CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

65-100

Trade Name:	Panixine DisperDose, 125mg and 250mg
Generic Name:	Cephalexin Tablets for Oral Suspension
Sponsor:	Ranbaxy Pharmaceuticals, Inc.
Approval Date:	September 11, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 65-100

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-100

APPROVAL LETTER

ANDA 65-100

SEP 11 2003

Ranbaxy Pharmaceuticals, Inc.
Attention: Abha Pant
U.S. Agent for: Ranbaxy Laboratories Limited
600 College Road East
Princeton, NJ 08540

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated July 19, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Panixine DisperDose™ Tablets for Oral Suspension, 125 mg and 250 mg (Cephalexin Tablets for Oral Suspension, 125 mg and 250 mg. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated March 12, June 13, November 11, and December 11, 2002; and July 3, August 6, August 22, and September 4, 2003. Reference is also made to the ANDA Suitability Petition submitted under Section 505(j)(2)(C) of the Act and approved on June 13, 2000, permitting you to file this ANDA for a drug product that differs in dosage form from that of the reference listed drug product, Keflex for Oral Suspension 125 mg/5 mL and 250 mg/5 mL of Ceph International Corp. Specifically, your ANDA provides for Cephalexin Tablets for Oral Suspension in contrast to Cephalexin for Oral Suspension (powder for reconstitution) represented by the reference product.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. Panixine DisperDose™ Tablets for Oral Suspension 125 mg and 250 mg, (Cephalexin Tablets for Oral Suspension, 125 mg and 250 mg), can be expected to have the same therapeutic effect as an equivalent dose of the reference listed drug product upon which the agency relied as the basis of safety and effectiveness. Your dissolution testing should be

incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated 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 final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Robert Lumpkin for 9/11/2003

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-100

FINAL PRINTED LABELING(S)

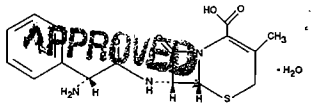
PANIXINE
DisperDose™

(cephalexin tablets for oral suspension)
Rx only

DESCRIPTION

Cephalexin, USP is a semisynthetic cephalosporin antibiotic intended for oral administration. It is 7-(D-α-amino-α-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid monohydrate. Cephalexin has the molecular formula $C_{16}H_{17}N_3O_4S \cdot H_2O$ and the molecular weight is 365.41.

Cephalexin has the following structural formula:



The nucleus of cephalexin is related to that of other cephalosporin antibiotics. The compound is a zwitterion; i.e., the molecule contains both a basic and an acidic group. The isoelectric point of cephalexin in water is approximately 4.5 to 5.

The crystalline form of cephalexin which is available is a monohydrate. It is a white crystalline solid having a bitter taste. Solubility in water is low at room temperature; 1 or 2 mg/mL may be dissolved readily, but higher concentrations are obtained with increasing difficulty.

The cephalosporins differ from penicillins in the structure of the bicyclic ring system. Cephalexin has a *D*-phenylglycyl group as substituent at the 7-amino position and an unsubstituted methyl group at the 3-position.

Each cephalexin tablet for oral administration contains cephalexin monohydrate equivalent to 125 mg (360 mcmol) or 250 mg (720 mcmol) of cephalexin.

In addition, each cephalexin tablet for oral suspension contains the following inactive ingredients: aspartame*, colloidal silicon dioxide, crospovidone, D&C yellow No. 10 aluminum lake, fruit gum flavor, magnesium stearate, mannitol, microcrystalline cellulose, peppermint flavor, povidone.

* See **PRECAUTIONS**

CLINICAL PHARMACOLOGY

Human Pharmacology - Cephalexin is acid stable and may be given without regard to meals. It is rapidly absorbed after oral administration. Following doses of 250 mg, 500 mg, and 1 g, of conventional cephalexin, average peak serum levels of approximately 9, 18, and 32 mcg/mL respectively were obtained at 1 hour. Measurable levels were present 6 hours after administration.

Following a dose of Ranbaxy's Panixine *DisperDose™* tablets, equivalent to 500 mg of cephalexin, the average peak serum level of 15.25 mcg/mL was obtained at 1 hour. Following a dose of conventional cephalexin suspension equivalent to 500 mg of cephalexin, the average peak serum level of 14.67 mcg/mL was obtained at 1 hour. Measurable levels were present 6 hours after administration of Ranbaxy's Panixine *DisperDose™*.

Cephalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies showed that over 90% of the drug was excreted unchanged in the urine within 8 hours. During this period, peak urine concentrations following the 250 mg, 500 mg, and 1 g doses were approximately 1,000, 2,200, and 5,000 mcg/mL respectively.

Microbiology - *In vitro* tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cephalexin 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.

Aerobes, Gram-positive:
- *Staphylococcus aureus* (including penicillinase-producing strains)
- *Staphylococcus epidermidis* (penicillin-susceptible strains)
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

Aerobes, Gram-negative:
- *Escherichia coli*
- *Haemophilus influenzae*
- *Klebsiella pneumoniae*
- *Moraxella (Branhamella) catarrhalis*
- *Proteus mirabilis*

Note — Methicillin-resistant staphylococci and most strains of enterococci (*Enterococcus faecalis* [formerly *Streptococcus faecalis*]) are resistant to cephalosporins, including cephalexin. It is not active against most strains of *Enterobacter* spp, *Morganella morganii*, and *Proteus vulgaris*. It has no activity against *Pseudomonas* spp or *Acinetobacter calcoaceticus*.

