CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-973

Approval Letter

NDA 74-973

JAN 24 2000

Ascent Pediatrics, Inc.
Attention: William E. Brochu
187 Ballardvale St., Suite B125
Wilmington, MA 01887

Dear Sir:

This is in reference to your new drug application dated October 4, 1996, submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (Act), for Primsol Solution (Trimethoprim Hydrochloride Oral Solution, 50 mg (base)/5 mL).

Reference is also made to your amendments dated July 16, September 11, October 29, December 23, and December 31, 1997; January 8, March 16, March 31 April 15, May 6, May 8, June 1, and August 6, 1998; June 4, June 30, July 22, September 7, September 23, October 12, October 15, November 24, December 27, 1999; and January 10, 2000.

We have completed the review 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 product, Primsol Solution (Trimethoprim Hydrochloride Oral Solution, 50 mg (base)/5 mL) can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness.

Under section 506A of the Act, 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 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that 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-40). Please do not use Form FD-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-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-973

FINAL PRINTED LABELING

℞ ONLY

Store between 15°-25°C (59°-77°F).
Professional Sample - Not to be Sold

ASCENT®
PEDIATRICS, INC.
Manufactured for
Aptalis Pharma, Inc.
Wilmington, MA 01887
by
Lyne Laboratories, Inc.
Brockton, MA 02301

Primsol
Solution

20 mL (⅔ fl oz)

LOT
EXP JAN 24 20

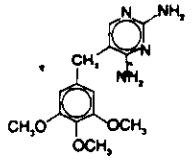
LLA0569

Primsol® Solution
(trimethoprim hydrochloride oral solution)
Dye-free, alcohol-free, flavored solution,
50 mg trimethoprim per 5 mL
P0017

Primsol® Solution
(trimethoprim hydrochloride oral solution)
Dye-free, alcohol-free, flavored solution,
50 mg trimethoprim per 5 mL
P0017

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 50 mg trimethoprim and the inactive ingredients bubble gum flavor, fructose, glycerin, methylparaben, monoammonium glycyrrhizinate, povidone, propylparaben, propylene glycol, saccharin sodium, sodium benzoate, sorbitol, water and hydrochloric acid and/or sodium hydroxide 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.

Trimethoprim half-life, clearance, and volume of distribution vary with age. Excluding newborns, an apparent trend of increasing half-life, volume of distribution, and decreasing clearance is observed with increasing age until adulthood.

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 concentrates into middle ear fluid (MEF) very efficiently. In a study in children aged 1 to 12 years, administration of a single 4 mg/kg dose resulted in a mean peak MEF concentration of 2.0 mcg/mL.

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

Microbiology: Trimethoprim 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, trimethoprim selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

Trimethoprim has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobic gram-positive microorganisms

Staphylococcus species (coagulase-negative strains, including *S. saprophyticus*)
Streptococcus pneumoniae (penicillin-susceptible strains)

Aerobic gram-negative microorganisms

Enterobacter species
Escherichia coli
Haemophilus influenzae (excluding beta-lactamase negative, ampicillin resistant strains)
Klebsiella pneumoniae
Proteus mirabilis

NOTE: *Moraxella catarrhalis* isolates were found consistently resistant to trimethoprim.

Susceptibility Tests

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of trimethoprim powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms isolated from urinary tract infections:

MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)
≥16	Resistant (R)

When testing *Haemophilus influenzae*[a]

MIC (mcg/mL)	Interpretation
≤ 0.5	Susceptible (S)
1-2	Intermediate (I)
≥4	Resistant (R)

When testing *Streptococcus pneumoniae*[b]

MIC (mcg/mL)	Interpretation
≤2	Susceptible (S)
≥4	Resistant (R)

[a] Interpretive criteria applicable only to tests performed by broth microdilution method using *Haemophilus* Test Medium (HTM).[1]

[b] Interpretive criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.[1]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard trimethoprim[a] powder should provide the following MIC values:

Microorganism		MIC (mcg/mL)
Escherichia coli	ATCC 25922	0.5 - 2
Haemophilus influenzae[b]	ATCC 49247	0.06 - 0.5
Staphylococcus aureus	ATCC 29213	1 - 4
Streptococcus pneumoniae[c]	ATCC 49619	1 - 4

[a] Trimethoprim very medium-dependent.

[b] Range applicable only to tests performed by broth microdilution method using *Haemophilus* Test Medium (HTM).[1]

[c] Range applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.[1]

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 mcg trimethoprim to test the susceptibility of microorganisms to trimethoprim.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 mcg trimethoprim[a] disk should be interpreted according to the following criteria:

For testing aerobic microorganisms isolated from urinary tract infections:

Zone diameter (mm)	Interpretation
≥16	Susceptible (S)
11-15	Intermediate (I)
≤10	Resistant (R)

For testing *Haemophilus influenzae*[b]:

Zone diameter (mm)	Interpretation
≥16	Susceptible (S)
11-15	Intermediate (I)
≤10	Resistant (R)

[a] Blood-containing media (except for lysed horse blood) are generally not suitable for testing trimethoprim. Mueller-Hinton agar should be checked for excessive levels of thymidine. To determine whether Mueller-Hinton medium has sufficiently low levels of thymidine and thymine, an *Enterococcus faecalis* (ATCC 29212 or ATCC 33186) may be tested with trimethoprim/sulfamethoxazole disks. A zone of inhibition ≥20 mm that is essentially free of fine colonies indicates a sufficiently low level of thymidine and thymine.

[b] Interpretative criteria applicable only to tests performed by disk diffusion method using *Haemophilus* Test Medium (HTM).[2]

Note:

Diffusion techniques are not recommended for determining susceptibility of *Streptococcus pneumoniae* to trimethoprim.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for trimethoprim.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5 mcg trimethoprim[a] disk should provide the following zone diameters in this laboratory test quality control strain:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	21 - 28
Haemophilus influenzae[b]	ATCC 49247	27 - 33
Staphylococcus aureus	ATCC 25923	19 - 26

[a] Blood-containing media (except for lysed horse blood) are generally not suitable for testing trimethoprim. Mueller-Hinton agar should be checked for excessive levels of thymidine. To determine whether Mueller-Hinton medium has sufficiently low levels of thymidine and thymine, an *Enterococcus faecalis* (ATCC 29212 or ATCC 33186) may be tested with trimethoprim/sulfamethoxazole disks. A zone of inhibition ≥20 mm that is essentially free of fine colonies indicates a sufficiently low level of thymidine and thymine.

[b] Range applicable only to tests performed by disk diffusion method using *Haemophilus* Test Medium (HTM).[2]

Note:

Diffusion techniques are not recommended for determining susceptibility of *Streptococcus pneumoniae* to trimethoprim.

INDICATIONS AND USAGE

PRIMSOL Solution is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Pediatric Patients:

Acute Otitis Media: For the treatment of acute otitis media due to

susceptible strains of *Streptococcus pneumoniae* and *Haemophilus influenzae*.

NOTE: *Moraxella catarrhalis* isolates were found consistently resistant to trimethoprim *in vitro*. Therefore, when infection with *Moraxella catarrhalis* is suspected, the use of alternative antimicrobial agents should be considered. PRIMSOL is not indicated for prophylactic or prolonged administration in otitis media at any age.

Adults:

Urinary Tract Infections: 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.

CLINICAL STUDIES

The results of one multicenter, 30-day, comparative, randomized clinical trial without tympanocentesis in 262 pediatric patients with acute otitis media (AOM) are shown below. In this clinical trial, strict evaluability criteria were used to determine clinical response.

	PRIMSOL	SMX + TMP*
Enrolled	133	129
Evaluable	130	129
Clinical Cure	64/130 (49%)	63/129 (49%)
Clinical Improvement	30/130 (23%)	31/129 (24%)
Relapse/Recurrence	19/130 (15%)	18/129 (14%)
Outcome (based on 95% confidence interval)	[redacted]	PRIMSOL equivalent to TMP + SMX

*sulfamethoxazole + trimethoprim oral suspension

The results of an uncontrolled 30-day trial with tympanocentesis in 120 pediatric patients with AOM are shown below:

	Number of patients	
Enrolled	120	
Clinically Evaluable	102	
Microbiologically Evaluable	58	
Clinical Cure	50/102 (49%)	
Clinical Improvement	22/102 (22%)	
Clinical Relapse/Recurrence	20/102 (20%)	
Microbiologic Eradication Rates n=58	Day 5 post-therapy	Day 20 post-therapy
Streptococcus pneumoniae	16/20 (80%)	14/20 (70%)
Haemophilus influenzae	14/17 (82%)	13/17 (77%)

Moraxella catarrhalis, isolated from five patients, was found consistently resistant to trimethoprim *in vitro*.

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. Folates 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: PRIMSOL 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 Jaffé alkaline picrate reaction assay for creatinine resulting in overestimations of about 10% in the range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate carcinogenic potential have not been conducted with trimethoprim. 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 PRIMSOL. 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,[3] 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.[4]

Because trimethoprim may interfere with folic acid metabolism, PRIMSOL 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 PRIMSOL is administered to a nursing woman.

Pediatric Use: The safety of trimethoprim has not been established in pediatric patients below the age of 2 months. The effectiveness of trimethoprim in the treatment of acute otitis media has not been established in patients below the age of 6 months.

ADVERSE REACTIONS

Adverse Events Reported During Pediatric Clinical Trials With PRIMSOL:

The following table lists those drug-related adverse events reported most frequently during the clinical trials in pediatric patients aged 6 months to 12 years. Most of these events were determined to be mild. The incidence of drug-related adverse events was significantly lower for PRIMSOL, which was most apparent for those events related to skin/appendages as a body system.

Drug-related Adverse Event	Percent of Pediatric Patients	
	PRIMSOL (N=310)	SMX + TMP* (N=197)
Body as a whole		
abdominal pain	<1	2.5
Digestive system		
diarrhea	4.2	4.6
vomiting	1.6	1.5
Skin/Appendages		
rash	1.3	6.1

*sulfamethoxazole + trimethoprim oral suspension

An increase in lymphocytes and eosinophils was noted in some pedi-

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atric patients following treatment with PRIMSOL or sulfamethoxazole + trimethoprim oral suspension.

Adverse Reactions Reported For Trimethoprim:

In addition to the adverse events listed above which have been observed in pediatric patients receiving PRIMSOL, the following adverse reactions and altered laboratory tests have been previously reported for trimethoprim and therefore, may occur with PRIMSOL therapy:

Dermatologic reactions: pruritus and exfoliative dermatitis. At the recommended adult 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 in adults, 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, and glossitis.

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

Metabolic reactions: Hyperkalemia, hyponatremia.

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 OVERDOSAGE-Chronic).

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

Acute Otitis Media in Pediatric Patients: The recommended dose for pediatric patients with acute otitis media is 10 mg/kg trimethoprim per 24 hours, given in divided doses every 12 hours for 10 days. The following table is a guideline for the attainment of this dosage:

Pediatric patients 6 months of age or older:

Weight		Dose (every 12 hours)	
lb	kg	tsp	mL
11	5	1/2	2.5
22	10	1	5
33	15	1 1/2	7.5
44	20	2	10
55	25	2 1/2	12.5
66	30	3	15
77	35	3 1/2	17.5
≥88	≥40	4	20

Uncomplicated Urinary Tract Infections: The usual oral adult dosage is 100 mg (10 mL) every 12 hours or 200 mg (20 mL) every 24 hours, each for 10 days.

Patients with Impaired Renal Function: The use of trimethoprim in patients with a creatinine clearance of less than 15 mL/min is not recommended. Patients with a creatinine clearance of 15 to 30 mL/min should receive half the dose recommended for patients of the same age with normal renal function.

HOW SUPPLIED

PRIMSOL (trimethoprim hydrochloride oral solution), dye-free, alcohol-free, bubble gum flavored, containing trimethoprim hydrochloride equivalent to 50 mg of trimethoprim in each 5 mL; bottle of 473 mL (1 pint). NDC 59439-478-02. Store between 15°-25°C (59°-77°F). Dispense in tight, light-resistant glass or PET plastic containers as defined in USP. Do not dispense if tamper-evident neck seal is broken prior to initial use.

℞ Only

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically – Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25. NCCLS, Villanova, PA, December, 1993.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24. NCCLS, Villanova, PA, December, 1993.
3. Brumfitt W, Pursell R: Trimethoprim/Sulfamethoxazole in the Treatment of Bacteriuria in Women, *J Infect Dis* 128 (suppl): S657-S663, 1973.

Revised May 3, 1999
Manufactured for Ascent Pediatrics, Inc., Wilmington, MA 01887
by Lyne Laboratories, Inc., Brockton, MA 02301

ASCENT PEDIATRICS INC.

NDC 59439-478-02

Primsol® Solution

(trimethoprim hydrochloride oral solution)

trimethoprim, 50 mg / 5 mL

For important prescribing information, read accompanying package insert

℞ Only

Store between 15° - 25°C (59° - 77°F)

473 mL (1 pint)

ASCENT PEDIATRICS INC

Pharmacist: Dispense in tight, light-resistant glass or PET plastic containers as defined in USP.

Do not dispense if tamper-evident neck seal is broken prior to first use.

Manufactured for
Ascent Pediatrics, Inc.
Wilmington, MA 01887
by
Lyne Laboratories, Inc.
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L2A0599

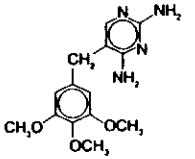
Primsol® Solution

(trimethoprim hydrochloride oral solution)

Dye-free, alcohol-free, flavored solution,
50 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 50 mg trimethoprim and the inactive ingredients bubble gum flavor, fructose, glycerin, methylparaben, monoammonium glycyrrhizinate, povidone, propylparaben, propylene glycol, saccharin sodium, sodium benzoate, sorbitol, water and hydrochloric acid and/or sodium hydroxide 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 dose of 100 mg, urine concentrations of trimeth ranged from 30 to 160 mcg/mL during the 0- t period and declined to approximately 18 to 91 during the 8- to 24-hour period. A 200 mg sing will result in trimethoprim urine concentrations mately twice as high. After oral administration 60% of trimethoprim is excreted in the urine w hours, approximately 80% of this being unmet trimethoprim.

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Trimethoprim also concentrates into middle ea

than are the concentrations in the blood. After a single oral dose of 100 mg, urine concentrations of trimethoprim ranged from 38 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.

Trimethoprim half-life, clearance, and volume of distribution vary with age. Excluding newborns, an apparent trend of increasing half-life, volume of distribution, and decreasing clearance is observed with increasing age until adulthood.

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 concentrates into middle ear fluid (MEF) very efficiently. In a study in children aged 1 to 12 years, administration of a single 4 mg/kg dose resulted in a mean peak MEF concentration of 2.0 mcg/mL.

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

Microbiology: Trimethoprim 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, trimethoprim selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

Trimethoprim has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobic gram-positive microorganisms

Staphylococcus species (coagulase-negative strains, including *S. saprophyticus*)

Streptococcus pneumoniae (penicillin-susceptible strains)

Aerobic gram-negative microorganisms

Enterobacter species

Escherichia coli

Haemophilus influenzae (excluding beta-lactamase negative, ampicillin resistant strains)

Klebsiella pneumoniae

Proteus mirabilis

NOTE: *Moraxella catarrhalis* isolates were found consistently resistant to trimethoprim.

Susceptibility Tests

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of trimethoprim powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms isolated from urinary tract infections:

MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)
≥ 16	Resistant (R)

When testing *Haemophilus influenzae*[a]

MIC (mcg/mL)	Interpretation
≤ 0.5	Susceptible (S)
1-2	Intermediate (I)
≥ 4	Resistant (R)

When testing *Streptococcus pneumoniae*[b]

MIC (mcg/mL)	Interpretation
≤ 2	Susceptible (S)
≥ 4	Resistant (R)

[a] Interpretive criteria applicable only to tests performed by broth microdilution method using *Haemophilus* Test Medium (HTM).[1]

[b] Interpretive criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.[1]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedur trimethoprim[a] powder should provide th values:

Microorganism	
Escherichia coli	ATCC 2592
Haemophilus influenzae[b]	ATCC 4924
Staphylococcus aureus	ATCC 2921
Streptococcus pneumoniae[c]	ATCC 4961

[a] Trimethoprim very medium-dependent

[b] Range applicable only to tests perform microdilution method using *Haemophi* (HTM).[1]

[c] Range applicable only to tests perform microdilution method using cation-adj ton broth with 2 to 5% lysed horse blo

Diffusion techniques:

Quantitative methods that require measu diameters also provide reproducible esti ceptibility of bacteria to antimicrobial co such standardized procedure[2] requires t dardized inoculum concentrations. This paper disks impregnated with 5 mcg trim the susceptibility of microorganisms to t

Reports from the laboratory providing r dard single-disk susceptibility test with prim[a] disk should be interpreted accord ing criteria:

s pneumoniae[b]

Interpretation
Susceptible (S)
Resistant (R)

licable only to tests performed method using *Haemophilus* Test

licable only to tests performed method using cation-adjusted ith 2 to 5% lysed horse blood.[1]

ndicates that the pathogen is antimicrobial compound in the trations usually achievable. A ndicates that the result should be . If the microorganism is not ative, clinically feasible drugs, the This category implies possible dy sites where the drug is physi- r in situations where high dosage category also provides a buffer ll uncontrolled technical factors repancies in interpretation. A icates that the pathogen is not e antimicrobial compound in the ntrations usually achievable; other ted.

lity test procedures require the use croorganisms to control the technical aspects of the laboratory procedures. Standard trimethoprim[a] powder should provide the following MIC values:

Microorganism		MIC (mcg/mL)
Escherichia coli	ATCC 25922	0.5 - 2
Haemophilus influenzae[b]	ATCC 49247	0.06 - 0.5
Staphylococcus aureus	ATCC 29213	1 - 4
Streptococcus pneumoniae[c]	ATCC 49619	1 - 4

[a] Trimethoprim very medium-dependent.

