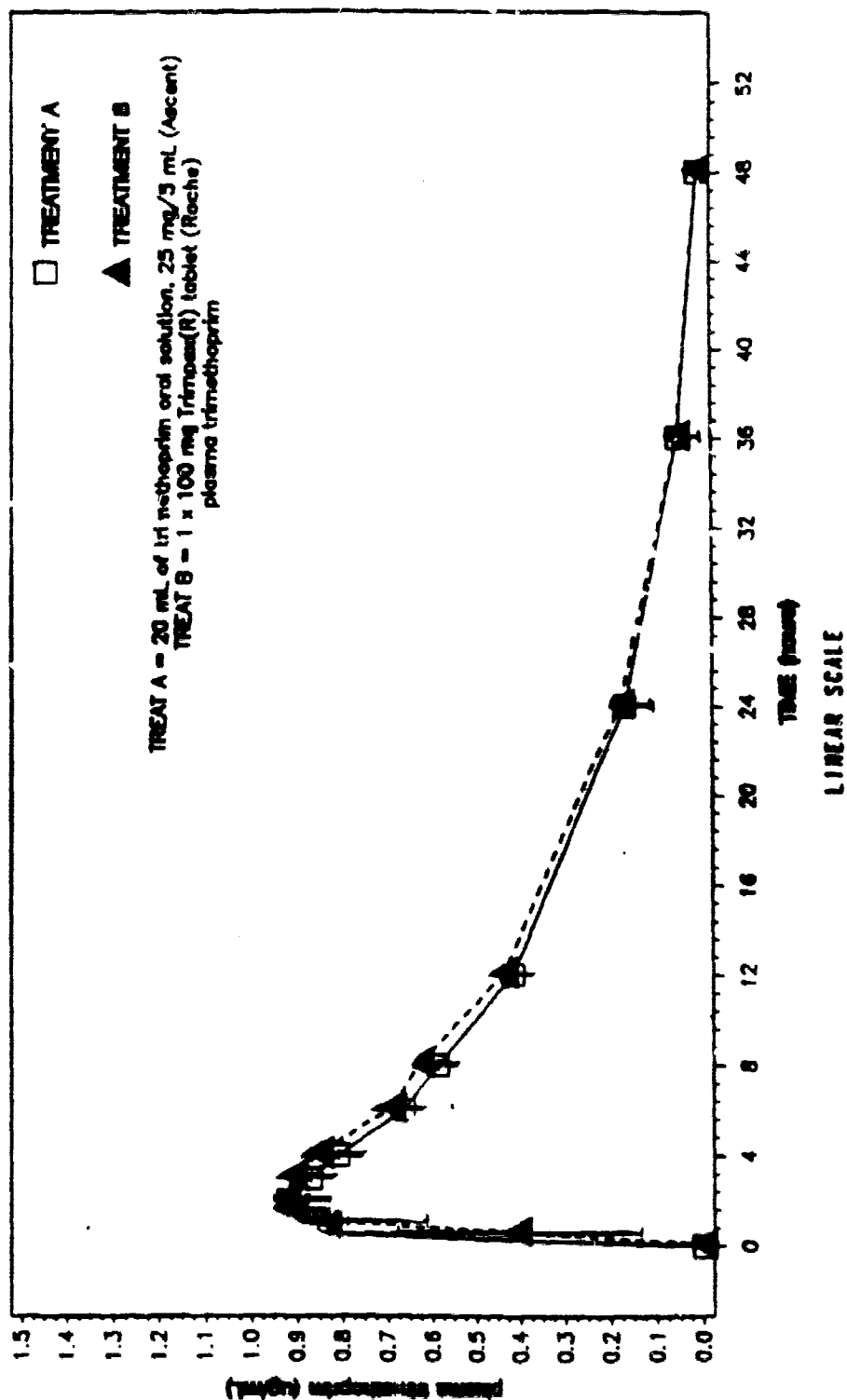


FIGURE 2
MEAN OF ALL VOLUNTEERS

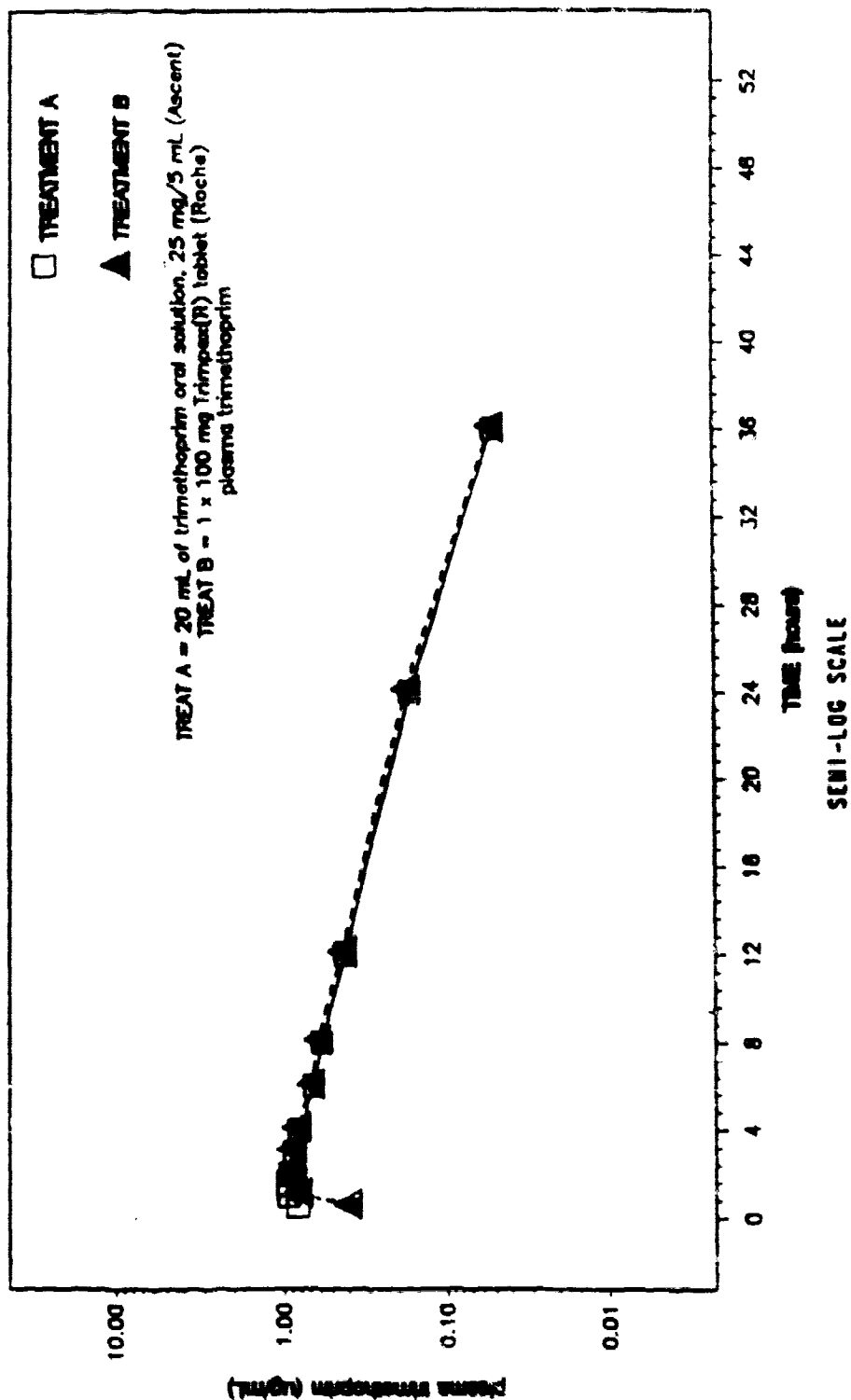


FIGURE 3
