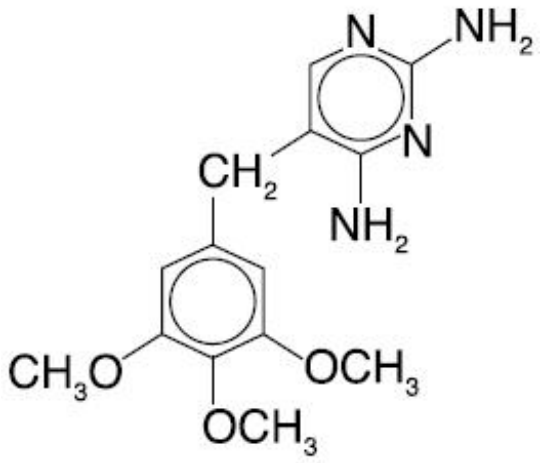
PRIMSOL- trimethoprim hydrochloride solution
FSC Laboratories, Inc

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 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* [1]

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

When testing *Streptococcus pneumoniae* [2]

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

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[3] powder should provide the following MIC values:

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

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

[†] Range applicable only to tests performed by broth microdilution method using

cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.[1]

---

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

2 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]

3 Trimethoprim very medium-dependent.

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[4] 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* [5]:

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

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[4] 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[*]	ATCC 49247	27 - 33
Staphylococcus aureus	ATCC 25923	19 - 26

[*] 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.

---

[4] 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.

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

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 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 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

To report SUSPECTED ADVERSE REACTIONS, contact FSC Laboratories, Inc. at 1-866-764-7822, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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 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 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) is a dye-free, alcohol-free, bubble gum flavored, oral solution containing trimethoprim hydrochloride equivalent to 50 mg of trimethoprim in each 5 mL.
NDC 13551-501-01: 20 mL (3/4 ounce)
NDC 13551-501-05: 473 mL (1 Pint)

Store between 15-25°C (59-77°F). Dispense in tight, light-resistant glass or PET plastic containers as defined in USP. Protect from light.

Rx 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.

071714001 Revised April 2013

Manufactured for:
FSC Laboratories, Inc., Charlotte, NC 28210 USA
www.fsclabs.com

Manufactured by:
Halo Pharmaceutical Inc., Whippany, NJ 07981 USA

U. S. Patent No. 5,698,562

FSC laboratories

PRINCIPAL DISPLAY PANEL - 473 mL Bottle Label

NDC 13551-501-05

PRIMSOL® solution
trimethoprim hydrochloride
oral solution

50 mg/5 mL

Rx Only

473 mL (1 pint)

FSC laboratories

PRIMSOL

trimethoprim hydrochloride solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:13551-501
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TRIMETHOPRIM HYDROCHLORIDE (UNII: 9XE000OU9B) (TRIMETHOPRIM - UNII:AN164J8Y0X)	TRIMETHOPRIM	50 mg in 5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
FRUCTOSE (UNII: 6YSS42VSEV)	
GLYCERIN (UNII: PDC6A3C0OX)	
METHYLPARABEN (UNII: A2I8C7HI9T)	
AMMONIUM GLYCYRRHIZATE (UNII: 3VRD35U26C)	
POVIDONES (UNII: FZ989GH94E)	
PROPYLPARABEN (UNII: Z8IX2SC1OH)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
SACCHARIN SODIUM (UNII: SB8ZUX40TY)	
SODIUM BENZOATE (UNII: OJ245FE5EU)	
SORBITOL (UNII: 506T60A25R)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics			
Color		Score	
Shape		Size	
Flavor	BUBBLE GUM	Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13551-501-05	473 mL in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
2	NDC:13551-501-01	20 mL in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA074973	01/24/2000	

Labeler - FSC Laboratories, Inc (169886244)

Revised: 9/2014 FSC Laboratories, Inc