[b] Range applicable only to tests performed by broth microdilution method using *Haemophilus* Test Medium (HTM).[1]

[c] Range applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.[1]

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 mcg trimethoprim to test the susceptibility of microorganisms to trimethoprim.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 mcg trimethoprim[a] disk should be interpreted according to the following criteria:

For testing aerobic microorganisms isolated from urinary tract infections:

Zone diameter (mm)	Interpretation
≥16	Susceptible (S)
11-15	Intermediate (I)
≤10	Resistant (R)

For testing *Haemophilus influenzae*[b]:

Zone diameter (mm)	Interpretation
≥16	Susceptible (S)
11-15	Intermediate (I)
≤10	Resistant (R)

[a] Blood-containing media (except for lysed horse blood) are generally not suitable for testing trimethoprim. Mueller-Hinton agar should be checked for excessive levels of thymidine. To determine whether Mueller-Hinton medium has sufficiently low levels of thymidine and thymine, an *Enterococcus faecalis* (ATCC 29212 or ATCC 33186) may be tested with trimethoprim/sulfamethoxazole disks. A zone of inhibition ≥20 mm that is essentially free of fine colonies indicates a sufficiently low level of thymidine and thymine.

[b] Interpretative criteria applicable only to tests performed by disk diffusion method using *Haemophilus* Test Medium (HTM).[2]

Note:

Diffusion techniques are not recommended for determining susceptibility of *Streptococcus pneumoniae* to trimethoprim.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for trimethoprim.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5 mcg trimethoprim[a] disk should provide the following zone diameters in this laboratory test quality control strain:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	21 - 28
Haemophilus influenzae[b]	ATCC 49247	27 - 33
Staphylococcus aureus	ATCC 25923	19 - 26

[a] Blood-containing media (except for lysed horse blood) are generally not suitable for testing trimethoprim. Mueller-Hinton agar should be checked for excessive levels of thymidine. To determine whether Mueller-Hinton medium has sufficiently low levels of thymidine and thymine, an *Enterococcus faecalis* (ATCC 29212 or ATCC 33186) may be tested with trimethoprim/sulfamethoxazole disks. A zone of inhibition ≥20 mm that is essentially free of fine colonies indicates a sufficiently low level of thymidine and thymine.

[b] Range applicable only to tests performed by disk diffusion method using *Haemophilus* Test Medium (HTM).[2]

Note:

Diffusion techniques are not recommended for determining susceptibility of *Streptococcus pneumoniae* to trimethoprim.

INDICATIONS AND USAGE

PRIMSOL Solution is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Pediatric Patients:

Acute Otitis Media: For the treatment of acute otitis media due to susceptible strains of *Streptococcus pneumoniae* and *Haemophilus influenzae*.

NOTE: *Moraxella catarrhalis* isolates were found consistently resistant to trimethoprim *in vitro*. Therefore, when infection with *Moraxella catarrhalis* is suspected, the use of alternative antimicrobial agents should be considered. PRIMSOL is not indicated for prophylactic or prolonged administration in otitis media at any age.

Adults:

Urinary Tract Infections: 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.

CLINICAL STUDIES

The results of one multicenter, 30-day, comparative, randomized clinical trial without tympanocentesis in 262 pediatric patients with acute otitis media (AOM) are shown below. In this clinical trial, strict evaluability criteria were used to determine clinical response.

	PRIMSOL	SMX + TMP*
Enrolled	133	129
Evaluable	130	129
Clinical Cure	64/130 (49%)	63/129 (49%)
Clinical Improvement	30/130 (23%)	31/129 (24%)
Relapse/Recurrence	19/130 (15%)	18/129 (14%)
Outcome (based on 95% confidence interval)		PRIMSOL equivalent to TMP + SMX

*sulfamethoxazole + trimethoprim oral suspension

The results of an uncontrolled 30-day trial with tympanocentesis in 120 pediatric patients with AOM are shown below:

	Number of patients	
Enrolled	120	
Clinically Evaluable	102	
Microbiologically Evaluable	58	
Clinical Cure	50/102 (49%)	
Clinical Improvement	22/102 (22%)	
Clinical Relapse/Recurrence	20/102 (20%)	
Microbiologic Eradication Rates n=58	Day 5 post-therapy	Day 20 post-therapy
Streptococcus pneumoniae	16/20 (80%)	14/20 (70%)
Haemophilus influenzae	14/17 (82%)	13/17 (77%)

Moraxella catarrhalis, isolated from five patients, was found consistently resistant to trimethoprim *in vitro*.

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. Folates 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: PRIMSOL 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 Jaffé alkaline picrate reaction assay for creatinine resulting in overestimations of about 10% in the range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate carcinogenic potential have not been conducted with trimethoprim. 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 PRIMSOL. 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,[3] 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 sulfa-zole. There were no abnormalities in the 10 ch- whose mothers received the drug during the fi- trimester. In a separate survey, Brumfitt and P- found no congenital abnormalities in 35 childr- mothers had received trimethoprim plus sulfa- at the time of conception or shortly thereafter.

Because trimethoprim may interfere with folic metabolism, PRIMSOL should be used during only if the potential benefit justifies the potent- fetus.

Nonteratogenic Effects: The oral administratio- trimethoprim to rats at a dose of 70 mg/kg/da- ing with the last third of gestation and continu- parturition and lactation caused no deleterious gestation or pup growth and survival.

Nursing Mothers: Trimethoprim is excreted i- milk. Because trimethoprim may interfere wit- metabolism, caution should be exercised whe- is administered to a nursing woman.

Pediatric Use: The safety of trimethoprim ha- established in pediatric patients below the ag- months. The effectiveness of trimethoprim in- ment of acute otitis media has not been estab- patients below the age of 6 months.

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, PRIMSOL 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 metabolism, caution should be exercised when PRIMSOL is administered to a nursing woman.

Pediatric Use: The safety of trimethoprim has not been established in pediatric patients below the age of 2 months. The effectiveness of trimethoprim in the treatment of acute otitis media has not been established in patients below the age of 6 months.

ADVERSE REACTIONS

Adverse Events Reported During Pediatric Clinical Trials With PRIMSOL:

The following table lists those drug-related adverse events reported most frequently during the clinical trials in pediatric patients between the ages of 6 months to 12 years. Most of these events were determined to be mild. The incidence of drug-related adverse events was significantly lower for PRIMSOL. This was most apparent for those events related to skin rashes as a body system.

Drug-related Adverse Event	Percent of Pediatric Patients	
	PRIMSOL (N=310)	SMX + TMP* (N=197)
As a whole		
Abdominal pain	<1	2.5
Digestive system		
diarrhea	4.2	4.6
vomiting	1.6	1.5
Skin/Appendages		
rash	1.3	6.1

*sulfamethoxazole + trimethoprim oral suspension

An increase in lymphocytes and eosinophils was noted in some pediatric patients following treatment with PRIMSOL or sulfamethoxazole + trimethoprim oral suspension.

Adverse Reactions Reported For Trimethoprim:

In addition to the adverse events listed above which have been observed in pediatric patients receiving PRIMSOL, the following adverse reactions and altered laboratory tests have been previously reported for trimethoprim and therefore, may occur with PRIMSOL therapy:

Dermatologic reactions: pruritus and exfoliative dermatitis. At the recommended adult 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 in adults, 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, and glossitis.

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

Metabolic reactions: Hyperkalemia, hyponatremia.

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 OVERDOSAGE-Chronic).

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

Acute Otitis Media in Pediatric Patients: The recommended dose for pediatric patients with acute otitis media is 10 mg/kg trimethoprim per 24 hours, given in divided doses every 12 hours for 10 days. The following table is a guideline for the attainment of this dosage:

Pediatric patients 6 months of age or older:

Weight		Dose (every 12 hours)	
lb	kg	tsp	mL
11	5	½	2.5
22	10	1	5
33	15	1½	7.5
44	20	2	10
55	25	2½	12.5
66	30	3	15
77	35	3½	17.5
≥88	≥40	4	20

Uncomplicated Urinary Tract Infections: The usual adult dosage is 100 mg (10 mL) every 12 hours or 200 mg (20 mL) every 24 hours, each for 10 days.

Patients with Impaired Renal Function: The use of trimethoprim in patients with a creatinine clearance of less than 15 mL/min is not recommended. Patients with creatinine clearance of 15 to 30 mL/min should receive one-half the dose recommended for patients of the same age with normal renal function.

HOW SUPPLIED

PRIMSOL (trimethoprim hydrochloride oral solution), sugar-free, alcohol-free, bubble gum flavored, contains 50 mg trimethoprim hydrochloride equivalent to 50 mg trimethoprim in each 5 mL: bottle of 473 mL (16 fl oz) NDC 59439-478-02. Store between 15°-25°C (59°-77°F). Dispense in tight, light-resistant glass or PET plastic containers as defined in USP. Do not dispense if tamper-evident neck seal is broken prior to initial use.

℞ Only

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically --Third Edition. Approved Standard NCCLS Document M7-A, Vol. 13, No. 25. NCCLS, Villanova, PA, December, 1993.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Fifth

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Pediatric patients 6 months of age or older:

Weight		Dose (every 12 hours)	
lb	kg	tsp	mL
11	5	1/2	2.5
22	10	1	5
33	15	1 1/2	7.5
44	20	2	10
55	25	2 1/2	12.5
66	30	3	15
77	35	3 1/2	17.5
≥88	≥40	4	20

Uncomplicated Urinary Tract Infections: The usual oral adult dosage is 100 mg (10 mL) every 12 hours or 200 mg (20 mL) every 24 hours, each for 10 days.

Patients with Impaired Renal Function: The use of trimethoprim in patients with a creatinine clearance of less than 15 mL/min is not recommended. Patients with a creatinine clearance of 15 to 30 mL/min should receive half the dose recommended for patients of the same age with normal renal function.

HOW SUPPLIED

PRIMSOL (trimethoprim hydrochloride oral solution), dye-free, alcohol-free, bubble gum flavored, containing trimethoprim hydrochloride equivalent to 50 mg of trimethoprim in each 5 mL; bottle of 473 mL (1 pint). NDC 59439-478-02. Store between 15°-25°C (59°-77°F). Dispense in tight, light-resistant glass or PET plastic containers as defined in USP. Do not dispense if tamper-evident neck seal is broken prior to initial use.

℞ Only

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically --Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.
3. Brumfitt W, Pursell R. Trimethoprim/Sulfamethoxazole in the Treatment of Bacteriuria in Women. *J Infect Dis* 128 (suppl): S657-S663, 1973

Revised May 3, 1999.
Manufactured for Ascent Pediatrics, Inc., Wilmington, MA 01887 by Lyne Laboratories, Inc., Brockton, MA 02301

ASCENT PEDIATRICS INC

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-973

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER
5

2. ANDA NUMBER
74-973

3. NAME AND ADDRESS OF APPLICANT
Ascent Pediatrics, Inc.
Attention: William E. Brochu, Ph.D.
187 Ballardville Street, Suite B125
Wilmington, MA 01887

4. LEGAL BASIS for ANDA SUBMISSION
This application is based on the provisions of §505(b)(2) of the Act. It is an application for the approval of a new strength (50 mg (base) per 5 mL) of the RLD, Primsol® Solution (trimethoprim hydrochloride oral solution) 25 mg (base)/5 mL. The applicant owns the approved NDA 74-374 for the RLD. The RLD is not entitled to a period of marketing exclusivity and there is no unexpired patent.

5. SUPPLEMENT(s)
None

6. NAME OF DRUG
Primsol®

7. NONPROPRIETARY NAME
Trimethoprim Hydrochloride Oral Solution

8. SUPPLEMENT(s) PROVIDE(s) FOR
None

9. AMENDMENTS AND OTHER DATES

10/4/96	Original submission
11/12/96	New corresponding
11/26/96	New corresponding
5/13/97	Amendment
5/16/97	New corresponding
8/1/97	Major amendment
2/5/98	Addendum to 8/1/97 amendment
2/24/98	Amendment
3/31/98	Addendum to 2/24/98 Amendment
6/29/98	Amendment
12/4/98	Major amendment (new formulation)

2/19/1999 Amendment (stability data)
6/30/1999 Minor amendment
10/12/1999 Telephone amendment
11/24/1999 Telephone amendment
12/27/1999 Telephone amendment
1/10/2000 Telephone amendment (2 pieces)

10. PHARMACOLOGICAL CATEGORY

Antibacterial

11. HOW DISPENSED

Prescription

12. RELATED IND/NDA/DMF(s)

Product	Holder	DMF No.	LOA
Trimethoprim USP			
Bubble Gum Flavor			
Plastic Containers			
Plastic Containers			
Clic-Loc Closures			

13. DOSAGE FORM

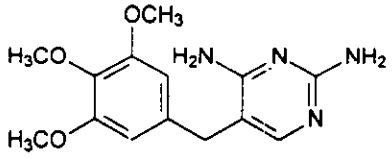
Solution

14. POTENCY

50 mg/5mL

15. CHEMICAL NAME AND STRUCTURE

Trimethoprim. 2,4-Pyrimidinediamine, 5-[(3,4,5-trimethoxyphenyl)methyl]-. $C_{14}H_{18}N_4O_3$. 290.32. 738-70-5.



16. RECORDS AND REPORTS

None

17. COMMENTS

None

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER AND DATE COMPLETED

Naiqi Ya/January 11, 2000

Page(s) 14

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry Review #5

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-973

BIOEQUIVALENCE REVIEW(S)

Trimethoprim-HCL
50 mg/ 5 mL Oral Solution
ANDA # 74-973
Reviewer: Andre Jackson

Ascent Pharmaceuticals
Wilmington, Ma.
Submission Date:
December 4, 1998
June 4, 1999

WP# V:\Firmsam\Ascent\Ltrs&Rev\74973AC.D98

Review of Correspondence and an Amendment to a Bioavailability Study

Background

The firm submitted a bioavailability study for their 50 mg/ 5 mL solution on December 23, 1997. The study was found to be acceptable by the Division of Bioequivalence. In the current submission, the firm is requesting a change in their formulation(. However, during the review of their latest submission it was apparent that there were inconsistencies in the formulations presented by the firm in the past. Therefore the firm was requested to address and clarify the following items for the amendment to their original study to be considered.

Item 1.

1. What is the chronology of product formulations, including formula numbers where available, in your submissions since 1996.

Our application 74-973 contains 4 formulations, In Table 1 (and Tab #1) we have provided a comparative product composition table followed by the formula page from the respective master production records for each of these formulations. Formulation was included in our original submission and in our bioequivalence study TMP-09 submitted on 12/23/97. In considering the changes that were subsequently made the main features of re that it (1) contains (2) contains , and (3) is adjusted to final volume with Formulation differs from in that contains vs the contained in Formulation is free, contains and includes a defined amount of in each batch and thus the final batch volume is adjusted with

rather than Formulation
resulted from a minor adjustment in the included
in the product such that the target as achieved in
the final product. Formulations were the result of
specific responses to FDA reviewer comments. Formulation
resulted from a minor calculation error found in

Table 1. Primsol 50mg/5ml- (trimethoprim HCL Oral Solution)
Product Composition(quantities given in mg/5ml- of final
product)

Ingredient
Trimethoprim
Sorbitol
Propylene Glycol
Povidone 25
Maltitol
Glycerin*
Monoammonium Glycyrrhizinate
Saccharin Sodium
Bubblegum Flavor
Methylparaben
Sodium Benzoate
Propylparaben
Fructose
Hydrochloric Acid
Sodium Hydroxide
Purified Water

*The total glycerin in the final product reflected in this table is derived directly from the addition of and indirectly from the addition of which contains in a ehicle.

**The quantity of- . in the final product was estimated from the quantitiy of :e used to prepare individual batches of product. was used to adjust the final of these product formulations.

FDA Comment:

The firm's response is acceptable.

Item 2.

2. Explain the differences In the formulations included in your 4/31/98 (page 12) and 12/4/98 (page 7) submissions.

FDA Comment:

The firm's response is acceptable.

Item 3.

3. Provide detailed calculations relating the product composition and manufacturing formulations in your 4/31/98 and 12/4/98 submissions.

Under Tab #3 we have provided the detailed calculations including the required constants used in translating the manufacturing formula to the final product composition for formulation numbers

FDA Comment:

The firm's response is acceptable.

4. Explain the differences in the levels in the formulations in your 4/31/98 and 12/4/98 submissions.

Page(s) 2

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

formulation

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Ascent Pharmaceuticals demonstrates that Trimethoprim HCL 50 mg/5 mL falls under 21 CFR Section 320.24(b)(6) of the Bioavailability/Bioequivalence regulations. The waiver of an in vivo bioavailability study requirement for the new formulation is granted.

Andre Jackson /S/
Division of Bioequivalence
Review Branch I

RD Initialed YC Huang /S/
FT Initialed YC Huang _____ Date: 6/16/97

cc: Concur: /S/ Date: 6/24/97
Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-973 APPLICANT: Ascent Pharmaceuticals

DRUG PRODUCT: Trimethoprim HCL 50 mg/ 5mL

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC:

BIOEQUIVALENCY - ACCEPTABLE submission date: December 4, 1999
June 6, 1999

1. **STUDY AMENDMENT**(STA) Strength: 50 mg/ 5mL
December 4, 1999

Outcome: AC

2. Study Amendment(STA)
June 6, 1999

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

Trimethoprim HCL
50 mg/ 5 mL Oral Solution
ANDA # 74-973
Reviewer: Andre Jackson
WP # 74973S.D97

Ascent Pharmaceuticals
Wilmington, Ma.
Submission Date:
December 23, 1997
April 15, 1998

REVIEW OF A BIOAVAILABILITY STUDY ON A 50 MG/5 ML ORAL SOLUTION

Background:

The firm submitted a waiver request to the Division of Bioequivalence on July 16, 1997 which was denied because the formulation contained inactive ingredients not found in their approved 25 mg/ 5mL formulation. The firm was requested to do a bioequivalence study to prove that the inactive ingredients did not affect trimethoprim absorption.

OBJECTIVE

To compare the Trimethoprim serum levels produced after administration of two oral solution test formulations with those produced after administration of a marketed tablet reference product, under fasting conditions.

Methods

The clinical portion of the study was conducted by

follows:

Period I October 9-11, 1997
Period II October 16-18, 1997
Period III October 23-25, 1997

STUDY DESIGN:

The study design was a single dose, three-treatment, three-period, three-sequence crossover with at least a one-week washout

between the three periods of the study.