MEAN (S.D.) OF ALL VOLUNTEERS

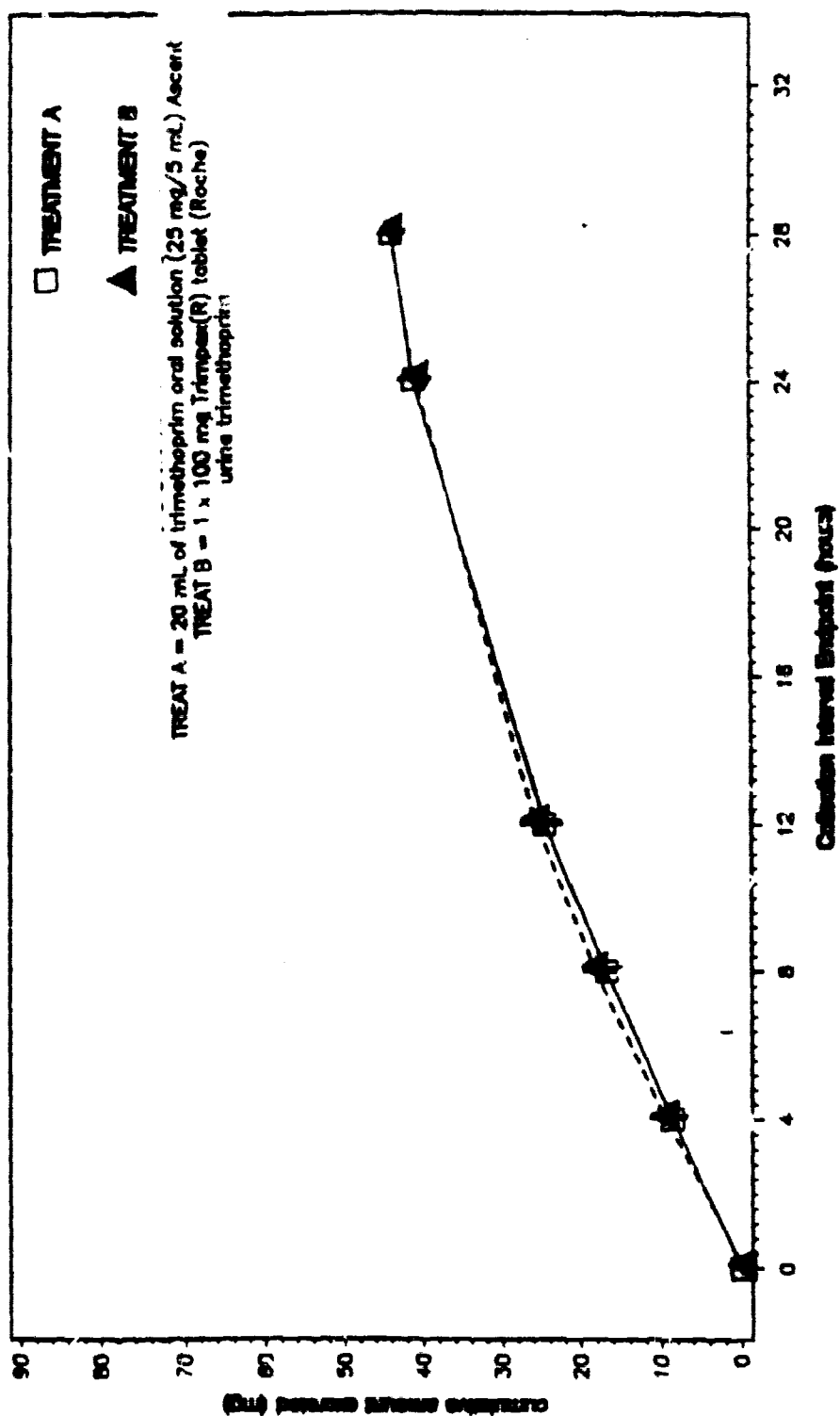
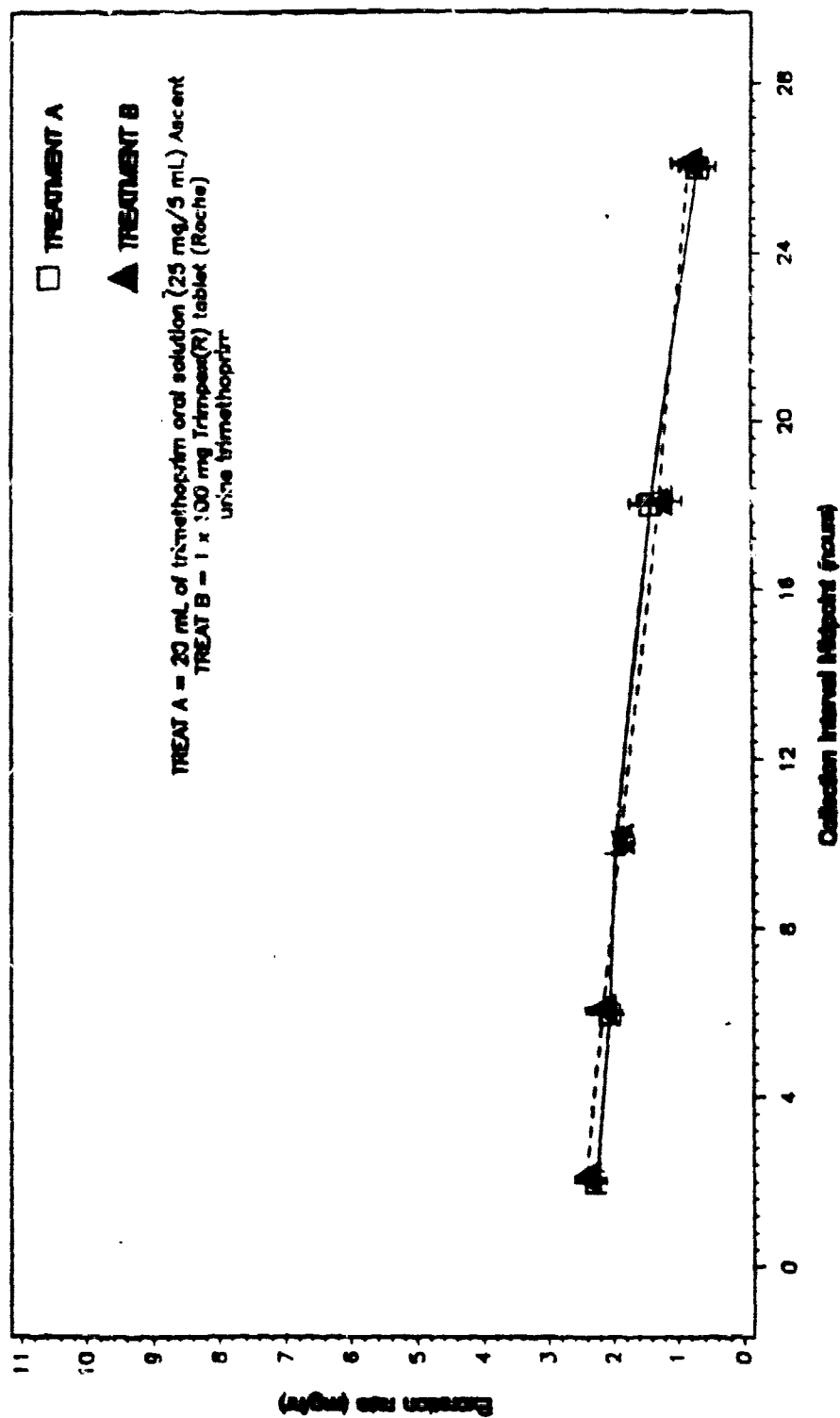


FIGURE 4
MEAN (SD) OF ALL VOLUNTEERS



FORMULATION

Ingredients

Amount per 5 mL

Syrup, NF
Propylene Glycol, USP
Hydrochloric Acid, NF
Trimethoprim, USP
Bubble Gum Flavor
Saccharin Sodium, USP
Methylparaben, NF
Propylparaben, NF
Purified water, USP

2.925 g

END

MD

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