Susceptibility Tests — **Diffusion techniques:** Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[1] that has been recommended for use with disks to test the susceptibility of microorganisms to cephalexin uses the 30 mcg cephalothin disk. Interpretation involves correlation of the diameter obtained in the disk test with the minimal inhibitory concentration (MIC) for cephalexin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 mcg cephalothin disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ 18	(S) Susceptible
15 to 17	(I) Intermediate
≤ 14	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate" indicates that the result should be considered equivocal, and, if 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 that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See **CLINICAL PHARMACOLOGY** section for information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standardized susceptibility test procedures require the use of laboratory control microorganisms. The 30 mcg cephalothin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
E. coli ATCC 25922	15 to 21
S. aureus ATCC 25923	29 to 37

Dilution techniques: Quantitative methods that are used to determine MICs provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[2] (broth, agar, microdilution) or equivalent with cephalothin powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 8	(S) Susceptible
16	(I) Intermediate
≥ 32	(R) Resistant

Interpretation should be as stated above for results using diffusion techniques.

As with standard diffusion techniques, dilution methods require the use of laboratory control microorganisms. Standard cephalothin powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
E. coli ATCC 25922	4 to 16
E. faecalis ATCC 29212	8 to 32
S. aureus ATCC 29213	0.12 to 0.5

INDICATIONS AND USAGE

Cephalexin is indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Respiratory tract infections caused by *S. pneumoniae* and *S. pyogenes* (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cephalexin is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of cephalexin in the subsequent prevention of rheumatic fever are not available at present.)

Otitis media due to *S. pneumoniae, H. influenzae, staphylococci, streptococci* and *M. catarrhalis*

Skin and skin structure infections caused by staphylococci and/or streptococci

Bone infections caused by staphylococci and/or *P. mirabilis*

Genitourinary tract infections, including acute prostatitis, caused by *E. coli, P. mirabilis*, and *K. pneumoniae*

Note — Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS

Cephalexin is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE CEPHALEXIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to cephalexin.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cephalexin, and may range from mild to life threatening. Therefore, it is important to consider this diagnosis in patients with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Usage in Pregnancy — Safety of this product for use during pregnancy has not been established.

PRECAUTIONS

General — Patients should be followed carefully so that any side effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to cephalexin occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or cortico-steroids).

Prolonged use of cephalexin may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Cephalexin should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

As a result of administration of cephalexin, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets.

As with other β-lactams, the renal excretion of cephalexin is inhibited by probenecid.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Phenylketonurics: Each 125 mg cephalexin tablet for oral suspension contains 2.8 mg phenylalanine; each 250 mg cephalexin tablet for oral suspension contains 5.6 mg phenylalanine.

PANIXINE
DisperDose™
(cephalexin tablets
for oral suspension)
Rx only

Usage in Pregnancy — Pregnancy Category B — The daily oral administration of cephalexin to rats in doses of 250 or 500 mg/kg prior to and during pregnancy, or to rats and mice during the period of organogenesis only, had no adverse effect on fertility, fetal viability, fetal weight, or litter size. Note that the safety of cephalexin during pregnancy in humans has not been established.

Cephalexin showed no enhanced toxicity in weanling and newborn rats as compared with adult animals. Nevertheless, because the studies in humans cannot rule out the possibility of harm, cephalexin should be used during pregnancy only if clearly needed.

Nursing Mothers — The excretion of cephalexin in the milk increased up to 4 hours after a 500 mg dose; the drug reached a maximum level of 4 mcg/mL, then decreased gradually, and had disappeared 8 hours after administration. Caution should be exercised when cephalexin is administered to a nursing woman.

Information for Patients:

A Patient Information Sheet is provided with the drug product.

ADVERSE REACTIONS

Gastrointestinal — Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. The most frequent side effect has been diarrhea. It was very rarely severe enough to warrant cessation of therapy. Dyspepsia, gastritis, and abdominal pain have also occurred. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hypersensitivity — Allergic reactions in the form of rash, urticaria, angioedema, and, rarely, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis have been observed. These reactions usually subsided upon discontinuation of the drug. In some of these reactions, supportive therapy may be necessary. Anaphylaxis has also been reported.

Other reactions have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, arthralgia, arthritis, and joint disorder. Reversible interstitial nephritis has been reported rarely. Eosinophilia, neutropenia, thrombocytopenia, and slight elevations in AST and ALT have been reported.

OVERDOSAGE

Signs and Symptoms — Symptoms of oral overdose may include nausea, vomiting, epigastric distress, diarrhea, and hematuria. If other symptoms are present, it is probably secondary to an underlying disease state, an allergic reaction, or toxicity due to ingestion of a second medication.

Treatment — To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Unless 5 to 10 times the normal dose of cephalexin has been ingested, gastrointestinal decontamination should not be necessary.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of cephalexin; however, it would be extremely unlikely that one of these procedures would be indicated.

The oral median lethal dose of cephalexin in rats is 5,000 mg/kg.

DOSAGE AND ADMINISTRATION

Panixine *DisperDose™* (cephalexin tablets for oral suspension) is administered orally after complete dispersion in water.

Directions for Panixime *DisperDose™* (cephalexin tablets for oral suspension): Mix one tablet in a small amount of water [approximately 2 teaspoonfuls]. Drink the entire mixture. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken. **Do not chew or swallow the tablets.** The tablets will not rapidly dissolve in your mouth.

Adults — The adult dosage ranges from 1 to 4 g daily in divided doses. The usual adult dose is 250 mg every 6 hours. For the following infections, a dosage of 500 mg may be administered every 12 hours: streptococcal pharyngitis, skin and skin structure infections, and uncomplicated cystitis in patients over 15 years of age. Cystitis therapy should be continued for 7 to 14 days. For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of cephalexin greater than 4 g are required, parenteral cephalosporins, in appropriate doses, should be considered.