Characterization of Study Group

Subjects selected for the study were:

1. Healthy, men or women, 18-45 years of age.

2. No more than plus or minus 15% from ideal weight for subject's height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983.

3. Without a history of anemia, tuberculosis, epilepsy, diabetes, psychosis, glaucoma, drug abuse, asthma, psychiatric illness, organ-system (cardiovascular, neurological, hepatic, hematopoietic, renal, or gastrointestinal) disorders, ongoing infectious diseases, or alcohol abuse or drug abuse as determined by a medical history and/or physical examination within 30 days prior to the start of the study. Deviations were acceptable if deemed not clinically significant by the investigator.

4. Blood chemistry including alkaline phosphatase, glucose, AST, ALT, LDH, SUN, SGT, creatinine, bilirubin), hematology (including hemoglobin, hematocrit, red blood cell count, white blood cell count, differential, platelet count), and urinalysis values within clinically acceptable limits upon evaluation by the investigator. The above tests were performed within 30 days prior to the start of the study.

5. No known allergy or sensitivity to trimethoprim, sulfa drugs, or to related drugs.

6. No prescription drugs (excluding contraceptives) within 14 days, or OTC medications (excluding OTC acetaminophen, aspirin, ibuprofen, vitamins, medicated lozenges, dietary supplements, and topical medications) within 7 days of the first drug administration.

7. No caffeine for at least 12 hours prior to drug administration.

8. No alcohol consumption for at least 48 hours prior to drug administration,. each period.

9. Subjects must have a minimum screening and/or check-in blood pressure of at least 100/60 mmHg.

10. No investigational drugs within 30 days prior to entering the study.

11. Women volunteers should not be pregnant or nursing. They had to be practicing contraception with a reliable and recognized method.

12. Negative serum pregnancy test at screening and a negative urine pregnancy test at check-in for each period.

13. Negative HIV 1, hepatitis 8 surface antigen, and urine screen for drugs of abuse within 30 days prior to the start of the study.

DRUG ASSIGNMENT:

The subjects were assigned to three dosing sequences as follows:

	Period I	Period II	Period III
1/3 subjects, sequence 1	A	B	C
1/3 subjects, sequence 2	B	C	A
1/3 subjects, sequence 3	C	A	B

Each subject was assigned a subject number. Each subject was randomly assigned to one of the dosing sequences. They were dosed in order of subject number. Actual assignments are given in appended Table 1.

INFORMED CONSENT AND CONSENT DOCUMENT

The study was explained to all prospective subjects by an investigator or a member of the staff. The explanation described the drug product being evaluated, the potential hazards involving drug allergies and possible adverse reactions. Each participant acknowledged receipt of this information and they freely offered to volunteer in this study by reading, signing and dating an informed consent form.

INSTITUTIONAL REVIEW BOARD

The study protocol and consent document was reviewed by the appropriate Investigational Review Board prior to initiation. In accordance with FDA regulations, written evidence of the review and approval of the protocol and consent document by an appropriate Institutional Review Board was obtained and a copy provided to the sponsor. All revisions and amendments to the protocol were approved by the sponsor and the Institutional Review Board.

STUDY CONDUCT

Twenty-one (21) male and female subjects were recruited for this study. Twenty-one (21) subjects began the study but 3 failed to complete the entire study. Subject #19 did not return for period 2 and subjects 6 and 20 did not return for period 3. Eighteen (18) subjects completed the clinical portion of the study.

SUBJECT CONTROL

The subjects were housed in the live-in facility from at least 12 hours before until at least 24 hours after drug administration.

Subjects were not permitted to smoke from 1 hour prior to until 4 hours after dosing or within one hour prior to scheduled blood pressure measurements, each period.

Subjects were allowed to ambulate freely throughout the study. Subjects were not permitted to lie down for 4 hours. No strenuous physical activity was permitted during the in-house portion of the study.

Subjects fasted for at least 10 hours prior to and 4 hours after the drug administration. During the fasting period, only water ad lib(except within one hour of drug administration) and that given with drug administration was allowed. Standard meals were served during the in-house portion of the study. Only xanthine-free (including caffeine-free) foods and beverages were provided. Only the food served was allowed during the in-house confinement period.

PRODUCTS STUDIED:

A) Trimethoprim hydrochloride oral solution, trimethoprim, 50 mg/5 mL, distributor. Ascent Pediatrics, Inc., lot # 97C02, expiration date January 1999.

B) Trimethoprim hydrochloride oral solution, trimethoprim, 25 mg/5 mL, distributor Ascent Pediatrics, Inc., lot # 6EX23, expiration date October 1998.

C) Trimethoprim tablet (Trimpex^{R}), 100 mg; manufacturer Roche Laboratories Lot # 0439, expiration February 1999.

There was a one week washout period between doses.

DRUG ADMINISTRATION:

Product A: 100 mg/10 mL at 0 hour followed by 120 mL of water.

The dose was drawn up and measured in a 10 mL syringe. Each syringe was weighed before and after it is filled with the 10 mL dose, and the weights recorded. The dose was mixed in the syringe before it was administered to the subject. After the dose was administered, the syringe was rinsed with approximately 10 mL of water which was then administered to the subjects, followed by the remainder of the water.

Product B: 100 mg/20 mL at 0 hour followed by 120 mL of water.

The dose was drawn up and measured in a 20 mL syringe. Each syringe was weighed before and after it was filled with the 20 mL dose, and the weights recorded. The dose was mixed in the syringe before it was administered to the subject. After the dose was administered, the syringe was rinsed with approximately 10 mL of water which was then be administered to the subjects, followed by the remainder of the water.

Product C: 100 mg (1 tablet) at 0 hour followed by 120 mL of water.

SUBJECT MONITORING:

1. Blood pressure and pulse were measured after the subject had been seated at least 3 minutes. Blood pressure and pulse were monitored at 0 hour (prior to dosing), 4 and 24 hours post-dose.

2. At the time of blood pressure monitoring, subjects were observed and/or questioned by the nurse to detect any adverse reactions. These were recorded.

3. Post-study clinical diagnostic samples were obtained following the last blood sample for period 3.

4. Any interphase use of prescription and OTC medications and alcohol was documented.

BLOOD SAMPLES:

Ten (10) mL venous blood samples were taken in Vacutainers with no anticoagulant at: 0 (pre-dose), 0.33, 0.67, 1.0, 1.5, 2, 2.5, 3, 4.5, 6, 8, 12, 16, and 24 hours (15 samples). The serum was separated, transferred to labeled tubes and stored frozen at -20°C until analysis.

Composition

Comparison between the approved formulation in 74-374 (25 mg/5 mL) and the proposed formulation in 74-973 (50 mg/5 ML)

Ingredient	74-973 (AMT/5 mL)	74-374 (AMT/5 mL)
Purified Water		
Sodium Hydroxide		
Propylene Glycol		
Methylparaben		
Propylparaben		
Sodium Benzoate	0	
Saccharin Sodium		
Hydrochloric Acid		
Trimethoprim USP (TMP)		
Povidone		

Glycerin
Maltitol Solution
Sorbitol Solution
Monoammonium Glycyrrhizinate
Solution (.0)
Fructose
Bubblegum Flavor

Monoammonium glycyrrhizinate is GRAS (21 CFR 184.1408(a)(2)). It is prepared from the water extract of The use of Bubblegum Flavor was justified in NDA 74-374. The same product number (Al 123600) is being used in NDA 74-973.
Fructose is not listed in the IIG or in 21 CFR, or in the Food Chemicals Codex.

ANALYTICAL METHODOLOGY

Sample analysis began on October 29, 1997 and was completed on December 2, 1997. Therefore, the total time for sample storage was approximately 60 days.

The serum samples were assayed for trimethoprim by a sensitive and specific procedure with developed at y. The internal standard for the assay was mple and control concentrations were determined by interpolation of their peak height ratios from the standard curve obtained in the same run.

Assay sensitivity:

The assay was linear over the range of 0.1 to 4 ug/mL. The limit of sensitivity of the assay was defined as 0.1 ug/mL, with values less than this reported as zero.

Precision and Reproducibility:

Reproducibility was assessed by comparing the results of standard samples assayed on different days. The coefficient of variation was 1.76% at a concentration of 0.1 ug/mL and 0.84% at 4 ug/mL.

Accuracy

Inter-day accuracy was assessed by comparing the results of quality control samples analyzed on different days. Accuracy was 95.8% at 3.5 ug/mL and 97.2% at 0.25 ug/mL. Respective coefficients of variation at these concentrations were 2.29% and 2.90% respectively.

Pre-assay Validation

Recovery

Recovery was based on the comparison of the mean peak heights of extracted serum QC samples at 4 ug/mL, 1.0 ug/mL, 0.2 ug/mL and 0.1 ug/mL compared with unextracted water standards. For each concentration, the peak heights of six replicates of extracted and unextracted samples were compared. The mean recovery from serum was 79.6% (Volume 7.1, Table 1A, page 526).

Selectivity

There were no interfering peaks in blank serum at the retention times of trimethoprim and internal standard as seen in the chromatograms. All the peaks were separated. During the validation, blank serum from six lots of serum was evaluated, and all control serum was found to be satisfactory.

Stability

Freeze-Thaw Stability

QC samples prepared at 3.0 ug/mL and 0.20 ug/mL were divided into 3 cycles consisting of 3 sets of QC samples per cycle. Cycle 1 was subjected to 1 freeze and thaw cycle, cycle 2 was subjected to 2 freeze and thaw cycles and cycle 3 was subjected to three freeze and thaw cycles. Each cycle consisted of freezing samples at -20C and thawing at room temperature for 2 hours. Samples from all three cycles were extracted and compared against a fresh mean calibration standard curve. The % change for all three cycles is presented in (Volume 7.1, Table 1B, page 527). The results indicate that the samples were stable during three freeze-thaw cycles.

Room Temperature Stability

The stability of spiked serum samples during 24 hours at room temperature was determined. Triplicate samples were spiked at concentrations of 3.0 and 2.0 ug/mL of trimethoprim and kept at room temperature for 24 hours. After 24 hours, the samples were extracted and injected using a fresh calibration standard curve. The results presented in Volume 7.1, Table 1C(page 527) show that the % change from the nominal values indicated that the serum samples were stable at room temperature for 24 hours.

Long Term Freezer Stability

The stability of trimethoprim in serum during frozen storage was documented over the course of 55 days. The stored solutions were 101% of nominal. The raw data is supplied in the firm's April 15, 1998 submission.

The validation and analytical data are acceptable.

STATISTICAL ANALYSIS:

The concentration versus time data were used to calculate the areas under the concentration-time curves (AUC) by linear interpolation between consecutive blood drug levels. AUC-T was calculated from zero time to the last non-zero concentration (CT). AUCi was calculated by extrapolation of AUCT to time infinity by adding CT/K., to AUC-T. The elimination rate constant (K) was estimated by linear least squares fitting of the logarithm of the concentrations over the log-linear terminal phase of the concentration versus time profile. Half-life (HL=0.693/K), maximum concentration attained, Cmax and the time of maximum concentration, Tmax was also calculated.

AUCT, AUCI, Cmax and log transformed AUCT, AUCI, and Cmax were analyzed by Analysis of Variance (ANOVA) with effects for treatments, sequence of dosing, subjects within sequence, and study period. In the statistical model the Sequence effect was used to test the [subject(sequence)] mean square as an error term. All other main effects were tested against the residual error from the ANOVA. The least squares means for treatments, the difference in least squares means **and the** standard error of these differences were reported.

The two one-sided hypotheses at the alpha=0.05 level of significance was tested for AUCT, AUCI, Cmax in original scale and after log transformation by constructing the 90% confidence intervals for the differences between the test and the reference least squares means, and was reported relative to the reference means.

RESULTS

Table 1. Mean serum concentrations ug/mL for trimethoprim HCL in 18 subjects. Values are mean ± sd.

	50 mg/mL Solution		25 mg/mL Solution		100 mg Tablet	
	Mean	SD	Mean	SD	Mean	SD
HOUR0	0	0	0	0	0	0
HOUR0.33	0.55	0.41	0.72	0.48	0.29	0.28
HOUR0.67	0.94	0.32	0.97	0.31	0.85	0.37
HOUR1	1	0.25	1.03	0.27	1.03	0.31
HOUR1.5	1.01	0.21	1.05	0.24	1.09	0.26
HOUR2	0.99	0.23	0.97	0.2	1.04	0.24
HOUR2.5	0.95	0.21	0.97	0.21	0.99	0.21
HOUR3	0.93	0.21	0.95	0.2	0.97	0.21
HOUR4	0.86	0.18	0.87	0.17	0.91	0.18
HOUR5	0.79	0.15	0.81	0.16	0.83	0.18
HOUR6	0.69	0.14	0.72	0.14	0.72	0.15
HOUR8	0.6	0.12	0.61	0.11	0.63	0.14
HOUR12	0.42	0.11	0.43	0.1	0.45	0.1
HOUR16	0.3	0.09	0.29	0.07	0.31	0.08
HOUR24	0.15	0.09	0.15	0.09	0.16	0.06

Table 2. Summary of Mean Bioavailability Parameters for Trimethoprim. Values are Means ± SD.

Parameter	Test Product 1 Ascent 50mg/5mL	Test Product 2 Ascent 25mg/5mL	Reference Product Roche 100mg Tablet	Test1/ Test2	Test1/ Ref	Test2/ Ref
AUC 0-T(ug/mLxhr)	11.55±2.57	11.71±2.57	12.07±2.56	0.99	0.96	0.97
Ln AUC 0-T	2.42±0.23	2.44±0.22	2.47±0.21	0.99	0.96	0.97
Geometric Mean	11.27	11.44	11.81			
AUC0-Inf(ug/mLxhr)	13.92±3.46	14.02±3.22	14.24±3.17	0.99	0.98	0.99
Ln AUC 0-Inf	2.60±0.26	2.62±0.23	2.63±0.22	0.99	0.98	0.99
Geometric Mean	13.51	13.68	13.90			
Cmax(ug/mL)	1.09±0.23	1.12±0.26	1.13±0.29	0.97	0.97	1.00
Ln Cmax	0.065±0.21	0.09±0.23	0.09±0.24	0.97	0.97	1.00
Geometric Mean	1.067	1.098	1.096			
Tmax (hr)	1.21±0.51	1.20±0.73	1.40±0.49	--	--	--
Rate Constant (hr-1)	0.087±0.029	0.086±0.022	0.085±0.020	--	--	--
Half-Life(hr)	8.65	8.43	8.46			

Table 3. 90% Confidence Intervals

Parameter	Ascent 50 mg/Roche	Ascent 25mg/Roche	Ascent 50mg/Ascent 25 mg
LnAUC(0-T)	92-100	93-101	95-103
LnAUC(0-Inf)	93-102	94-103	94-103
LnCmax	94-102	96-105	93-101

ALL CALCULATIONS WERE VERIFIED BY THE REVIEWER

Sample Repeats

Three of the 810 samples analyzed were reassayed.

Adverse Reactions

Six subjects reported ten adverse events which are presented in Table 5 page 39 volume 7.1. All were mild in severity.

Comment:

1.The 90% confidence intervals for Cmax and AUC for the 50 mg/5mL trimethoprim solution were within 80-125% versus the reference product Roche 100 mg tablet and its approved 25mg/5mL solution.

2.The firm has submitted pharmacology/toxicity data on several components of their formulation for review.

Recommendation

1.The fasting bioavailability study conducted by Ascent on its Trimethoprin Hydrochloride oral solution 50 mg/5 mL, lot 97C02 comparing it to Roche's 100 mg Trimethoprim tablet and Ascent's 25 mg/mL oral solution has been found to be acceptable by the Division of Bioequivalence. The study demonstrates that Ascent's 50 mg/mL oral solution is bioavailable compared to Roche's 100 mg Trimethoprim tablet and Ascent's 25 mg/mL oral solution. However, final acceptability of this submission depends upon the outcome of the review of the pharmacology/toxicity data by the medical officer.