Pediatric Patients — The usual recommended daily dosage for pediatric patients is 25 to 50 mg/kg in divided doses. For streptococcal pharyngitis in patients over 1 year of age and for skin and skin structure infections, the total daily dose may be divided and administered every 12 hours.

Cephalexin Tablets For Oral Suspension

Child's Weight	Cephalexin Suspension 125 mg/5 mL	Cephalexin Suspension 250 mg/5 mL	Cephalexin Tablets for Oral Suspension 125 mg*	Cephalexin Tablets for Oral Suspension 250 mg*
10 kg (22 lb)	1/2 to 1 tsp q.i.d.	1/4 to 1/2 tsp q.i.d.	1/2* to 1 tablet q.i.d.	- - -
20 kg (44 lb)	1 to 2 tsp q.i.d.	1/2 to 1 tsp q.i.d.	1 to 2 tablets q.i.d.	1/2* to 1 tablet q.i.d.
40 kg (88 lb)	2 to 4 tsp q.i.d.	1 to 2 tsp q.i.d.	2 to 4 tablets q.i.d.	1 to 2 tablets q.i.d.

or

Cephalexin Tablets For Oral Suspension

Child's Weight	Cephalexin Suspension 125 mg/5 mL	Cephalexin Suspension 250 mg/5 mL	Cephalexin Tablets for Oral Suspension 125 mg*	Cephalexin Tablets for Oral Suspension 250 mg*
10 kg (22 lb)	1 to 2 tsp b.i.d.	1/2 to 1 tsp b.i.d.	1 to 2 tablets b.i.d.	1 tablet b.i.d.
20 kg (44 lb)	2 to 4 tsp b.i.d.	1 to 2 tsp b.i.d.	2 to 4 tablets b.i.d.	1 to 2 tablets b.i.d.
40 kg (88 lb)	4 to 8 tsp b.i.d.	2 to 4 tsp b.i.d.	4 to 8 tablets b.i.d.	2 to 4 tablets b.i.d.

* CERTAIN DOSES FOR PEDIATRIC PATIENTS MAY NOT BE OBTAINABLE BY TAKING A WHOLE OR HALF TABLET. THEREFORE, CEPHALEXIN ORAL SUSPENSION MAY BE BETTER SUITED FOR DOSES IN THE PEDIATRIC POPULATION.

For 1/4 and 1/2 tsp dosing, cephalexin suspension is available from Ranbaxy. See **HOW SUPPLIED** section.

In severe infections, the dosage may be doubled.

In the therapy of otitis media, clinical studies have shown that a dosage of 75 to 100 mg/kg/day in 4 divided doses is required.

In the treatment of β-hemolytic streptococcal infections, a therapeutic dosage of cephalexin should be administered for at least 10 days.

HOW SUPPLIED:

Cephalexin Tablets for Oral Suspension:

Each tablet for oral suspension contains 125 mg or 250 mg cephalexin as the monohydrate.

125 mg Tablet for Oral Suspension

The 125 mg is a light yellow colored, capsule-shaped tablet debossed with "RX" and "573" on either side of the scoreline and plain on the other side with a characteristic fruity peppermint flavor.

NDC 63304-573-20	Bottles of 20
NDC 63304-573-01	Bottles of 100
NDC 63304-573-41	Blister unit-dose pack of 40s (5 x 8s)
NDC 63304-573-80	Strip unit-dose pack of 100s (10 x 10s)
NDC 63304-573-42	Strip unit-dose of 40s (5 x 8s)
NDC 63304-573-77	Blister unit-dose pack of 100s (10 x 10s)

250 mg Tablet for Oral Suspension

The 250 mg is a light yellow colored, capsule-shaped tablet debossed with "RX" and "574" on either side of the scoreline and plain on the other side with a characteristic fruity peppermint flavor.

NDC 63304-574-20	Bottles of 20
NDC 63304-574-01	Bottles of 100
NDC 63304-574-41	Blister unit-dose pack of 40s (5 x 8s)
NDC 63304-574-80	Strip unit-dose pack of 100s (10 x 10s)
NDC 63304-574-42	Strip unit-dose pack of 40s (5 x 8s)
NDC 63304-574-77	Blister unit-dose pack of 100s (10 x 10s)

The bottle packages contain desiccant.
Dispense in tight, light-resistant container.
Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

Cephalexin for Oral Suspension:

125 mg/5 mL
NDC 63304-958-01 - 100 mL bottles
NDC 63304-958-02 - 200 mL bottles

250 mg/5 mL
NDC 63304-959-01 - 100 mL bottles
NDC 63304-959-02 - 200 mL bottles

See the package insert for Cephalexin Suspension for complete prescribing information.

REFERENCES

1. National Committee for Clinical Laboratory Standards: Performance standards for antimicrobial disk susceptibility tests - 5th ed. Approved Standard NCCLS Document M2-A5, Vol 13, No 24, NCCLS, Villanova, PA 1993.
2. National Committee for Clinical Laboratory Standards: Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically -3rd ed. Approved Standard NCCLS Document M7-A3, Vol 13, No 25, NCCLS, Villanova, PA 1993.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32216 USA
by: Ranbaxy Laboratories Ltd.
New Delhi - 110 019, India
August 2003

PATIENT INFORMATION SHEET
PANIXINE
DisperDose™
(cephalexin tablets for oral suspension)
PATIENT'S DIRECTIONS FOR USE

Mix one Panixene *DisperDose™* tablet in water before you take it.

1. Remove one tablet from the bottle, or unit dose pack.
2. Place the tablet in a small amount of water (approximately 2 teaspoonfuls).
3. Swirl or stir until thoroughly mixed.
4. Drink the mixture immediately after mixing. (The mixture is light yellow colored and has a fruity peppermint flavor.)
5. Be sure to drink the entire mixture.
6. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken.