Andre J. Jackson /S/
Division of Bioequivalence
Review Branch I

RD INITIALLED YC HUANG
FT INITIALLED YC HUANG /S/ Date: 4/22/98

Concur: /S/ Date: 4/29/98
Dale P. Conner, Pharm.D.
Director,
Division of Bioequivalence
c

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-973
APPLICANT: Ascent Pharmaceuticals
DRUG PRODUCT: Trimethoprim HCL 50 mg/ 5mL oral solution

The Division of Bioequivalence has completed its review and has no further questions at this time. However, final acceptability of this submission depends upon the outcome of the review of the pharmacology/toxicity data by the medical officer.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Filed in Final on / /

BIOAVAILABILITY - ACCEPTABLE submission date: 12-23-97

1. **FASTING STUDY** (STF)
Strengths: 50 MG/ 5 ML
Clinical:
Outcome: AC
Analytical:

Outcome Decisions: **AC** - Acceptable

[redacted]

DOSING SCHEDULE
TRIMETHOPRIM FORMULATIONS
PROJECT #145-11-11308

PERIOD I Administered 10/10/97
PERIOD II Administered 10/17/97
PERIOD III Administered 10/24/97

SUBJECT NO.	PERIOD I	PERIOD II	PERIOD III	DOSING TIME
1	A	B	C	0900
2	B	C	A	0902
3	C	A	B	0904
4	B	C	A	0906
5	A	B	C	0908
6	C	A	-	0910
7	B	C	A	0912
8	A	B	C	0914
9	C	A	B	0916
10	A	B	C	0918
11	C	A	B	0920
12	B	C	A	0922
13	B	C	A	0924
14	C	A	B	0926
15	A	B	C	0928
16	C	A	B	0930
17	A	B	C	0932
18	B	C	A	0934
19	B	-	-	0936
20	C	A	-	0938
21	A	B	C	0940

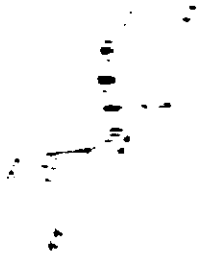
Treatment A = Trimethoprim Hydrochloride Oral Solution (Primsol), 50 mg/5 mL (1.0%)
Mfg: Lyne Laboratories, Inc.
Supplied by: Ascent Pediatrics, Inc.
Lot: #97C02
Dose = 10 mL of solution administered with 120 mL of water

Treatment B = Trimethoprim Hydrochloride Oral Solution (Primsol), 25 mg/5 mL (0.5%)
Mfg: Lyne Laboratories, Inc.
Supplied by: Ascent Pediatrics, Inc.
Lot: #6EX23
Dose = 20 mL of solution administered with 120 mL of water

Treatment C = Trimethoprim Tablets (TRIMPEX®), 100 mg
Mfg: Roche Laboratories (A Division of Hoffmann-LaRoche Inc.)
Lot: #0439
Dose = 1 tablet administered with 120 mL of water

OBS	SUBJ	PER	SEQ	TRT	AUCL	AUCI	CPEAK	LAUCL	LAUCI	LCPEAK
	1									
2	2									
3	3									
4	4									
5	5									
6	7									
7	8									
8	9									
9	10									
10	11									
11	12									
12	13									
13	14									
14	15									
15	16									
16	17									
17	18									
18	21									
19	1									
20	2									
21	3									
[illegible]	4									
	5									
24	7									
25	8									
26	9									
27	10									
28	11									
29	12									
30	13									
31	14									
32	15									
33	16									
34	17									
35	18									
36	21									
37	1									
38	2									
39	3									
40	4									
41	5									
42	7									
	8									
	9									
45	10									
46	11									
47	12									
48	13									
49	14									

50 15
51 16
52 17
53 18
54 21



TRT=A

Variable	N	Mean	Std Dev	Minimum	Maximum
AUCL	18	11.5455556	2.5724427		
LAUCL	18	2.4222050	0.2280419		
AUCI	18	13.9205556	3.4557820		
LAUCI	18	2.6030833	0.2566868		
CPEAK	18	1.0897778	0.2335465		
LCPEAK	18	0.0649827	0.2092955		

TRT=B

Variable	N	Mean	Std Dev	Minimum	Maximum
AUCL	18	11.7077778	2.5690363		
LAUCL	18	2.4372779	0.2212735		
AUCI	18	14.0238889	3.2250930		
LAUCI	18	2.6158249	0.2301325		
CPEAK	18	1.1250556	0.2602294		
LCPEAK	18	0.0931200	0.2277401		

TRT=C

Variable	N	Mean	Std Dev	Minimum	Maximum
AUCL	18	12.0700000	2.5588371		
LAUCL	18	2.4691758	0.2144888		
AUCI	18	14.2350000	3.1688266		
LAUCI	18	2.6319282	0.2253374		
CPEAK	18	1.1273889	0.2881687		
LCPEAK	18	0.0915236	0.2410043		

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SUBJ	18	1 2 3 4 5 7 8 9 10 11 12 13 14 15 16 17 18 21
SEQ	3	ABC BCA CAB
PER	3	1 2 3
TRT	3	A B C

Number of observations in data set = 54

General Linear Models Procedure

ident Variable: LAUCL

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	2.33510802	0.11119562	19.33	0.0001
Error	32	0.18409680	0.00575302		
Corrected Total	53	2.51920481			

R-Square	C.V.	Root MSE	LAUCL Mean
0.926923	3.104880	0.07584870	2.44288624

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.37383858	0.18691929	32.49	0.0001
SUBJ(SEQ)	15	1.93248713	0.12883248	22.39	0.0001
PER	2	0.00987125	0.00493563	0.86	0.4336
TRT	2	0.01891105	0.00945552	1.64	0.2092

e	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.37383858	0.18691929	32.49	0.0001
SUBJ(SEQ)	15	1.93248713	0.12883248	22.39	0.0001
PER	2	0.00807669	0.00403835	0.70	0.5031
TRT	2	0.01891105	0.00945552	1.64	0.2092

Tests of Hypotheses using the Type III MS for SUBJ(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.37383858	0.18691929	1.45	0.2654

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
B VS C	-0.01243372	-0.49	0.6278	0.02540077

General Linear Models Procedure

ıdent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	2.68400125	0.12780958	19.74	0.0001
Error	32	0.20716388	0.00647387		
Corrected Total	53	2.89116513			

R-Square	C.V.	Root MSE	LAUCI Mean
0.928346	3.074591	0.08046037	2.61694547

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.50088896	0.25044448	38.69	0.0001
SUBJ(SEQ)	15	2.17285703	0.14485714	22.38	0.0001
PER	2	0.00357288	0.00178644	0.28	0.7606
TRT	2	0.00668238	0.00334119	0.52	0.6017

:e	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.50088896	0.25044448	38.69	0.0001
SUBJ(SEQ)	15	2.17285703	0.14485714	22.38	0.0001
PER	2	0.00273307	0.00136654	0.21	0.8108
TRT	2	0.00668238	0.00334119	0.52	0.6017

Tests of Hypotheses using the Type III MS for SUBJ(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.50088896	0.25044448	1.73	0.2110

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
B VS C	-0.01266881	-0.47	0.6414	0.02694516

General Linear Models Procedure

ident Variable: LCPEAK

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	2.44995387	0.11666447	21.60	0.0001
Error	32	0.17284274	0.00540134		
Corrected Total	53	2.62279661			

R-Square	C.V.	Root MSE	LCPEAK Mean
0.934100	88.32455	0.07349378	0.08320878

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.10411556	0.05205778	9.64	0.0005
SUBJ(SEQ)	15	2.32849484	0.15523299	28.74	0.0001
PER	2	0.00859598	0.00429799	0.80	0.4600
TRT	2	0.00874748	0.00437374	0.81	0.4539

:e	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.10411556	0.05205778	9.64	0.0005
SUBJ(SEQ)	15	2.32849484	0.15523299	28.74	0.0001
PER	2	0.00835145	0.00417572	0.77	0.4700
TRT	2	0.00874748	0.00437374	0.81	0.4539

Tests of Hypotheses using the Type III MS for SUBJ(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.10411556	0.05205778	0.34	0.7203

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
B VS C	-0.02908827	-1.18	0.2460	0.02461214

General Linear Models Procedure
Least Squares Means

TRT	LAUCL LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0
A	2.42980309	0.01798981	0.0001
B	2.44223681	0.01798981	0.0001
C	2.47442178	0.01798981	0.0001

TRT	LAUCI LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0
A	2.60868355	0.01908360	0.0001
B	2.62135236	0.01908360	0.0001
C	2.63603449	0.01908360	0.0001

TRT	LCPEAK LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0
A	0.06900252	0.01743127	0.0004
B	0.09809078	0.01743127	0.0001
C	0.09360519	0.01743127	0.0001

OBS	_NAME_	TRT	TLSMEAN	TSTDERR
1	LAUCL	A	2.42980	0.017990
2	LAUCI	A	2.60868	0.019084
3	LCPEAK	A	0.06900	0.017431

OBS	_NAME_	TRT	RLSMEAN	RSTDERR
1	LAUCL	B	2.44224	0.017990
2	LAUCI	B	2.62135	0.019084
3	LCPEAK	B	0.09809	0.017431

OBS	_NAME_	TRT	RLSMEAN	RSTDERR	TLSMEAN	TSTDERR	T
1	LAUCL	A	2.44224	0.017990	2.42980	0.017990	1.69389
2	LAUCI	A	2.62135	0.019084	2.60868	0.019084	1.69389
3	LCPEAK	A	0.09809	0.017431	0.06900	0.017431	1.69389

OBS	EST	CI_U	CI_L	CIU	CIL
1	-0.012434	0.030655	-0.055522	1.03113	0.94599
2	-0.012669	0.033039	-0.058377	1.03359	0.94329
3	-0.029088	0.012662	-0.070839	1.01274	0.93161

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SUBJ	18	1 2 3 4 5 7 8 9 10 11 12 13 14 15 16 17 18 21
SEQ	3	ABC BCA CAB
PER	3	1 2 3
TRT	3	A B C

Number of observations in data set = 54

General Linear Models Procedure

Dependent Variable: LAUCL

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	2.33510802	0.11119562	19.33	0.0001
Error	32	0.18409680	0.00575302		
Corrected Total	53	2.51920481			

R-Square	C.V.	Root MSE	LAUCL Mean
0.926923	3.104880	0.07584870	2.44288624

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.37383858	0.18691929	32.49	0.0001
SUBJ(SEQ)	15	1.93248713	0.12883248	22.39	0.0001
PER	2	0.00987125	0.00493563	0.86	0.4336
TRT	2	0.01891105	0.00945552	1.64	0.2092

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.37383858	0.18691929	32.49	0.0001
SUBJ(SEQ)	15	1.93248713	0.12883248	22.39	0.0001
PER	2	0.00807669	0.00403835	0.70	0.5031
TRT	2	0.01891105	0.00945552	1.64	0.2092

Tests of Hypotheses using the Type III MS for SUBJ(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.37383858	0.18691929	1.45	0.2654

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
A VS C	-0.01243372	-0.49	0.6278	0.02540077

General Linear Models Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	2.68400125	0.12780958	19.74	0.0001
Error	32	0.20716388	0.00647387		
Corrected Total	53	2.89116513			

R-Square	C.V.	Root MSE	LAUCI Mean
0.928346	3.074591	0.08046037	2.61694547

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.50088896	0.25044448	38.69	0.0001
SUBJ(SEQ)	15	2.17285703	0.14485714	22.38	0.0001
PER	2	0.00357288	0.00178644	0.28	0.7606
TRT	2	0.00668238	0.00334119	0.52	0.6017

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.50088896	0.25044448	38.69	0.0001
SUBJ(SEQ)	15	2.17285703	0.14485714	22.38	0.0001
PER	2	0.00273307	0.00136654	0.21	0.8108
TRT	2	0.00668238	0.00334119	0.52	0.6017

Tests of Hypotheses using the Type III MS for SUBJ(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.50088896	0.25044448	1.73	0.2110

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
A VS C	-0.01266881	-0.47	0.6414	0.02694516

General Linear Models Procedure

Dependent Variable: LCPEAK

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	2.44995387	0.11666447	21.60	0.0001
Error	32	0.17284274	0.00540134		
Corrected Total	53	2.62279661			

R-Square	C.V.	Root MSE	LCPEAK Mean
0.934100	88.32455	0.07349378	0.08320878

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.10411556	0.05205778	9.64	0.0005
SUBJ(SEQ)	15	2.32849484	0.15523299	28.74	0.0001
PER	2	0.00859598	0.00429799	0.80	0.4600
TRT	2	0.00874748	0.00437374	0.81	0.4539

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.10411556	0.05205778	9.64	0.0005
SUBJ(SEQ)	15	2.32849484	0.15523299	28.74	0.0001
PER	2	0.00835145	0.00417572	0.77	0.4700
TRT	2	0.00874748	0.00437374	0.81	0.4539

Tests of Hypotheses using the Type III MS for SUBJ(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.10411556	0.05205778	0.34	0.7203

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
A VS C	-0.02908827	-1.18	0.2460	0.02461214

General Linear Models Procedure
Least Squares Means

TRT	LAUCL LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0
A	2.42980309	0.01798981	0.0001
B	2.44223681	0.01798981	0.0001
C	2.47442178	0.01798981	0.0001

TRT	LAUCI LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0
A	2.60868355	0.01908360	0.0001
B	2.62135236	0.01908360	0.0001
C	2.63603449	0.01908360	0.0001

TRT	LCPEAK LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0
A	0.06900252	0.01743127	0.0004
B	0.09809078	0.01743127	0.0001
C	0.09360519	0.01743127	0.0001

OBS	_NAME_	TRT	TLSMEAN	TSTDERR
1	LAUCL	A	2.42980	0.017990
2	LAUCI	A	2.60868	0.019084
3	LCPEAK	A	0.06900	0.017431

OBS	_NAME_	TRT	RLSMEAN	RSTDERR
1	LAUCL	B	2.44224	0.017990
2	LAUCI	B	2.62135	0.019084
3	LCPEAK	B	0.09809	0.017431

OBS	_NAME_	TRT	TLSMEAN	TSTDERR	RLSMEAN	RSTDERR	T
1	LAUCL	B	2.42980	0.017990	2.44224	0.017990	1.69389
2	LAUCI	B	2.60868	0.019084	2.62135	0.019084	1.69389
3	LCPEAK	B	0.06900	0.017431	0.09809	0.017431	1.69389

OBS	EST	CI_U	CI_L	CIU	CIL
1	-0.012434	0.030655	-0.055522	1.03113	0.94599
2	-0.012669	0.033039	-0.058377	1.03359	0.94329
3	-0.029088	0.012662	-0.070839	1.01274	0.93161

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SUBJ	18	1 2 3 4 5 7 8 9 10 11 12 13 14 15 16 17 18 21
SEQ	3	ABC BCA CAB
PER	3	1 2 3
TRT	3	A B C

Number of observations in data set = 54

General Linear Models Procedure

Dependent Variable: LAUCL

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	2.33510802	0.11119562	19.33	0.0001
Error	32	0.18409680	0.00575302		
Corrected Total	53	2.51920481			

R-Square	C.V.	Root MSE	LAUCL Mean
0.926923	3.104880	0.07584870	2.44288624

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.37383858	0.18691929	32.49	0.0001
SUBJ(SEQ)	15	1.93248713	0.12883248	22.39	0.0001
PER	2	0.00987125	0.00493563	0.86	0.4336
TRT	2	0.01891105	0.00945552	1.64	0.2092

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.37383858	0.18691929	32.49	0.0001
SUBJ(SEQ)	15	1.93248713	0.12883248	22.39	0.0001
PER	2	0.00807669	0.00403835	0.70	0.5031
TRT	2	0.01891105	0.00945552	1.64	0.2092

Tests of Hypotheses using the Type III MS for SUBJ(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.37383858	0.18691929	1.45	0.2654

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
A VS B	-0.01243372	-0.49	0.6278	0.02540077

General Linear Models Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr >
Model	21	2.68400125	0.12780958	19.74	0.000
Error	32	0.20716388	0.00647387		
Corrected Total	53	2.89116513			

R-Square	C.V.	Root MSE	LAUCI Mea
0.928346	3.074591	0.08046037	2.6169454

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.50088896	0.25044448	38.69	0.0001
SUBJ(SEQ)	15	2.17285703	0.14485714	22.38	0.0001
PER	2	0.00357288	0.00178644	0.28	0.7606
TRT	2	0.00668238	0.00334119	0.52	0.6017

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.50088896	0.25044448	38.69	0.0001
SUBJ(SEQ)	15	2.17285703	0.14485714	22.38	0.0001
PER	2	0.00273307	0.00136654	0.21	0.8108
TRT	2	0.00668238	0.00334119	0.52	0.6017

Tests of Hypotheses using the Type III MS for SUBJ(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.50088896	0.25044448	1.73	0.2110

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
A VS B	-0.01266881	-0.47	0.6414	0.02694516

General Linear Models Procedure

Dependent Variable: LCPEAK

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	21	2.44995387	0.11666447	21.60	0.000
Error	32	0.17284274	0.00540134		
Corrected Total	53	2.62279661			

R-Square	C.V.	Root MSE	LCPEAK Mean
0.934100	88.32455	0.07349378	0.08320878

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	2	0.10411556	0.05205778	9.64	0.0005
SUBJ(SEQ)	15	2.32849484	0.15523299	28.74	0.0001
PER	2	0.00859598	0.00429799	0.80	0.4600
TRT	2	0.00874748	0.00437374	0.81	0.4539

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.10411556	0.05205778	9.64	0.0005
SUBJ(SEQ)	15	2.32849484	0.15523299	28.74	0.0001
PER	2	0.00835145	0.00417572	0.77	0.4700
TRT	2	0.00874748	0.00437374	0.81	0.4539

Tests of Hypotheses using the Type III MS for SUBJ(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	2	0.10411556	0.05205778	0.34	0.7203

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
A VS B	-0.02908827	-1.18	0.2460	0.02461214

General Linear Models Procedure
Least Squares Means

TRT	LAUCL LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0
A	2.42980309	0.01798981	0.0001
B	2.44223681	0.01798981	0.0001
C	2.47442178	0.01798981	0.0001

TRT	LAUCI LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0
A	2.60868355	0.01908360	0.0001
B	2.62135236	0.01908360	0.0001
C	2.63603449	0.01908360	0.0001

TRT	LCPEAK LSMEAN	Std Err LSMEAN	Pr > |T| HO:LSMEAN=0
A	0.06900252	0.01743127	0.0004
B	0.09809078	0.01743127	0.0001
C	0.09360519	0.01743127	0.0001

OBS	_NAME_	TRT	TLSMEAN	TSTDERR
1	LAUCL	B	2.44224	0.017990
2	LAUCI	B	2.62135	0.019084
3	LCPEAK	B	0.09809	0.017431

OBS	_NAME_	TRT	RLSMEAN	RSTDERR
1	LAUCL	B	2.44224	0.017990
2	LAUCI	B	2.62135	0.019084
3	LCPEAK	B	0.09809	0.017431

OBS	_NAME_	TRT	TLSMEAN	TSTDERR	RLSMEAN	RSTDERR	T	EST	CI_U	CI_L	CIU	CIL
	LAUCL	B	2.44224	0.017990	2.44224	0.017990	1.69389	0	0.043088	-0.043088	1.04403	0.95783
	_AUCI	B	2.62135	0.019084	2.62135	0.019084	1.69389	0	0.045708	-0.045708	1.04677	0.95532
3	LCPEAK	B	0.09809	0.017431	0.09809	0.017431	1.69389	0	0.041751	-0.041751	1.04263	0.95911

OBS	SUBJ	TRT	FDACMAX	SEQ	FDAAREA	FDAAUCI	FRMAUCL	FRMAUCI	FRMCPEAK	RAUCL	RAUCI	RCMAX	PAUCNFDA	PAUCNFDR
1	1	A												
2	1	E												
3	1	C												
4	2	A												
5	2	B												
6	2	C												
7	3	A												
8	3	B												
9	3	C												
10	4	A												
11	4	B												
12	4	C												
13	5	A												
14	5	B												
15	5	C												
16	7	A												
17	7	B												
18	7	C												
19	8	A												
20	8	B												
21	8	C												
22	9	A												
23	9	B												
24	9	C												
25	10	A												
26	10	B												
27	10	C												
28	11	A												
29	11	B												
30	11	C												
31	12	A												
32	12	B												
33	12	C												
34	13	A												
35	13	B												
36	13	C												
37	14	A												
38	14	B												
39	14	C												
40	15	A												
41	15	B												
42	15	C												

OCT 2 1 1997

Trimethoprim Hydrochloride
50 mg/5 ml Oral Solution
ANDA #74-973

Ascent Pediatrics, Inc.
Billerica, MA
July 16, 1997

DIVISION DIRECTOR REVIEW
of Gratuitous Bioequivalence Amendment

BACKGROUND:

The applicant has submitted a request for a waiver of in-vivo bioavailability under 21 CFR 320.22(b)(3) on October 4, 1996 (date on Form 356h). The submission was reviewed by Dr. Man Kochar, received secondary review by Dr. Ramakant Mhatre and concurrence by Dr. Rabindra Patnaik, with a final recommendation to grant the waiver. In the July 16, 1997 submission the applicant has provided additional information to support their waiver.

DISCUSSION:

I do not concur with the previous recommendation of granting the waiver under 21 CFR 320.22(b)(3) since the applicant's product does not meet all of the criteria of the cited regulation. In the latest submission, the applicant misinterprets 21 CFR 320.22(b)(3) by implying that subsections (ii) and (iii) do not apply to their product since there is a period after subsection (i). This is an incorrect interpretation of the regulations. The subject of this application does not contain an active ingredient in the same concentration as a drug product which is the subject of an approved full new drug application (21 CFR 320.22(b)(3)(ii)). The approved product (ANDA 74-374) is 25 mg/5 ml and not 50 mg/5 ml. In addition, in the original submission the applicant has not provided any scientific evidence to show that their proposed formulation contains no inactive ingredient that is known to significantly affect absorption of the active drug ingredient (21 CFR 320.22(b)(3)(iii)).

The product approved under ANDA 74-374 is a syrup based formula whereas, the product in this application is
Fructose based with additional in smaller quantities
(sorbitol, propylene glycol, and glycerin).
not listed as an approved ingredient in the Agency's Inactive Ingredients Guide. It appears that this application most likely should not have been filed. Whether the and/or the
or the other inactive ingredients will impact the

bioavailability of this product to a significant extent from the approved syrup based 25 mg/5 ml formulation is not known. The applicant has provided an analysis by a "world-renowned academic consultant", Dr. Gerhard Levy, who has concluded that the new formulation will be bioequivalent to the original formulation. No scientific evidence was provided to support that conclusion. and a similar excipient, have been shown to alter gastrointestinal absorption of drugs. Specifically, a solution of cimetidine was shown to have a significantly reduced AUC and Cmax compared to a sucrose solution[1]. Whether a similar effect would occur with a trimethoprim solution is unknown. Trimethoprim may be more permeable than cimetidine (F may be near 1) and therefore should not have a significant formulation effect on its bioavailability.

The bioavailability/bioequivalence (BA/BE) of the product which is the subject of this application is linked to the demonstration of BA/BE of the 25 mg/5 ml (ANDA 74-374)solution. The study conducted under ANDA 74-374, comparing 100 mg of the 25 mg/5 ml solution to a 100 mg trimethoprim tablet was less than optimal in demonstrating bioequivalence. The optimal reference product should have been Trimpex^{R} 200 mg tablet (the Agency designated RLD) and not the 100 mg tablet. In addition, the study design called for the first blood sample to be drawn at 0.5 hours which may have resulted in missing the true Cmax (and a potential difference between the tablet) of the solution. In fact, six of the 21 subjects had Cmax occur as the first time point (0.5 h). A more optimally designed study would have included a 0.25 h sample.

The applicant has conducted a clinical trial to extend the indications of trimethoprim solution to children 6 months to 12 years old for treatment of otitis media and urinary tract infections. The results of the clinical trial were submitted as an efficacy supplement to ANDA 74-374. The Division of Anti-Infective Drug Products has approved the otitis media indication but did not approve the urinary tract indication. The applicant is requesting that the efficacy supplement approval from ANDA 74-374 be extended to the current ANDA. The formulation which is the subject of this ANDA has not ben studied clinically or in a bioequivalence trial.

Based on the above information, I do not concur with the granting of the waiver of in vivo bioavailability. The applicant's formulation is assumed to be bioavailable, however, it can not be concluded that it will be bioequivalent to the 25 mg/5 ml formulation which is also the link to the new indication for this product, treatment of otitis media in children.

RECOMMENDATION:

The inclusion of an unapproved excipient needs to be resolved. In addition, the applicant has not submitted information to show that the drug product is bioequivalent to the 25 mg/5 ml Primsol[R] solution, and their product does not meet the criteria for waiver under 21 CFR 320.22(b)(3).

/S/

Nicholas M. Fleischer, R.Ph.,M.S.,Ph.D.
Director, Division of Bioequivalence

CONCUR: _____

DO NOT CONCUR: _____

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science

NFleischer/8-13-97

REFERENCE

(1) Adkin, D.A.; et al: Effect of mannitol on the oral bioavailability of cimetidine. Journal of Pharmaceutical Sciences 84:1405-1409 (1995).

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street Suite B125 Wilmington, MA 01887 Phone 508-658-2500 Fax 508-658-3939

July 16, 1997

BIOAVAILABILITY

For his review
7/25/97

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: NDA #74-973, Primsol Solution, 50 mg per 5 mL, Gratuitous Bioequivalence Amendment

The purpose of this amendment is to provide further information regarding the Request for Biowaiver contained in the original application. Ascent believes that this information will be sufficient to support the assurance of bioequivalence between the Reference Listed Drug, Primsol 25 mg per 5 mL, and the subject drug, Primsol 50 mg per 5 mL.

The initial review of this application with its Request for Biowaiver contained therein, led the Division to conclude that it had no questions at that time. A letter to this effect was issued on March 13, 1997. It is my understanding that a desire for additional information has recently arisen.

I believe that I first need to address my understanding of the regulatory status of oral solution dosage forms. In 21 CFR 320.22 (b), there is an unequivocal statement that "FDA shall waive the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability or bioequivalence of these drug products...if the product meets one of the following criteria:" in subparagraph (3) (i) "The drug product is...an oral solution, elixir, syrup...". Please note that there is a period at the end of this subparagraph, thus separating it from the statements listed in subparagraphs (ii) and (iii) which set forth a different and unrelated set of criteria. It is my understanding that oral solutions and syrups historically have been granted waivers in virtually every case.

Despite our belief that this application is entitled to the waiver on this basis alone, we have taken steps to develop information to address the probability of different formulations of the same drug in true solution having different bioavailabilities.

To this end, we have done the following:

1. Conducted a thorough literature search matching the terms "bioavailability", "bioequivalence" and "drug absorption" with terms describing appropriate individual excipients as well as collective terms such as "excipients", "sugars", "solutions", "solvents", etc.

2. Employed the services of a world-renowned academic consultant in the field, Dr. Gerhard Levy, to analyze the information at his disposal and prepare a scholarly opinion on the subject.
3. Searched the literature for a report on trimethoprim's bioavailability based on an oral vs IV trimethoprim biostudy.

To summarize the results of these activities, we were unable to find any suggestion from either the literature search or Dr. Levy's research that the formulation differences between the 25 mg and 50 mg trimethoprim hydrochloride syrups might lead to a bioequivalence issue. Further, the oral vs IV literature abstract (Klepser, et al) reported an oral bioavailability of ~102% for trimethoprim compared to the IV (in a comparison of TMP/SMX in AIDS patients). This would strongly suggest that TMP is a highly permeable drug which is also known to be highly soluble in gastric fluid, and therefore meets the criteria for classification as a "Case A" drug.

Based on the above, Ascent continues to believe that this application is entitled to a waiver of *in vivo* bioequivalence. We would very much appreciate a timely review of the enclosed information.

Yours truly,
ASCENT PEDIATRICS, INC.

Robert W. Mendes, Ph. D.
Vice President, Regulatory Affairs

ANDA 74973

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

MAR 13 2007

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Trimethoprim Hydrochloride Oral Solution, (50 mg(base)/5 mL).

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

Letter Out, Bio Acceptable

Endorsements:

L. Sanchez 3/11/97

DRAFTED: STM 3/11/97 X:\WPFILE\BIO\FINAL\74973BIO.FAP

MAR 4 1997

MAR 4 1997

Trimethoprim (Primsol)
Hydrochloride 50 mg/5 mL
Oral Solution
ANDA # 74-973
Reviewer: Man M. Kochhar
74973W.1196

Ascent Pharmaceuticals, Inc.
Billerica, MA
Submission Date:
November 26, 1996

REVIEW OF A WAIVER REQUEST

Background:

The company has an approved trimethoprim hydrochloride oral solution, 25 mg/5 mL. The sponsor conducted an acceptable bioequivalence study on their 5 mg/mL (25 mg/5 mL) oral solution. The administered dose was 100 mg.

The product is formulated and manufactured using trimethoprim, USP, since trimethoprim hydrochloride is not available component for use in manufacturing. It is not, therefore, possible to isolate, identify or characterize the hydrochloride chemically

Comparative Formulation

Ingredients	50 mg/5 mL percent per 5 mL	25 mg/5 mL
Trimethoprim,	0.05	0.025 g
Hydrochloric Acid,	5	
Sodim hydroxide,	5	
Purified Water,		L
Sorbitol Solution		
Propylene Glycol,		
Povidone		
Maltitol Solution,		
Syrup,		
Glycerin,		
Monoammonium Glycyrrhizinate Solution		
Saccharin Sodium,		
Bubblegum Flavor		
Methylparaben,		
Propylparaben,		
Sodium Benzoate,		
Fructose		

Comments:

1. The company has requested the approval of new concentration (50 mg trimethoprim per 5 mL). Since both the approved product and proposed new product (new strength) are oral solutions, the sponsor has requested a waiver for in vivo bioequivalence study based on 21 CFR 320.22 (b)(3).

2. The formulation of both products is similar in concentration of active ingredient. The new formulation is using

fructose in place of syrup which was used in an approved product. This will not effect the bioequivalence of the finished product.

3. The dosage form, route of administration (oral), and labeling are identical to an approved product.

4. From the bioequivalence point of view, the waiver of in vivo bioequivalence study requirement should be granted based upon 21 CFR 320.22 (b)(3).

Recommendation:

The Division of Bioequivalence agrees that the information submitted by Ascent Pharmaceuticals on its Trimethorim Hydrochloride Oral Solution, 50 mg/5 mL fall under 21 CFR 320.22 (b)(3) of the Bioavailability/bioequivalence regulations. The waiver of in vivo bioequivalence study for Trimethoprim Hydrochloride Oral Solution, 50 mg/5 mL is granted.

The firm should be informed of the recommendation.

/S/

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

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

/S/ 2/17/97

Ramakant M. Mhatre, Ph.D.
Chief, Review Branch III

Concur: /S/ Date: 2/28/97

Rabindra Patnaik, Ph.D.
~~Acting~~ Director
Division of Bioequivalence

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-973 SPONSOR: Ascent Pharmaceuticals
DRUG: Trimethoprim Hydrochloride
DOSAGE FORM: Oral Solution
STRENGTH(s): 50mg/5mL
TYPE OF STUDY: Single/Multiple Fasting/Fed
STUDY SITE: waiver

STUDY SUMMARY: The company with an approved oral solution 25mg/5mL of Trimethoprim HCl has requested a waiver for 50mg/5mL. The formulation is similar with regard to active ingredient. The new formulation is using Sorbitol, maltitol sol., glycerin and fructose in place of Syrup. This should not effect the bio. / The route of administration, labeling and dosage are identical to approved product. The waiver is granted

DISSOLUTION: N/A

PRIMARY REVIEWER /S/ BRANCH: III

INITIAL: /S/ DATE: 3-3-97

BRANCH CHIEF: BRANCH:

INITIAL: /S/ DATE: 3/3/97

for DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: /S/ DATE: 3/4/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE:

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-973

ADMINISTRATIVE DOCUMENTS

ANDA APPROVAL SUMMARY

ANDA:	CHEMIST:	DATE:
74-973	Naiqi Ya	January 11, 2000

DRUG PRODUCT:
Primsol® (Trimethoprim Hydrochloride Oral Solution)

FIRM:
Ascent Pediatrics, Inc.

DOSAGE FORM:	STRENGTH:
Solution	50 mg/5 mL

cGMP:
EER was found acceptable for all the establishments on May 27, 1999.

BIO:
Reviewed by Andre Jackson and found satisfactory on June 6, 1999.

VALIDATION ***(Description of dosage form same as firm's):***
Method validation was completed on September 17, 1999. The method is acceptable.

STABILITY:
The containers in the stability studies are identical to those in the container section.

LABELING:
Container, carton, and insert labeling were approved by Lillie Golson on July 12, 1999.

STERILIZATION VALIDATION ***(If applicable)*****:**
Not applicable.

SIZE OF BIO BATCH ***(Firm's source of NDS ok?)*****:**
The bio batch (8EX19) size is

SIZE OF STABILITY BATCHES ***(If different from bio batch, were they Manufactured via the same process?):***
Same as the bio batch.

PROPOSED PRODUCTION BATCH MANUFACTURING PROCESS THE SAME?
The proposed production batches is The manufacturing processes are identical, except the vessel size changes in the certain steps.

Signature of chemist:	Signature of supervisor:
1/11/2000	1/11/00

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: Apnl 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

NDA 74-973

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Ascent Pediatrics, Inc.	January 3, 2000
TELEPHONE NO *(Include Area Code)*	**FACSIMILE (FAX) Number** (Include *Area Code*)
978-658-2500	978-658-3939

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:

187 Ballardvale Street, Suite B125
Wilmington, MA 01887

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIPCode, telephone &FAXnumber)* IFAPPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME (e.g., *Proper name, USP/USAN name*)	PROPRIETARY NAME *(trade name)* IF ANY
Trimethoprim hydrochloride oral solution	Primsol

CHEMICAUBIOCHEMICAUBLOOD PRODUCT NAME (If *any*): 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine

CODE NAME (If *any*):

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	50mg/5mL	oral

(PROPOSED) INDICATION(S) FOR USE:

Uncomplicated Urinary Tract Infections (Adults) and Otitis Media (Pediatric Patients)

APPLICATION INFORMATION

APPLICATION TYPE (check *one*) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, MDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☒ 505 (b) (2) ☐ 507

IF AN ANDA, OR MDA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

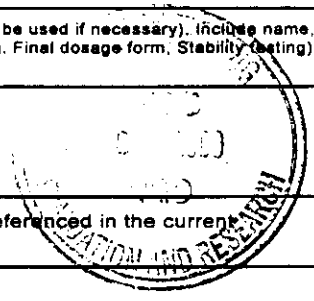
REASON FOR SUBMISSION: Telephone Amendment

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.



Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeiing ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
✓	4. Chemistry section
✓	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
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	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
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	11. Case report tabulations (e.g. 21 CFR 314.50 (fl (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (fl (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safet information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or advrse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CRF Part 600.
3. Labeling regulations in 21 CFR 210, 606, 610, 660 and/or 809 .
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regualtions on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree nto to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be tru and accurate.

Warning: a willfully false statement is a criminal offecse, U.S. Code, title 18, section 1001

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	William E. Brochu, Vice President, Regulatory Affairs	January 3, 2000

ADDRESS (Street, *City*, State, *and* ZIP Code)	Telephone Number
187 Ballardvale Street, Suite B125, Wilmington, MA 01887	978 658-2500

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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Please DO NOT RETURN this form to this address.

FORM FDA 356h (7/97)

RECORD OF TELEPHONE CONVERSATION

A phone call was placed to Dr. Brochu from Dr. Schwartz and Ms. Hu regarding ANDA 74-973, Trimethoprim HCl 10 mg/mL Oral Solution. Additional issues were identified. Dr. Schwartz explained that the major concern is the drug DMF from Technologies. We need the following information from the firm:

1. **What is Ascent's plan for launching?**
   Dr. Brochu explained that Ascent had prepared a launch batch for anticipated approval in July 1999 because they have been told that CMC issues have been closed. Since approval is delayed and since the expiration date is shorter than Ascent anticipated at the time the validation batches were made, these batches will not be commercially distributed. Ascent made production launch quantities in anticipation for launch this December. Since December approval may not be feasible, they are losing expiry period on the batches.

2. **Were these batches made from the same lot of material, or are there any batches from other sources?**
   Dr. Brochu explained that they have made other batches using another source, however, they are not commercial batches. They have made a batch with the source. This batch is newly made, and therefore, no stability data is available yet. the supplier used in the application.

3. **What are the lot numbers of the bulk active substance that have been used in its validation and launch production batches?**
   Dr. Brochu will provide the Agency with the information.

4. **Where does release their drug from?**
   Dr. Brochu will provide the Agency with the information.

5. **It is questionable whether Ascent's stability data supports the proposed and tability limits.**
   Dr. Brochu stated that through a previous conversation with the branch on October 25, 1999, it was agreed that the limits were acceptable.

6. **Since this product is for use in the pediatric population, there should be a heavy metal test and OVI test.**
   Dr. Brochu inquired how this will affect the material already made, and if Ascent could add this to their own specifications for future batches of drug substance. Dr. Schwartz said that the firm may add this to their own specifications for future batches.

(Continued on next page)

DATE:
12/27/1999

ANDA NUMBER:
74-973

PRODUCT NAME:
Trimethoprim HCl Oral Solution, 10 mg/mL

FIRM NAME:
Ascent Pediatric

FIRM REPRESENTATIVE:
William Brochu

PHONE NUMBER:
(978) 658-2500

FDA REPRESENTATIVES:
Elaine Hu
Paul Schwartz

SIGNATURES:
Elaine Hu 12/30/99
Paul Schwartz PS 12/30/99

CC: ANDA 74-973
Telecon Binder

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RECORD OF TELEPHONE CONVERSATION

7. **How long is the bulk product stored before it is packaged into the final container?**
Dr. Brochu stated that the product is stored for a maximum of . lays before final packaging.

8. **Is there any plan to extend the product expiration date?**
Dr. Brochu stated that Ascent commits to extend the tentatively approved 15-month product expiration date based on real-time room temperature data from 3 full-scale production batches. Dr. Schwartz stated that this statement needs to be submitted to the Agency.