DO NOT CHEW or **SWALLOW** the Panixene *DisperDose™* tablets whole. The tablets will not rapidly dissolve in your mouth.

Take all of the medicine as recommended by your doctor or other health care provider.

Do not mix Panixene *DisperDose™* with any liquid other than water.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32216 USA
by: Ranbaxy Laboratories Limited
New Delhi - 110 019, India
August 2003

5029414

RANBAXY

NDC 63304-574-80

Panixine DisperDose™

(cephalexin tablets for oral suspension)

250 mg

MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only **100 Unit-Dose Tablets** (10 Strips of 10 Unit-Dose Tablets)

This Unit-Dose Package Is Not Child Resistant

Each tablet for oral suspension contains: Cephalexin USP (monohydrate) equivalent to 250 mg cephalexin

Phenylketonurics: Contains phenylalanine 5.6 mg per tablet. See accompanying prescribing information.

Usual Dosage: See package insert. **This unit-dose package is not child resistant. This package is intended for institutional inpatient use. If dispensed for outpatient use, appropriate safety packaging must be provided.**

Directions for Use: Mix one tablet in a small amount of water [approximately 2 teaspoonfuls]. Drink the entire mixture. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken. **Do not chew or swallow the tablets.** The tablets will not rapidly dissolve in your mouth. Dispense in a tight, light-resistant container. Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

0803

APPROVED

RANBAXY

NDC 63304-574-80

Panixine DisperDose™

(cephalexin tablets for oral suspension)

250 mg

MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only 100 Unit-Dose Tablets (10 Strips of 10 Unit-Dose Tablets)

This Unit-Dose Package Is Not Child Resistant

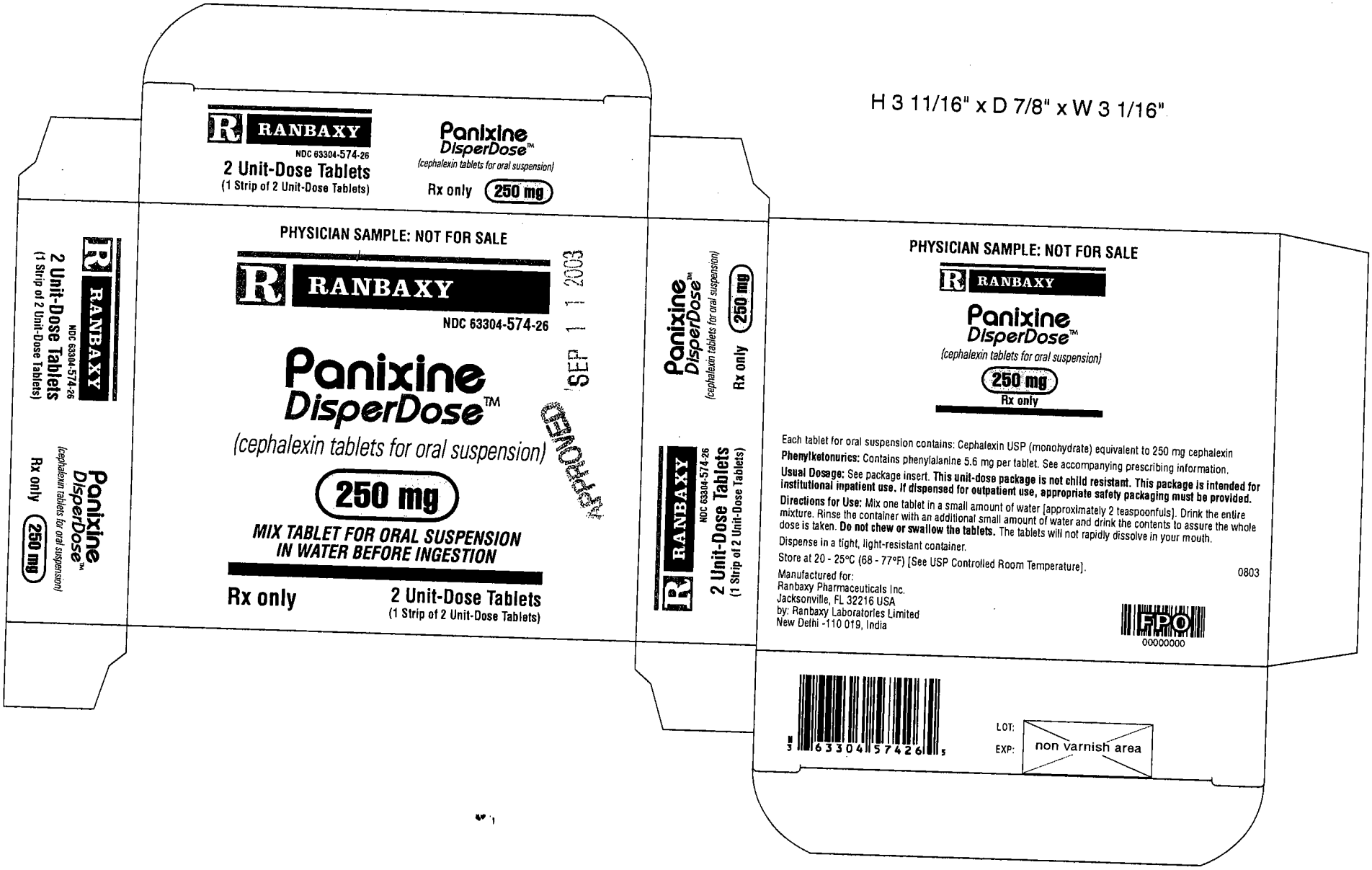
Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32216 USA
by: Ranbaxy Laboratories Ltd.
New Delhi - 110 019, India

LOT:
EXP: non varnish area

3 63304 57480 7

RANBAXY
NDC 63304-574-80
Panixine DisperDose™
(cephalexin tablets for oral suspension)
Rx only 250 mg
100 Unit-Dose Tablets
(10 Strips of 10 Unit-Dose Tablets)

26



H 3 11/16" x D 7/8" x W 3 1/16"

37

150cc 3.88" x 1.77"

SEP 11 2003

RANBAXY

NDC 63304-573-01

Panixine DisperDose™

(cephalexin tablets for oral suspension)

125 mg

MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only 100 Tablets

Usual Dosage: See package insert.