9. **Is Ascent planning to use the rectangular shaped bottles?**
Dr. Brochu stated that it is Ascent's intention to use the round bottles. Dr. Brochu stated that he had spoken with Ken Furnkranz at FDA regarding the round and rectangular bottles. Mr. Furnkranz indicated to Dr. Brochu that there would be no problem with stability between the two bottle shapes.

10. **Is Ascent working on improving their analytical methods?**
Dr. Brochu stated that Ascent is working on it, but has not been completed yet.

Dr. Brochu stated that he was "...advised in November 1999 that there are no more issues with this application. Through dicussions with Mr. Buccine, a December 15 approval date was possible. We tried to live with reasonable expectations with the people at OGD. We have our entire sales force ready and the entire company has been waiting for the approval of this application. We are a small company, and the delays in approval have been costing us money. We need more reliable information from OGD, and we need to be provided with all the issues. We are not trying to dodge commitments; we are just trying to provide OGD with information in a timely manner. However, we are not receiving this information from OGD."

Dr. Schwartz responded that the application is in its final stages of review, and that the next level may identify issues that the branch had not identified.

Ms. Hu stated that Dr. Brochu may submit the requested information via fax.

DATE:
12/27/1999

ANDA NUMBER:
74-973

PRODUCT NAME:
Trimethoprim HCl Oral Solution, 10 mg/mL

FIRM NAME:
Ascent Pediatric

FIRM REPRESENTATIVE:
William Brochu

PHONE NUMBER:
(978) 658-2500

FDA REPRESENTATIVES:
Elaine Hu
Paul Schwartz

SIGNATURES:

Elaine Hu 12/30/99
Paul Schwartz

CC: ANDA 74-973

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

NDA 74-973

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Ascent Pediatrics, Inc.	October 12, 1999
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number (Include *Area Code*)**
978-658-2500	978-658-3939

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:

187 Ballardvale Street, Suite B125
Wilmington, MA 01887

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIPCode, telephone &FAXnumber)* IFAPPLICABLE

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NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

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CHEMICAUBIOCHEMICAUBLOOD PRODUCT NAME (*If any*): 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine

CODE NAME (*If any*):

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
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(PROPOSED) INDICATION(S) FOR USE:

Uncomplicated Urinary Tract Infections (Adults) and Otitis Media (Pediatric Patients)

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☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Revised expiration date and trimethoprim related substances specifications

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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X	19. OTHER (Specify) Revised expiration date and trimethoprim related substances specifications

CERTIFICATION

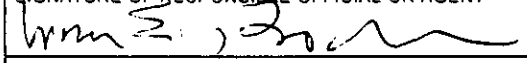
I agree to update this application with new safet information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or advrse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CRF Part 600.
3. Labeling regulations in 21 CFR 210, 606, 610, 660 and/or 809 .
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regualtions on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree nto to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be tru and accurate.

Warning: a willfully false statement is a criminal offecse, U.S. Code, title 18, section 1001

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	William E. Brochu, Vice President, Regulatory Affairs	October 12, 1999

ADDRESS (Street, *City*, State, *and* ZIP Code)	Telephone Number
187 Ballardvale Street, Suite B125, Wilmington, MA 01887	978 658-2500

002

Please DO NOT RETURN this form to this address.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1992
See OMB Statement on on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (*21 CFR Part 314*).

NAME OF APPLICANT	DATE OF SUBMISSION
Ascent Pediatrics, Inc.	November 26, 1996
	TELEPHONE NO. *(Include Area Code)* (508) 667-6300
ADDRESS (*Number, Street, City, State and Zip Code*) 9 Linnell Circle Billerica, MA 01821	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (*if previously issued*) 74-973

DRUG PRODUCT

ESTABLISHED NAME (*e.g., USP/USAN*)	PROPRIETARY NAME (*If any*)
Trimethoprim Hydrochloride Oral Solution	Primsol® Solution

CODE NAME (*If any*)	CHEMICAL NAME
	2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Solution	Oral	10mg/mL (50mg/5mL)

PROPOSED INDICATIONS FOR USE

Uncomplicated Urinary Tract Infections

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (*21 CFR Part 312*), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (*21 CFR Part 314.420*) REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION (*Check one*)

505(b)(2)

☒ THIS SUBMISSION IS A FULL APPLICATION (*21 CFR 314.50*) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (*21 CFR 314.55*)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
Primsol® Solution, 25mg/5mL	Ascent Pediatrics, Inc.

TYPE SUBMISSION (*Check one*)

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (*e.g., Part 314.70(b)(2)(iv)*)_____

PROPOSED MARKETING STATUS (*Check one*)

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (*Rx*) ☐ APPLICATION FOR AN OVER-THE-COUNTER-PRODUCT (*OTC*)

CONTENTS OF APPLICATION	
This application contains the following items: (*Check all that apply*)	
	1. Index
	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling (*4 copies*)
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and toxicology section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case report forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
X	15. OTHER (*Specify*) Response to FDA request for information

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Bert W. Mendes, Ph.D.		November 26, 1996

ADDRESS (*Street, City, State, Zip Code*)	TELEPHONE NO. (*Include Area Code*)
9 Linnell Circle Billerica, MA 01821	(508) 667-6300

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-973

CORRESPONDENCE

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street Suite B125 Wilmington, MA 01887 Phone 978-658-2500 Fax 978-658-3939

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

January 10, 2000

NDA 74-973
Trimethoprim HCl 50mg/5mL Oral Solution
Primsol
Telephone Amendment

Dear Mr. Sporn:

Reference is made to our application and to its several amendments. Reference is also made to a teleconference of 1/10/00 involving Dr. Ya, Dr. Schwartz, and Project Manager Ms Elaine Hu in which Ascent was provided with and agreed to the final terms for approval of our application. This amendment confirms Ascent's agreements to adopt FDA's requirements and hereby amends our application accordingly.

1. Heavy Metals Specification for bulk active Trimethoprim

2. Trimethoprim Related Compounds Specification in Primsol Oral Solution

   Total – NMT
   Largest Individual – NMT

We trust that Ascent's commitments to these changes will now allow the long awaited application approval to move forward. We thank all those involved in this application who have worked to achieve resolution of these final issues.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory and Quality Affairs

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street Suite B125 Wilmington, MA 01887 Phone 978-658-2500 Fax 978-658-3939

NC

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

January 10, 2000

NDA 74-973
Trimethoprim HCl 50mg/5mL Oral Solution
Primsol
Telephone Amendment

Dear Mr. Sporn:

Reference is made to our NDA and today's teleconference with Dr. Ya, Dr. Schwartz, and Ms. Elaine Hu of the Division and to a follow-up request for the following commitment.

Ascent hereby commits to testing the Trimethoprim bulk active ingredient for compliance with the new specification for Heavy Metals before releasing finished product to the market. The specification limit for Heavy Metals agreed to is NMT

Please advise if there are any additional questions or comments.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory and Quality Affairs

ASCENT
PEDIATRICS, INC.
187 Ballardvale Street, Suite B125, Wilmington MA 01887

Date: December 27, 1999

To: **Ms Elaine Hu**
Project Manager
FDA- Office of Generic Drugs
FAX: 301-594-0180
Phone: 301-827-5848

From: W.E. Brochu
FAX: 978-658-3939
Phone: 978-658-2500

Number of pages (excluding cover page): 3

NDA ORIG AMENDMENT

Telephone Amendment
NDA-74-973
Trimethoprim HCl 50mg/5mL Oral Solution
Primsol

Attached are responses to the questions identified in our telephone discussion of 12/27/99. This FAX will be followed with a hard copy to the Agency next week. A copy will also be provided to the New England District Office as required by regulation.

As indicated in the cover letter, please call as soon as possible if there is a need for any further information.

I will call on Monday 1/3/00 if I do not hear earlier concerning the timing for the next steps in finally achieving approval of our application.

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street, Suite B125 Wilmington, MA 01887 Phone 978-658-2500 Fax 978-658-3939

December 27, 1999

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Telephone Amendment

NDA-74-973
Trimethoprim HCl 50mg/5mL Oral Solution

Primsol

Dear Mr. Sporn:

Reference is made to our application and to a telephone discussion with Ms Hu and Dr. Schwartz on 12/27/99. Attached are responses to the requests for information made in that discussion. We trust that these will satisfactorily address all the remaining concerns related to the approval of this application.

Please advise if there is any further need for information. Since our office is officially closed until 1/3/00, I would appreciate either a voice mail message at the office (978-658-2500, ext 239) or a telephone call to my home at (508-541-2354) if there are any additional questions.

Sincerely,

W.E. Brochu, Ph.D.
Vice President Regulatory and Quality Affairs

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street • Suite B125 • Wilmington, MA 01887 • Phone 978-658-2500 • Fax 978-658-3939

Mr. Richard Penta
New England District
Food and Drug Administration
1 Montvale Ave
Stoneham MA 02180-3500

January 3, 2000

Telephone Amendment
Trimethoprim HCl 50mg/5mL
Oral Solution
Primsol
NDA 74-973

Dear Mr. Penta:

Enclosed is a true copy of CMC information provided to the Office of Generic Drugs by FAX on 12/27/99 and by hard copy today.

This copy is provided as required by 21CFR314.94(d)(5).

Please call if you have any questions related to this application or submission.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory & Quality Affairs

Where is the trimethoprim (TMP) bulk active drug released by . . and what are the specific lot numbers of bulk active that have been used by Ascent in its validation and launch production batches?

We have been advised by the Regulatory Affairs personnel at . . that they have provided Dr. Schwartz with information related to TMP bulk active drug substance lots that were provided to Ascent including the sites of manufacture and testing.

The TMP bulk active lot numbers used in Ascent's demonstration, validation and initial launch batches are provided in the table below. Please note that because of the delay in achieving the final approval of this application and an expiration date that is shorter than Ascent anticipated at the time the validation batches were manufactured, these will not be commercially distributed.

Product Batch Number	Intended Use of the Batch	TMP Lot Number
8EX19	600L demonstration batch	LM95-0038
99C05 99C06 99C07	Validation and production product stability	LH96-0138
99C11 99C13	Commercial distribution	LH96-0135

Please add specification tests and limits for the bulk active trimethoprim (TMP) for Heavy Metals and Organic Volatile Impurities.

Ascent has been advised by the Regulatory Affairs personnel at . . that OVI solvents are not used in the manufacture of TMP and that a letter to that effect was provided to Dr. Schwartz. Ascent commits to requiring this certification on all certificates of analysis for TMP used to manufacture Primsol.

Ascent has been advised that . . will agree to setting a specification for Heavy Metals based on data from its production batches and that this agreement has been communicated to FDA. Ascent commits to adopting the Heavy Metals specification agreed upon by . . and FDA. Additionally, should . . fail to establish a Heavy Metals specification in a timely manner, Ascent will set such a specification in its 1st Annual NDA report. The specification set by Ascent will be based on the results of Heavy Metals testing for TMP bulk active substance lots we receive for use in our production of Primsol.

Finally, as agreed with Dr. Schwartz, TMP lots previously released and used in the production of initial Primsol launch materials will not be subject to these additional specifications.

How long is bulk Primsol solution kept or stored before it is packaged in its final container?

Ascent commits that bulk Primsol will be held a maximum of days before final packaging. This maximum hold time is consistent with Good Manufacturing Practice and the standard practices at our product manufacturer and packager.

On what basis does Ascent plan to extend the product expiration date?

Ascent commits to extend the tentatively approved 15-month product expiration date based on real-time room temperature data from 3 full-scale production batches. As required by regulation, the data and any extension of the expiration date will be provided in the appropriate Primsol NDA Annual Report.

Which 16oz container shape does Ascent intend to use in commercial product?

Ascent intends to use the round container. Through consultation on 3/2/98 with Mr. Ken Furnkranz at FDA, Ascent obtained guidance that the two container shapes could be considered equivalent from stability data requirements, i.e. Ascent did not need to provide stability data in both container shapes to obtain approval for both in its application.

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street Suite B125 Wilmington, MA 01887 Phone 978-658-2500 Fax 978-658-3939

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville MD 20855-2773

November 24, 1999

Telephone Amendment
Trimethoprim HCl 50mg/5mL
Oral Solution
Primsol
NDA 74-973

Dear Mr. Sporn:

Reference is made to our NDA 74-973 for trimethoprim HCl oral solution 50mg/5mL, to our various amendments to this application, including our submission of 10/12/99 and telephone conference of 10/25/99.

Enclosed are updated stability data tables for demonstration batches 8EX19 and 8EX12. These include room temperature data for 15 months for batch 8EX19 and 16 months for batch 8EX12. As previously described to the Agency, these batches are the same in formulation, except for a small difference in the final amount of fructose resulting from a difference in the method of adjusting the final product volume. Demonstration batch 8EX19 represents our intended production process. As can be determined from these data, all test results are well within product specification and fully support a tentative expiration data of 15 months at room temperature.

Based on the telephone discussion of 10/25/99, we understand that these data represent the last piece of information required for the Agency's approval of our product including a tentative 15-month room temperature expiration date. Please advise as soon as possible if this is not the case. From the discussion of 10/25/99, we further understand that based on the Agency's receipt of these data before the end of November, we can reasonably expect receipt of the Agency's final approval letter within the month of December.

We thank the Agency for its patience and cooperation in its timely attention to our application in these final approval discussions.

Sincerely,

W.E. Brochu, Ph.D
Vice President, Regulatory and Quality Affairs

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street, Suite B125 Wilmington, MA 01887 Phone 978-658-2500 Fax 978-658-3939

NDA ORIG AMENDMENT
N/A

October 12, 1999

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Telephone Amendment

NDA 74-973
Trimethoprim Oral Solution
50mg/5mL
Primsol

Dear Mr. Sporn:

Reference is made to our NDA, our submissions of 12/4/98, 2/19/99, 6/30/99, 9/7/99, and 9/23/99. Reference is also made to a telephone discussion with FDA's Project Manager, Mr. Joseph Buccine on 9/23/99.

This submission provides additional stability data and analysis that is relevant to Ascent's proposed market formulation. We believe these data support the 24-month expiration dating period that we have requested. All stability indicators are well within specifications at the 12-month room temperature test interval. This submission also proposes a specification for related substances that is consistent with the available data. We request the Agency's reconsideration of its position on these two points.

In the telephone conversation of 9/23/99, Ascent was advised that our application was approvable if Ascent would agree to the following changes:

- 12 month room temperature expiration dating period
- Product and stability specifications for trimethoprim related substances (TMP-RS) NMT total, and NMT for any single individual
- Withdrawal of as a trimethoprim (TMP) supplier
- Revision of the product and stability specifications to reflect the agreed upon TMP-RS limits

Ascent hereby withdraws as an alternate supplier for TMP for our product. After approval of our application, we intend to submit a supplement to our application for the Agency's review with data supporting an alternate supplier for TMP. Similarly through our post-approval stability program Ascent will acquire

data to confirm the product expiration date and extend it as appropriate and supported by the data. Ascent commits to revising its product and stability specifications to reflect the agreed upon limits for TMP-RS once the Agency has reviewed this submission and a final disposition on this matter is taken. Ascent hereby reiterates its commitment made in our submission of 9/7/99 (page 14) to improve the analytical procedure by which TMP-RS is estimated.

Included in this submission are stability data for product batch 8EX12. This is a product batch having a formulation that is essentially the same as the demonstration batch of our intended market formulation. This batch was brought to final volume with while in the case of our intended commercial product (demonstration batch 8EX19) this is done with . There is therefore a small difference in the quantity of in the finished products for these two batches. Data beyond 6 months at room temperature was not available for this batch at the time our prior submissions were made. We have made projections of the expiration date for our product based on all of these data. Finally, we have also included data and information related to an experimental laboratory product batch (92697-3) with a formulation that is similar to our intended product (different amount of the flavor component , please see table 1. This also supports the appropriateness of a 24-month expiration date.

While Ascent believes these data continue to support a 24-month product expiration dating period, we propose a conservative 18 months expiration date for the Agency's consideration. TMP assay results, including 3 months/40°C, 12 months/30°C, 12 months/RT (24 months in the case of experimental batch 92697-3), and 11 months/refrigerated are all well within product specifications. Consistent with the available data and the proposed 18-month expiration date, we propose the following limits for TMP-RS: Total NMT ndividual NMT Finally, we also point out that our proposed limits and expiration dating period are based on considerations of the room temperature data only and therefore do not depend on extrapolations of observations at elevated temperatures.

After reviewing these data, we request the opportunity to discuss the Agency's position and to make any final commitments or changes to our application to achieve its approval.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory and Quality Affairs

ASCENT PEDIATRICS, INC.

187 Ballardvale Street • Suite B125 • Wilmington, MA 01887 • Phone 978-658-2500 • Fax 978-658-3939

October 12, 1999

Mr. Richard Penta
New England District
Food and Drug Administration
1 Montvale Ave
Stoneham MA 02180-3500

NDA 74-973
Trimethoprim Oral Solution 50mg/5mL
Primsol
Telephone Amendment

Dear Mr. Penta:

Enclosed is a true copy of a telephone chemistry amendment made to our application dated today. This submission proposes an alternative expiration dating period and specifications limits for trimethoprim related substances. This copy is provided as required by 21CFR314.94(d)(5).

Please call if you have any questions related to this application or submission.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory & Quality Affairs

003

Discussion of Stability Data and Expiration Date

We have estimated the room temperature expiration date individually for each of the 2 batches of product for which we have data, exhibit batch 8EX19A, and product batch 8EX12A. The suffixes A and B refer to the trade and sample package sizes, respectively. No projections were made for 8EX19B sub-lot because of the limited RT data available. Lot 8EX12A differs from the intended commercial product in that it contains a slightly higher level of The time projected with 95% confidence for the TMP assay to reach 90% of label is 25 months (8EX19A) and 55 months (8EX12A). When all of the data for these two batches (including 8EX19B) are evaluated the time to reach 90% potency for TMP is 44 months.

Ascent has conducted investigations into the nature of the TMP-RS's that are observed in our product. As reported to the Agency (submission of 12/4/98, page 474), these appear to be adducts of TMP with Since these are not TMP degradation products the usual concerns related to safety of related substances in significantly decreased. Correspondingly the levels of TMP-RS that can be reasonably tolerated without concern is significantly increased. Related to this, Ascent acknowledges that the values for TMP-RS observed in our stability programs are somewhat variable. We have committed to improving that method. Our investigation into the nature of the TMP-RS's however also suggests that the response factors for these substances may be significantly greater than is assumed in the calculations of their levels by the current method. This has the effect of overestimating the levels of TMP-RS in our product, perhaps by as much as several fold. Although not explicitly agreed, prior discussions with Agency reviewers suggest a general recognition of these facts.

Given these facts it seems reasonable to set the limits for TMP-RS in our product based on the observed data and those projected at the end of the expiration dating period.

In arriving at its proposal of NMT for total TMP-RS, the Agency indicated that the value observed for the 2-month/RT test period was discounted. This was done on the basis of the belief that the value was aberrant and a result of the method's variability. We agree with the aberrant nature of this value but point out that there is no technical basis to discount it. If such a value were observed in our post approval stability program, Ascent would potentially be required to recall its product.

Using the pooled room temperature TMP-RS data for batches 8EX19A, 8EX19B, and 8EX12A, we have made projections of the individual and total TMP-RS values expected after both 18 months storage at room temperature. Here we

have used the upper 95% confidence level. These values are % and respectively. Based on these data, a TMP-RS limit of NMT for an 18-month expiration date is appropriate.

As support for this discussion we have included the following:

- Summary of TMP assay and TMP-RS (individual and total) values for batches 8EX19A, 8EX19B, 8EX12A, and experimental batch 092697-3 (Table 1).
- Graphs showing the projections of the expiration date and TMP-RS values using the data for batches 8EX19A, 8EX19B, and 8EX12A (Figures 1, 2 and 3).
- Table comparing the formulations for batches 8EX12, 8EX19, and 092697-3 (Table 2).

Table 1: Summary of Room Temperature Date for Trimethoprim and Trimethoprim Related Substances in Primsol Oral Solution

	Initial	1 month	2 month	3 month	4 month	6 month	7 month	9 month	10 month	12 month	24 month
8EX19A											
TMP Assay	98.6		96.6	99.5	98.5		98.2		99.3	96.1	
Total TMP-RS	None Detected		3.1	0.5	1.1		0.9		2.1	1.4	
Individual TMP-RS	None Detected		0.3	None Detected	0.5		None Detected		1.1	0.7	
8EX19B											
TMP Assay	98.5								97.8	96.2	
Total TMP-RS	None Detected								2.2	0.8	
Individual TMP-RS	None Detected								0.7	0.5	
8EX12A											
TMP Assay	97.8	98.3	97.8	97.4		98		97.6			
Total TMP-RS	None Detected	4.2	0.9	1.6		0.6		1.6			
Individual TMP-RS	None Detected	3.4	0.7	0.9		0.6		0.8			
092697-3											
TMP Assay											95.6
Total TMP-RS											0.5
Individual TMP-RS											0.3

900

Figure 1

Calculated Expiry Date of Primsol Oral Solution at Room Temperature (25°C/60%RH)

Based on Lower 95% Confidence Interval Using Lots #8EX19A,B and 8EX12A

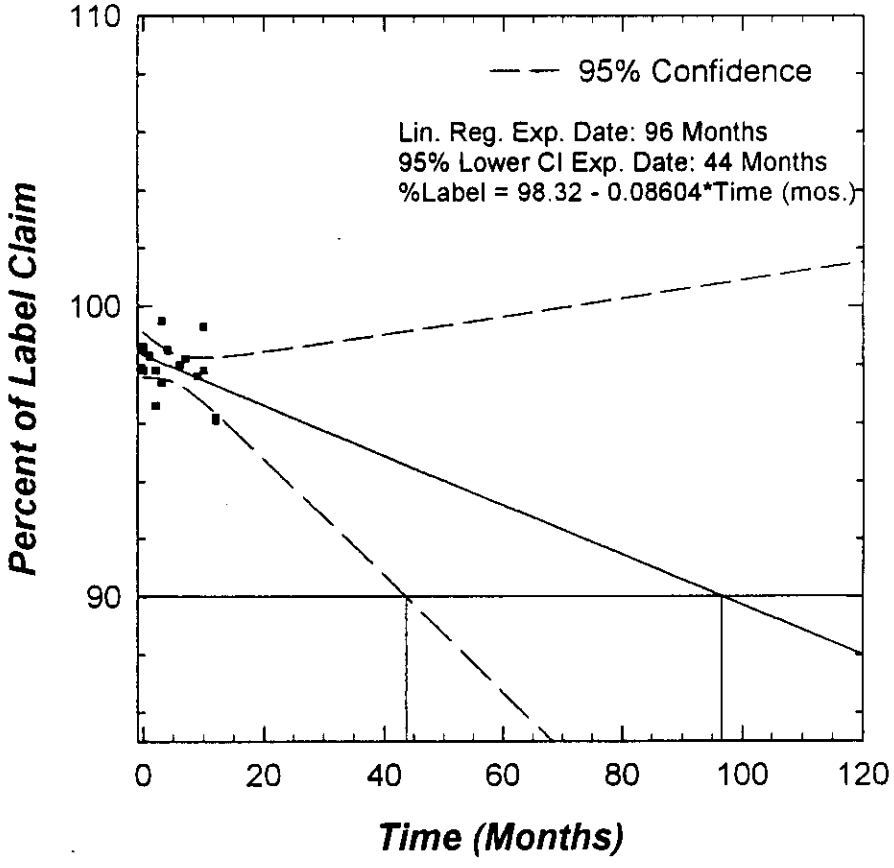


Figure 2

Extrapolated Total Related Substances for Primsol Oral Solution at Room Temperature (25°C/60%RH)

Based on Upper 95% Confidence Interval Using Lots #8EX19A,B and 8EX12A

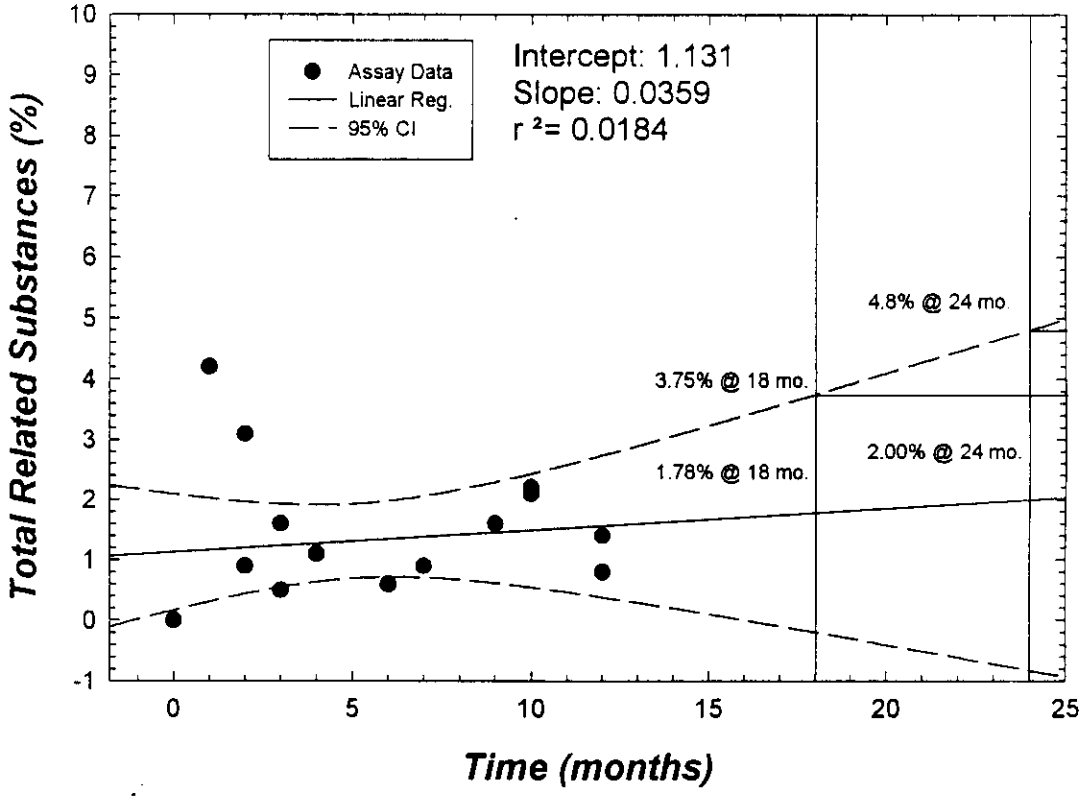


Figure 3

Extrapolated Individual Related Substances for Primsol Oral Solution at Room Temperature (25°C/60%RH)

Based on Upper 95% Confidence Interval Using Lots #8E19A,B and 8EX12A

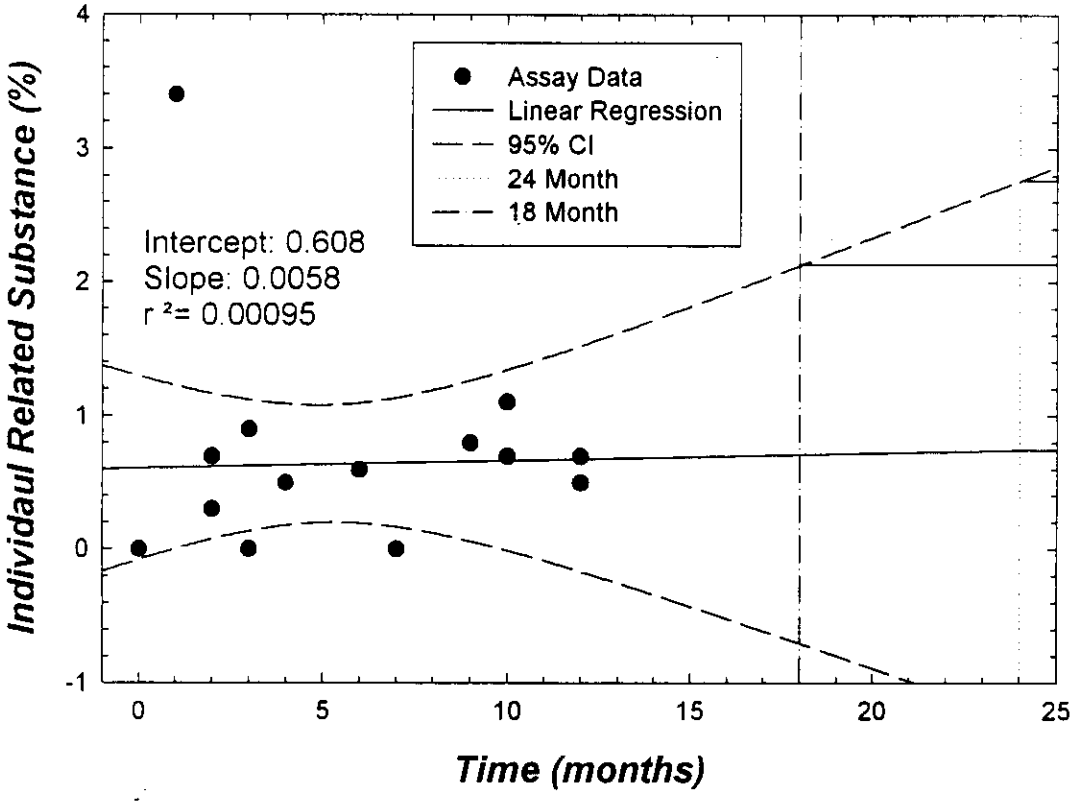


Table 2:
Primsol Product Composition
(quantities in mg/5mL of finished product)

Ingredient	8EX12	Lot 8EX19	092697-3
Trimethoprim	50	50	50
Sorbitol			
Propylene Glycol			
Povidone 25			
Glycerin[2]			
Monoammonium Glycyrrhizinate[2]			
Saccharin Sodium			
Bubblegum Flavor			
Methylparaben			
Sodium Benzoate			
Propylpraben			
Fructose			
Hydrochloric Acid			
Sodium Hydroxide			
Purified Water			
Batch size			

1. The amount of was estimated based on the amount used in batch 8EX12A.
2. Monoammonium glycyrrhizinate (MAG) is provided in the product by a solution of in glycerin. The difference in concentration between mL) reduces the content of the final product by a small amount.

Proposed Finished Product and Stability Specifications

Page(s) 3

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

release specification

ASCENT PEDIATRICS, INC.

187 Ballardvale Street Suite B125 Wilmington, MA 01887 Phone 978-658-2500 Fax 978-658-3939

NDA ORIG AMENDMENT

June 30, 1999

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

NDA 74-973
Trimethoprim HCl 50mg/5mL Oral Solution
Primsol
MINOR Amendment

Dear Mr. Sporn:

Reference is made to our NDA#74-973, to our major amendment of 12/4/98, to our stability update of 2/19/99, and to the MINOR deficiency letter of 6/11/99.

The attached information provides full responses to the Agency's comments. We believe these changes to our application will meet the reviewer's need and Agency requirements for approval of our application. We look forward to finally gaining the long awaited approval.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory and Quality Affairs

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street Suite B125 Wilmington, MA 01887 Phone 978-658-2500 Fax 978-658-3939

February 19, 1999

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

NDA 74-973
Primsol
Trimethoprim HCl Oral Solution
50mg/5mL
Stability Update

AC

Dear Mr. Sporn:

Reference is made to our NDA 74-973 (trimethoprim HCl oral solution 50mg/5mL) and to our amendment of 12/4/98.

This submission provides an update of the stability data for the new formulation included in our 12/4/98 amendment. That amendment included initial stability data for the new formulation demonstration batch (formula , lot # 8EX19) along with a commitment to provide 3 months of data as soon as it was available. The 3-month data provided here confirm that the stability characteristics of formula parallel those of the formulation originally included in our application as discussed on pages 414 through 468 of our amendment of 12/4/98. These data along with the long term stability data for the original formulation support the requested 2 year expiration dating period.

As requested in our amendment, we again request that the submission of the updated stability data at this time does not cause the restart for the Agency's review queue for our application.

We trust that we have now addressed all of the Agency's concerns related to the approval of this application and look forward to the results of your review. Please advise by phone or fax if there are any questions or concerns related to this application.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory and Quality Affairs

RECEIVED
FEB 22 1999
GENERIC DRUGS

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street, Suite B125 Wilmington, MA 01887 Phone 978-658-2500 Fax 978-658-3939

December 4, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Major Amendment - Formulation Change
Trimethoprim Oral Solution 50mg/5mL
NDA 74-973
Primsol

ORIG AMENDMENT
N/A C

Dear Mr. Sporn:

Reference is made to our NDA, our submissions of 8/1/97, 12/23/97, 2/5/98, 2/24/98, 3/31/98, 5/8/98, and 6/26/98. Reference is also made to the Agency's letter of 9/22/98 responding to our letter of 8/6/98 that requested guidance concerning the amendment of our application to a new formulation. The Agency's letter of 9/22/98 also provided MINOR chemistry deficiencies related to our current formulation. We also refer to our NDA #74-374 (trimethoprim HCl 25mg/5mL) approved on 6/26/95 and its supplement for acute otitis media approved on 6/1/97.

This amendment provides for a new formulation that contains a reduced level of Ascent wishes to delete the earlier ɔrmulation in favor of the formulation included in this amendment. As confirmed in the Agency's letter of 9/22/98, Ascent believes that no additional clinical data are required to achieve approval of this product formulation.

This amendment contains complete chemistry and labeling information to support the approval of a new formulation including an alternate supplier for trimethoprim, . We have revised the pH specification for and the method of determination of the ɔ content in response to the reviewer's comments of 9/22/98 we have added a test and specification for for product release and stability and have modified the specification for related substances. The only labeling changes

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GENERIC DRUGS

were made to reflect the change in product composition and graphics for the sample carton. Finally we have changed the sample carton to contain 6 sample units rather than 12 as previously specified. This amendment also includes specific responses to the Agency's chemistry comments of 9/22/98 as they apply to the new formulation.

The information in this submission includes executed batch records and test data for components and finished product from a demonstration batch, and proposed master production documents for batches. The demonstration batch was prepared with trimethoprim produced by The finished product and specifications proposed for the new formulation reflect our responses to the chemistry reviewer's comments of 9/22/98. We have made no changes in manufacturing or testing facilities or packaging components. As with the specifications, Agency minor deficiency comments of 9/22/98 resulting from the review of our previous submissions have been incorporated into the content of this amendment where relevant to the new formulation.

The new formulation contains no new components compared to the earlier one.

All components and their use levels in the new formulation are within the Agency's Inactive Ingredient Guide. The product is a solution intended for oral administration and as indicated above, there are no new components in the new formulation. Consequently, we believe the bioequivalence study submitted on 12/23/97 conducted with the previous product formulation obviates the need for any additional data to support the new formulation.

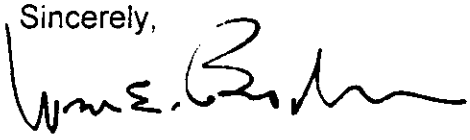
The 50mg/5mL trimethoprim HCl product was submitted as a new application under section 505(b)(2) of the FD&C act as directed by the Agency. It represents a more than our 25mg/5mL trimethoprim HCl product approved on 6/26/95. On 6/1/97 the Agency approved a clinical supplement for the 25mg product for acute acute otitis media. Ascent was awarded a 3-year exclusivity for this new indication that required clinical studies for approval. As agreed with the Agency, Ascent has not and does not intend to market the 25mg product and in fact has agreed to withdraw that application once the acute otitis media indication has been transferred to the 50mg product. With consideration to these facts, Ascent requests the Agency's consideration to provide a 3-year exclusivity period to our

50mg product to begin on the date of the Agency's approval of this new formulation and application.

We believe this supplement incorporates all of the comments and suggestions, made by Agency reviewers over the lengthy course of the history of this application. We trust that this experience can be applied to achieve a near term approval of this application. In an attempt to facilitate the review we have provided the labeling as a separate volume to our submission.

Please advise by telephone or FAX if I can provide any additional information that will facilitate the review and approval of this application.

Sincerely,



W.E. Brochu, Ph.D.
Vice President, Regulatory & Quality Affairs

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street Suite B125 Wilmington, MA 01887 Phone 978-658-2500 Fax 978-658-3939

NIHC

June 26, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

Application Amendment
New Bulk Active Supplier - IPCA
NDA 74-973
Trimethoprim HCl 50mg/5mL
Primsol

Dear Mr. Sporn:

Reference is made to our pending NDA for a 50mg/5mL tirmethoprim HCl oral syrup, to our pending chemistry submissions of 2/24/98, and 3/31/98, and to a 6/23/98 telephone conversation with the Agency's Mr. Joseph Buccine.