Directions for Use: Mix one tablet in a small amount of water (approximately 2 teaspoonfuls). Drink the entire mixture. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken. **Do not chew or swallow the tablets.** The tablets will not rapidly dissolve in your mouth.

50294000

3 63304 57301 5

LOT: non varnish

EXP: area

Each tablet for oral suspension contains: Cephalexin USP (monohydrate) equivalent to 125 mg cephalexin.

Pharmacokinetics: Contains phenylalanine 2.5 mg per tablet.

See accompanying prescribing information.

Dispense in a tight, light-resistant container. Contains desiccant.

Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32216 USA
by: Ranbaxy Laboratories Limited
New Delhi - 110 019, India.

0803

12

L 110mm x W 20mm x H 78mm

RANBAXY

NDC 63304-574-77

Panixine DisperDose™

(cephalexin tablets for oral suspension)

250 mg

MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only

100 Unit-Dose Tablets
(10 Blisters of 10 Unit-Dose Tablets)

Each tablet for oral suspension contains: Cephalexin USP (monohydrate) equivalent to 250 mg cephalexin
Phenylketonurics: Contains phenylalanine 5.6 mg per tablet. See accompanying prescribing information.
Usual Dosage: See package insert. **This unit-dose package is child resistant.**
Directions for Use: Mix one tablet in a small amount of water [approximately 2 teaspoonfuls]. Drink the entire mixture. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken. **Do not chew or swallow the tablets.** The tablets will not rapidly dissolve in your mouth. Dispense in a tight, light-resistant container. Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]. 0803

Manufactured by:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32216 USA
by: Ranbaxy Laboratories Ltd.
New Delhi - 110 019, India

LOT:
EXP:

non varnish area

00000000

FPO

RANBAXY

NDC 63304-574-77

Panixine DisperDose™

(cephalexin tablets for oral suspension)

250 mg

Rx only

100 Unit-Dose Tablets
(10 Blisters of 10 Unit-Dose Tablets)

L 88mm x W 40mm x H 78mm

23

RANBAXY

NDC 63304-574-41

Panixine DisperDose™

(cephalexin tablets for oral suspension)

250 mg

MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only **40 Unit-Dose Tablets**
(5 Blisters of 8 Unit-Dose Tablets)

Each tablet for oral suspension contains: Cephalexin USP (monohydrate) equivalent to 250 mg cephalexin

Phenylketonurics: Contains phenylalanine 5.6 mg per tablet. See accompanying prescribing information.

Usual Dosage: See package insert.

THIS UNIT-DOSE PACKAGE IS CHILD RESISTANT.

Directions for Use: Mix one tablet in a small amount of water (approximately 2 teaspoonfuls). Drink the entire mixture. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken. **Do not chew or swallow the tablets.** The tablets will not rapidly dissolve in your mouth.

Dispense in a tight, light-resistant container.

Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

0803

RANBAXY

NDC 63304-574-41

Panixine DisperDose™

(cephalexin tablets for oral suspension)

250 mg

MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only 40 Unit-Dose Tablets
(5 Blisters of 8 Unit-Dose Tablets)

00000000

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32216 USA
by: Ranbaxy Laboratories Ltd.
New Delhi - 110 019, India

N 3 63304 57441 8

non varnish area

LOT:

EXP:

RANBAXY

NDC 63304-574-41

Panixine DisperDose™

(cephalexin tablets for oral suspension)

250 mg

Rx only

40 Unit-Dose Tablets
(5 Blisters of 8 Unit-Dose Tablets)

L 110mm x W 20mm x H 78mm

RANBAXY

NDC 63304-573-77

Panixine DisperDose™

(cephalexin tablets for oral suspension)

125 mg

MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only

100 Unit-Dose Tablets
(10 Blisters of 10 Unit-Dose Tablets)

SEP 1 1 2003

Each tablet for oral suspension contains: Cephalexin USP (monohydrate) equivalent to 125 mg cephalexin
Phenyltetonerics: Contains phenylalanine 2.8 mg per tablet. See accompanying prescribing information.
Usual Dosage: See package insert. This unit-dose package is child resistant.
Directions for Use: Mix one tablet in a small amount of water [approximately 2 teaspoonfuls]. Drink the entire mixture. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken.
Do not chew or swallow the tablets. The tablets will not rapidly dissolve in your mouth.
Dispense in a tight, light-resistant container. Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].
0803

APPROVED

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32216 USA
by: Ranbaxy Laboratories Ltd.
New Delhi - 110 019, India

LOT:
EXP:

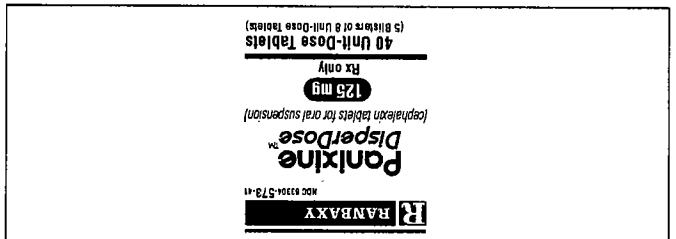
non varnish area

00000000

FPO

RANBAXY
NDC 63304-573-77
Panixine DisperDose™
(cephalexin tablets for oral suspension)
100 Unit-Dose Tablets
(10 Blisters of 10 Unit-Dose Tablets)
Rx only
125 mg

L 88mm x W 32mm x H 78mm



R RANBAXY

NDC 63304-573-41

Panixine DisperDose™

(cephalexin tablets for oral suspension)

125 mg

MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only **40 Unit-Dose Tablets**
(5 Blisters of 8 Unit-Dose Tablets)

Each tablet for oral suspension contains: Cephalexin USP (monohydrate) equivalent to 125 mg cephalexin

Phenylketonurics: Contains phenylalanine 2.8 mg per tablet. See accompanying prescribing information.

Usual Dosage: See package insert.

THIS UNIT-DOSE PACKAGE IS CHILD RESISTANT.

Directions for Use: Mix one tablet in a small amount of water [approximately 2 teaspoonfuls]. Drink the entire mixture. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken. **Do not chew or swallow the tablets.** The tablets will not rapidly dissolve in your mouth.

Dispense in a tight, light-resistant container.

Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

0803

R RANBAXY

NDC 63304-573-41

Panixine DisperDose™

(cephalexin tablets for oral suspension)

125 mg

MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only 40 Unit-Dose Tablets
(5 Blisters of 8 Unit-Dose Tablets)

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32216 USA
by: Ranbaxy Laboratories Ltd.
New Delhi - 110 019, India

3 63304 57341 1

non varnish area

LOT:

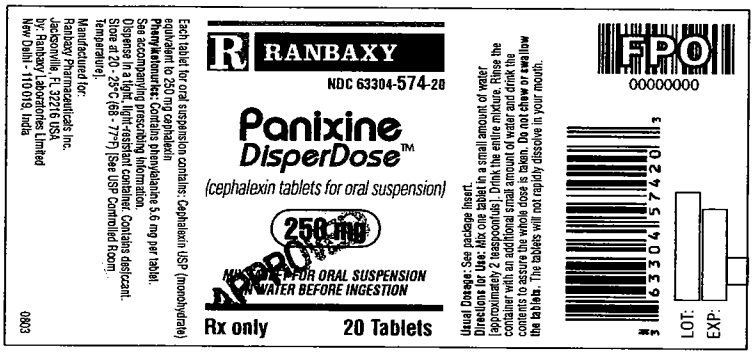
EXP:

00000000

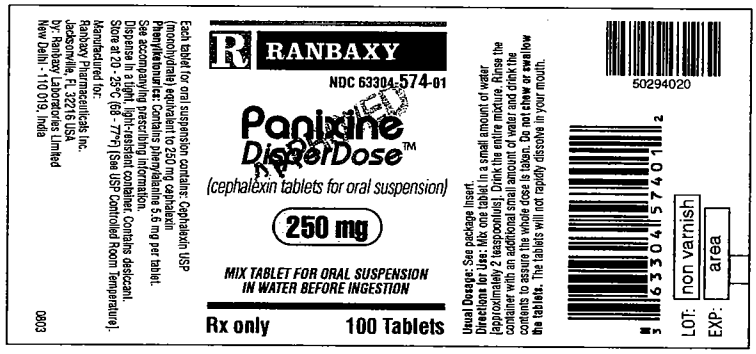
FPO

13

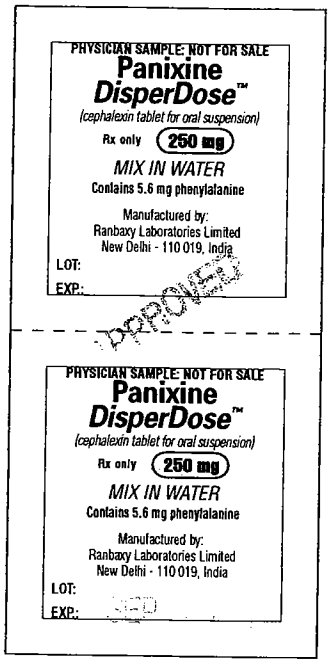
60cc 3.88" x 1.77"



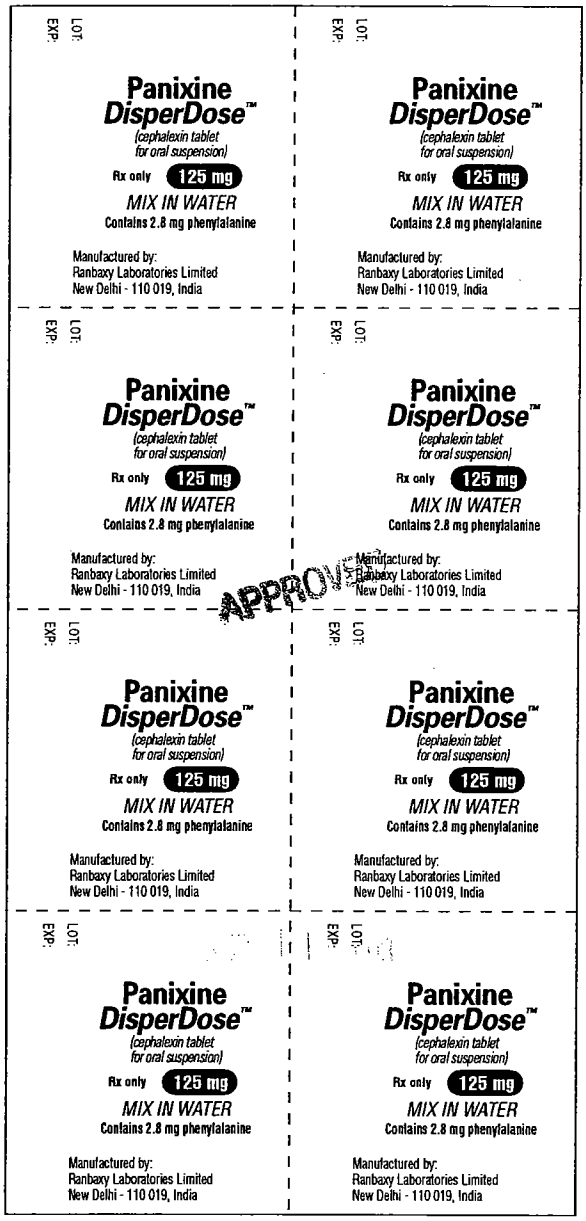
150cc 3.88" x 1.77"