We appreciate the Agency's consideration in accepting this submission within the current review cycle. We trust that the reviewer will find this and our pending submissions complete and adequate. Please advise if we can be of assistance in any way to finalize the acceptability of the chemistry aspects of this application.

We look forward to the Agency's input on our DRAFT gastrointestinal tolerance study protocol submitted on 5/6/98 and to the results of the Agency's review of our chemistry submissions.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory Affairs

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street • Suite B125 • Wilmington, MA 01887 • Phone 978-658-2500 • Fax 978-658-3939

March 31, 1998

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT

N/AC

Re: NDA 74-973
Primsol (trimethoprim hydrochloride oral solution), 50 mg / 5 mL
Addendum to our Amendment of February 24, 1998

Reference is made to our major amendment dated February 24, 1998 that was submitted in response to the deficiency letter dated February 19, 1998. Further reference is made to our conversation of March 4, 1998 during which these deficiencies were discussed. It was apparent during that discussion that some additional information/clarification of our responses was needed. Therefore, we are herewith submitting an addendum to our February 24, 1998 amendment.

A field copy, which Ascent certifies to be a true copy of this submission, is simultaneously being provided to the Boston District Office.

Sincerely,
Ascent Pediatrics, Inc.

William E. Brochu, Ph. D.
Vice President Regulatory Affairs

Enclosure

RECEIVED
APR 0 1 1998
GENERIC DRUGS

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street Suite B125 Wilmington, MA 01887 Phone 978-658-2500 Fax 978-658-3939

2/5/98

ORIG AMENDMENT
N/AC

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

NDA 74-973
Addendum to 8/1/97 Amendment
Primsol (trimethoprim HCl Oral Solution) 50mg/5mL

Dear Mr. Sporn:

Reference is made to our NDA 74-973, to our major CMC amendment of 8/1/97, and to a teleconference involving personnel from the Agency and Ascent Pediatrics, Inc. on 7/30/97.

On 8/1/97 Ascent Pediatrics, Inc. provided complete responses to CMC and Labeling issues included in the Agency's letter of 7/7/97 and fax of 7/21/97. As agreed in the teleconference that occurred on 7/30/97, we are providing certain additional data at this time. These include:

- A revised analytical method for the active ingredient that reflects the changes in the reporting of related substances.
- A complete description of the method to be employed in evaluating color intensity of our product.
- A revised finished product specification that includes the proper references to the analytical methods.
- Results of antimicrobial preservative effectiveness testing for a 12 month stability sample from sublot B (6EX01B)

Please note that, as agreed in the 7/30/97 teleconference, Ascent is conducting antimicrobial preservative testing for a product sample containing only of the intended level of preservative. These results are not yet available. This test was initiated on 1/30/98. We will provide these test results as soon as the test is completed.

We trust that the information now contained in our application will provide the reviewer with sufficient confidence to recommend approval. Please call (978-658-2500) if I can provide any additional information or assistance toward gaining approval for this product that is extremely important to Ascent's future.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory Affairs

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street Suite B125 Wilmington, MA 01887 Phone 978-658-2500 Fax 978-658-3939

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
Room 150
7500 Standish Place
Rockville MD 20855-2773

February 24, 1998

NDA 74-973
Primsol (trimethoprim HCl Oral Solution) 50mg/5mL

Dear Mr. Sporn:

Reference is made to our NDA 74-973 for Trimethoprim HCl Oral Solution 50mg/5mL and to our amendments of 5/13/97 and 8/1/97. Reference is also made to the Agency's letter of 2/19/98.

Enclosed are complete responses raised in the Agency's letter of 2/19/98.

The referenced letter has been designated as a MAJOR deficiency. We take serious objection to this classification and respectfully request a reclassification to MINOR status. The basis for our request is that with the apparent discontinuity of reviewers for this application within the Agency, a few new issues have been raised but more importantly questions are being asked which have already been addressed through prior discussion with Agency personnel and in our previous submissions.

None of the points raised in the 2/19/98 letter are complex and none are significant issues related to our major amendment of 8/1/97. Our formal responses have been fully developed and submitted to the Agency within 1 week of their receipt. We believe this is further evidence that the nature of the questions are minor and do not constitute the need for a major amendment.

This matter was discussed with Mr. Gordon Johnston on Friday 2/20/97. Mr. Johnston had suggested the matter be reviewed in a telephone conference call that is still in the process of being arranged. In the interim we have developed and are submitting our responses.

We trust that these final CMC issues can be resolved in a timely manner and we thank you for your efforts.

Sincerely,

W.E. Brochu, Ph.D.
Vice President, Regulatory Affairs

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street · Suite B125 Wilmington, MA 01887 Phone 978-658-2500 Fax 978-658-3939

December 23, 1997

Gordon Johnston
Office of Generic Drugs
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

N/A

RE: Primsol 50 mg/ 5 mL
NDA # 74-973

Dear Gordon:

Attached are 2 copies of the final report (an archival and a review copy) of the bioequivalence trial in which Primsol 50 mg/ 5mL, Primsol 25 mg/ 5 mL and Trimpex® 100 mg tablets were compared. The review copy contains a computer disk of the raw data to facilitate additional analysis. The trial was conducted as a three way crossover study, in twenty-one healthy subjects in which 18 completed the trial. The analysis of the data indicates that the means and confidence intervals of all the principal pharmacokinetic parameters fall within the standard range to demonstrate bioequivalency.

In reviewing this report I noticed that in the abstract and summary sent previously, December 19, a transcription error was made in reporting the 90% confidence intervals in the abstract page for the ratio of means Ascent 50 mg / Roche. The error was corrected and is reflected in the final report.

As previously stated we believe based upon these findings that the data strongly support the conclusions that these tested formulations are bioequivalent.

I understand that you will treat this information under an expedited review and to that end wish to confirm our offer to answer directly any questions that the reviewer may wish to discuss. My office number 978-658-2500.

Thank you for your advice and guidance in this important matter.

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Sincerely,

Emmett Clemente, Ph.D.
Chairman and Founder

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street - Suite B125 Wilmington, MA 01887 Phone 508-658-2500 Fax 508-658-3939

Mary Fanning, M.D.
Office of Generic Drugs
Metro Park North II
7500 Standish Place
Rockville, MD 20855

NEW CORRESP

DESK COPY

Re: NDA 74-973, Primsol Solution 50 mg / 5 mL

Dear Dr. Fanning:

Enclosed are 4 copies each of synopses of the following studies included in GRAS Affirmation Petition 3G0286 for Numbers 19,21,33, and 52 are tox studies, while number 38 is a pediatric tolerance study.

Please distribute these to the appropriate people for our meeting on Friday.

Thanks very much for your assistance.

Sincerely,

Robert W. Mendes, Ph. D.
Vice President Regulatory Affairs

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SEP 29 1997
GENERIC DRUGS

ASCENT
PEDIATRICS, INC.

Ballardvale Street Suite B125 Wilmington, MA 01887 Phone 508-658-2500 Fax 508-658-3939

st 1, 1997

AMENDMENT

NDA

ce of Generic Drugs
ER, FDA
ro Park North II
0 Standish Place, Room 150
kville, MD 20855

BIOAVAILABILITY

NDA 74-973 Primsol (trimethoprim hydrochloride oral solution), 50 mg / 5 mL
Response to Deficiency Letter
Major Amendment

losed are the original and one copy of an amendment to NDA 74-973 provided in response to r deficiency letter dated July 7, 1997 and the follow-up fax from L. Golson to M. Murray d July 21, 1997.

eld copy, which Ascent certifies to be a true copy of this submission, is simultaneously being vided to the Boston District Office.

greed during our telecon of July 30, 1997 Ascent commits to providing, in a timely manner, ain additional information in the form of an addendum to this amendment. This information include the following: (1) minor revisions to the analytical method to reflect changes in the cription of the method of reporting related substances, (2) a more complete description of the hod to be employed for evaluating color intensity, and (3) results of APET tests currently erway.

rs truly,

ert W. Mendes, Ph. D.
e President Regulatory Affairs

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street Suite B125 Wilmington, MA 01887 Phone 508-658-2500 Fax 508-658-3939

May 16, 1997

NEW CORRESP

Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: NDA 74-973
Primsol® Solution (trimethoprim hydrochloride oral solution) 50 mg (base)/5 mL
Proposed Launch Material

Enclosed please find a copy of a submission to Division of Drug Marketing, Advertising and Communications (DDMAC) to provide the initial launch promotional piece for Primsol® Solution (trimethoprim hydrochloride oral solution).

As the cover letter indicates, Ascent believes that the enclosed launch piece can be reviewed by DDMAC based on the labeling proposed in NDA 74-973. The rationale for this is that the labeling proposed in NDA 74-973 is identical to the final labeling submitted in the efficacy supplement to NDA 74-374, except where necessary to reflect the differences in the formulations. Since the enclosed piece does not discuss formulation other than to declare the product concentration, it should be possible for DDMAC to review it based on the labeling proposed in NDA 74-973.

Yours truly,
ASCENT PEDIATRICS, INC.

Mark Murray

Mark Murray
Director, Regulatory Affairs

Enclosure

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MAY 19 1997
GENERIC DRUGS

ASCENT
PEDIATRICS, INC.

187 Ballardvale Street Suite B125 Wilmington, MA 01887 Phone 508-658-2500 Fax 508-658-3939

May 13, 1997

ORIG AMENDMENT
N 74

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: NDA 74-973, Primsol 50 mg / 5 mL (trimethoprim hydrochloride oral solution)
MINOR amendment

The enclosed NDA amendment is submitted in under the provisions of §505(b)(2) of the Act. Included are an archival copy and a review copy. A Field Copy, which Ascent certifies is a true copy of the CMC section, is being concurrently provided to the Boston District Office.

Included in this amendment are four sets of labeling. This labeling submission would replace that provided in the original submission. This differs from the original in that it includes a new indication for otitis media in children ages 6 months to 12 years. This indication has been gained via an efficacy supplement to NDA 74-374 upon which application 74-973 is based. The new labeling has been approved by the Division of Anti-Infective Drug Products in a consult to OGD dated May 9, 1997. The side-by-side comparisons included herein consist of the newly approved labeling for 74-374 and the newly proposed labeling for 74-973. Effectively, the labeling section of the original 74-973 submission is replaced in its entirety by this amendment.

In addition, this amendment includes a revision to the intended trade packaging for the product. In the original submission, the intended container was a rectangular amber bottle. A backup container was also included: a round bottle. It is now Ascent's intent to reverse these, making the round bottle the intended container and the rectangular bottle the backup container. Full specifications and stability information was originally submitted for both container systems. In conjunction with this change, new labels described in this amendment include "tucked under" inserts, thus allowing for the deletion of the shelf carton with enclosed dose cups.

Finally, this amendment includes a revision to permit the packaging of the 20 mL sample bottles from a (full production) batch in addition to the originally submitted batch. Thus, the batch would serve for both trade pack and sample pack.

This amendment does not include any changes not previously discussed during the pre-approval inspection.

Should there be any questions, please feel free to contact me.

Yours truly,
ASCENT PEDIATRICS, INC.

Robert W. Mendes, Ph. D.
Vice President, Regulatory Affairs

ASCENT PEDIATRICS, INC.

9 Linnell Circle Billerica, MA 01821 Phone 508 667 6300 Fax 508 667 5322

FACSIMILE

TO:	Anna Marie Weikel	NEW CORRESP
FAX NUMBER:	301 594 1174	NC
FROM:	Robert Mendes	
DATE:	November 26, 1996	
SUBJECT:	Primsol Solution 50 mg / 5 mL, NDA 74-973, information request	

NUMBER OF PAGES INCLUDING COVER SHEET: 6

Dear Ms. Weikel:

Following is a copy of the information you requested regarding the new strength Primsol application.

The formal submission of this material is being sent overnight today, and should be delivered tomorrow.

Should you need anything further, please call me.

Thanks for your cooperation.

Sincerely,

Robert W. Mendes, Ph. D.
Vice President Regulatory Affairs

ASCENT
PEDIATRICS, INC.

3 Connell Circle, Billerica, MA 01821 Phone 508-667-6300 • Fax 508-667-5322

November 26, 1996

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: NDA 74-973, Primsol Solution, 50 mg per 5 mL (trimethoprim hydrochloride oral solution)
Minor amendment

Enclosed is a requested amendment to Item IV, pages 011 and 012 of this application. The amendment identifies the active ingredient of the Reference Listed Drug and the Applicant Drug as trimethoprim hydrochloride rather than as trimethoprim.

Ascent wishes to reiterate, however, that the product is formulated and manufactured using Trimethoprim, USP, and that trimethoprim hydrochloride is not an available component for use in manufacturing. It is not, therefore, possible to isolate, identify or characterize the hydrochoride chemically. The previously negotiated and approved labeling describes the product as a "solution of the synthetic antibacterial trimethoprim in water prepared with the aid of hydrochloric acid". All chemical reference is, therefore, to trimethoprim.

Should you have any questions, please feel free to call me.

Yours truly,
ASCENT PEDIATRICS, INC.

Robert W. Mendes, Ph. D.
Vice President, Regulatory Affairs

ASCENT
PEDIATRICS, INC.

9 Linnell Circle - Billerica, MA 01821 Phone 508-667-6300 Fax 508-667-5322

November 12, 1996

Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Primsol Solution, 50 mg/5 mL NDA: Minor Amendment # 74973

The following is written in response to the telephone request made by Ms. Anna-Marie Weikel on November 7, 1996.

1. The requested side-by-side label comparison for the containers is enclosed.

2. The requested conviction information is enclosed.

3. The requested address for the drug substance manufacturing site is enclosed.

4. The requested cGMP certification from Ascent is enclosed.

Yours truly,
ASCENT PEDIATRICS, INC.

Robert W. Mendes, Ph. D.
Vice President, Regulatory Affairs

COMPARISON BETWEEN APPLICANT DRUG AND REFERENCE LISTED DRUG

Reference Listed Drug: Primsol® Solution (trimethoprim hydrochloride oral solution, equivalent to trimethoprim, 25 mg/5 mL), NDA 74374

NDA Holder: Ascent Pediatrics, Inc.

Attribute	Listed Drug	Proposed Drug
Condition of Use	Uncomplicated urinary tract infection	Same
Active Ingredient	Trimethoprim hydrochloride*	Same
Route of Administration	Oral	Same
Dosage Form	Solution	Same
Strength (equivalent to trimethoprim)	25 mg/5 mL	50 mg/5 mL

* product is manufactured using Trimethoprim, USP

I. Conditions of Use

Applicant states that the conditions of use prescribed, recommended or suggested in the labeling proposed for the drug product have been previously approved for the reference listed drug.

Please see Item 5, Part D of this application in which is presented the highlighted differences between the current approved labeling for the reference listed drug and the proposed labeling for the proposed drug product. There are no differences except for those necessary to describe the differences between the approved and proposed solution concentrations.

ii. Active Ingredient

Applicant states that the active ingredient (trimethoprim hydrochloride) in the proposed drug product is the same as the active ingredient in the reference listed drug.

Please see Item 5, Part D of this application in which is presented the highlighted differences between the current approved labeling for the reference listed drug and the proposed labeling for the proposed drug product. It should be noted that no differences are annoted with respect to the active ingredient.

iii. Route of Administration, Dosage Form, and Strength

Applicant states that the route of administration (oral) for the proposed drug product is the same as the route of administration for the reference listed drug.

Please see Item 5, Part D of this application in which is presented the highlighted differences between the current approved labeling for the reference listed drug and the proposed labeling for the proposed drug product. It should be noted that no differences are annoted with respect to the route of administration.

The dosage form (solution) of the proposed drug product is the same as the dosage form (solution) of the reference listed drug.

The strength (concentration) of the proposed drug product differs from that of the reference listed drug product in that the proposed concentration is equivalent to 50 mg trimethoprim per 5 mL and the reference concentration is equivalent to 25 mg trimethoprim per 5 mL.

Ascent
Pharmaceuticals, Inc.

9 Linnell Circle
Billerica, MA 01821

Telephone: 508-667-6300
Facsimile: 508-667-5322

October 4, 1996

Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: NDA Submission persuant to §505(b)(2), based on NDA 74-374

Primsol Solution, 50 mg per 5 mL (trimethoprim hydrochloride oral solution)

The Agency has requested, for administrative reasons, that the enclosed be submitted under the provisions of §505(b)(2) of the Act as a new application rather than as a supplement to NDA 74-374. An executed User Fee Form is included, indicating that no clinical data is required for approval.

The application is for the approval of a new concentration (50 mg trimethoprim per 5 mL) intended to provide the same dose of drug in half the volume of product. It is expected that this would provide for higher patient compliance than might have been anticipated with the lower concentration. Labeling for the proposed new product is identical to that for the approved product, except as necessary to reflect the formulation change.

Since both the approved product and proposed new product are oral solutions, the application includes a request for waiver of the requirement for *in vivo* bioequivalence testing. The application consists otherwise of the typical CMC requirements found in an application to the Office of Generic Drugs. Also included are two separately bound copies of the Analytical Methods and Validation Package.

It should be noted that it is Ascent's intent, upon approval of this application, to voluntarily withdraw the approval of the 25 mg per 5 mL concentration from NDA 74-374. The latter, approved in June of 1995 has never been marketed. It should also be noted that an application for the approval of new therapeutic indications was filed as an efficacy supplement to NDA 74-374 and Ascent intends to employ its Right of Reference to attach the efficacy supplement approval to this new application upon its approval.

Ascent certifies that a field copy of the CMC section of the application has been submitted to the Boston District Office in accordance with the requirements of 21 CFR Part 314.

It should be noted that Ascent Pharmaceuticals, Inc. is in the midst of a change in its corporate name to Ascent Pediatrics, Inc. For this reason, you may note references to both names throughout the application. Once this name change has been completed, we will notify the agency so that appropriate records can be changed.

Should there be any questions, please feel free to contact me.

Sincerely,

Robert W. Mendes, Ph. D.
Vice President, Regulatory Affairs