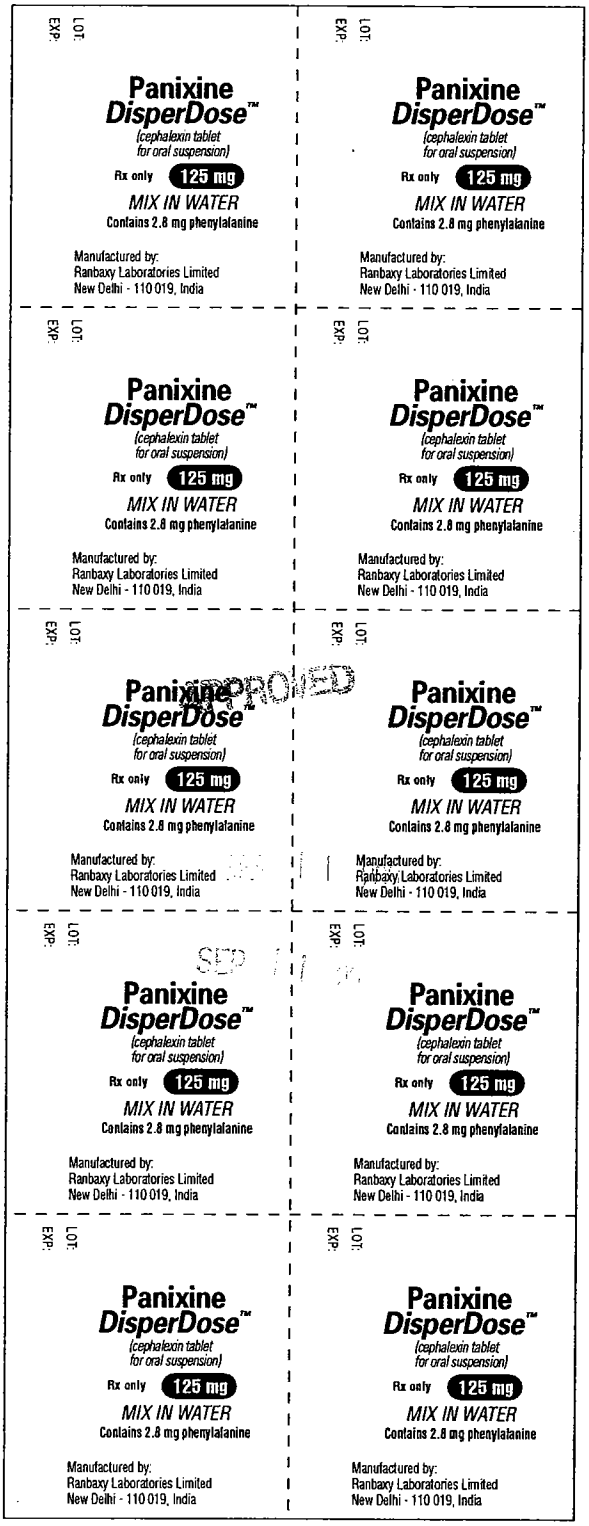
41mm x 86mm


PHYSICIAN SAMPLE: NOT FOR SALE
Panixine
DisperDose™
(cephalexin tablet for oral suspension)
Rx only
250 mg
MIX IN WATER
Contains 5.6 mg phenylalanine
Manufactured by:
Ranbaxy Laboratories Limited
New Delhi - 110 019, India
LOT:
EXP:
APPROVED
PHYSICIAN SAMPLE: NOT FOR SALE
Panixine
DisperDose™
(cephalexin tablet for oral suspension)
Rx only
250 mg
MIX IN WATER
Contains 5.6 mg phenylalanine
Manufactured by:
Ranbaxy Laboratories Limited
New Delhi - 110 019, India
LOT:
EXP:

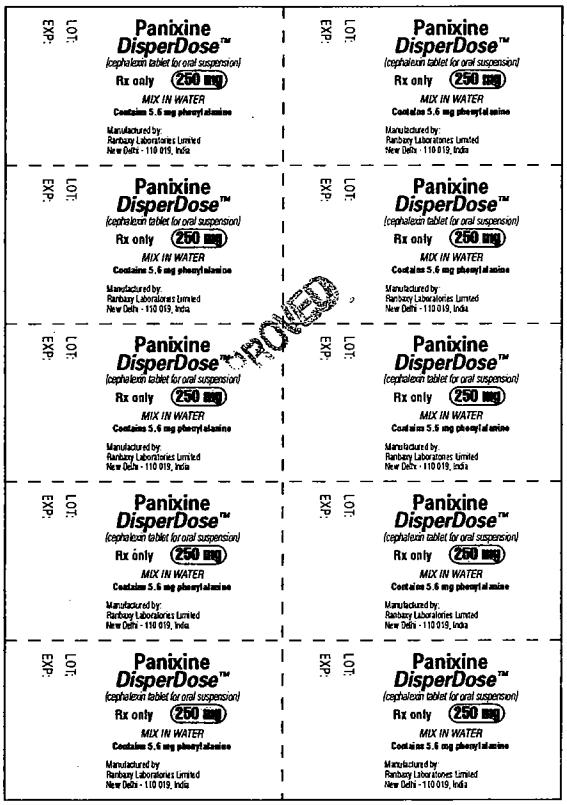
Width 76mm x Height 160mm



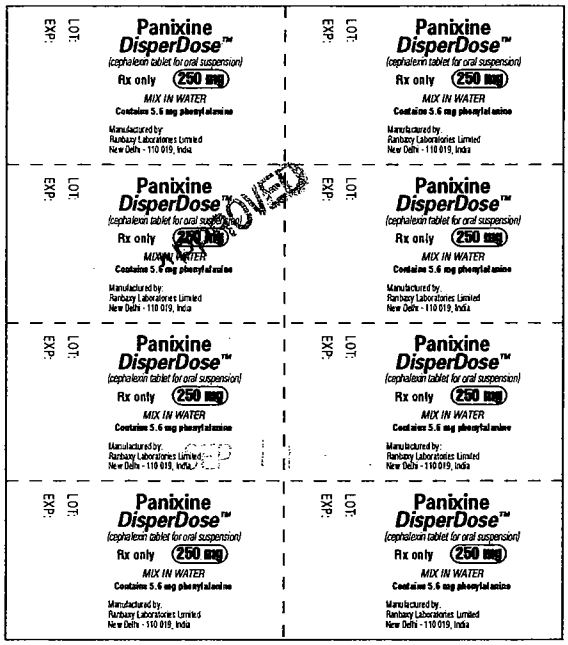
Width 76mm x Height 200mm



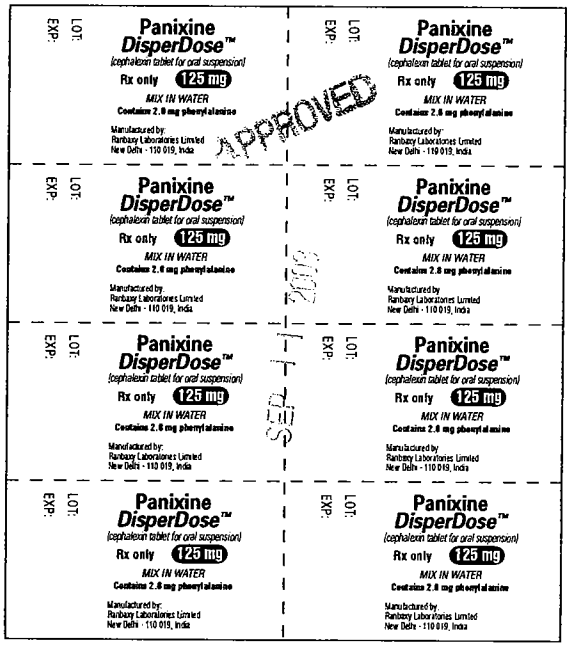
10's Blister Card
Width 74mm x Height 105mm



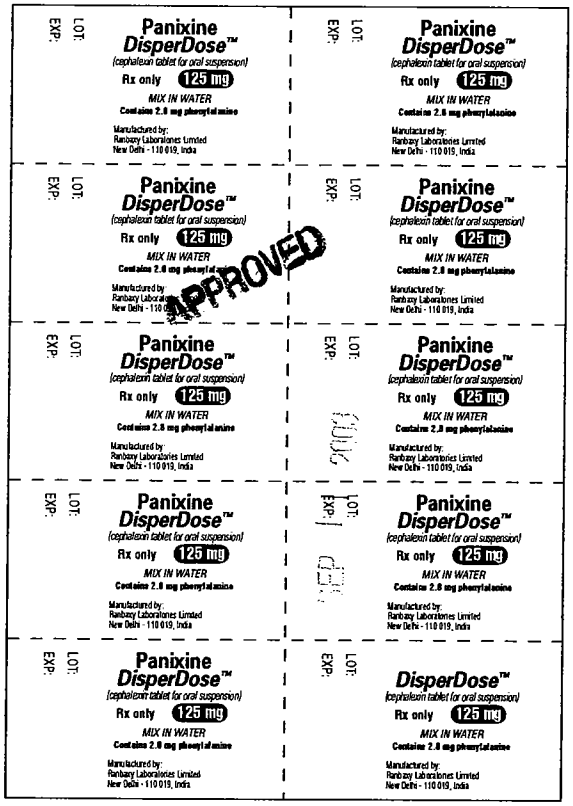
8's Blister Card
Width 74mm x Height 84mm



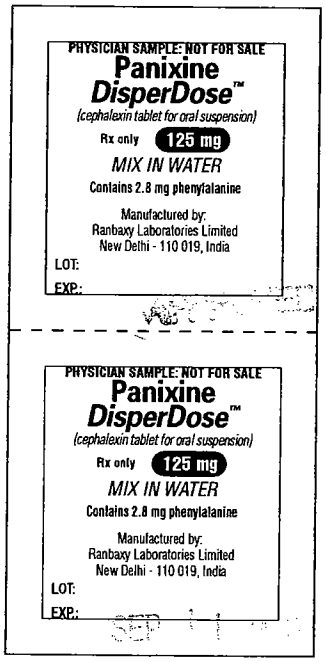
8's Blister Card
Width 74mm x Height 84mm



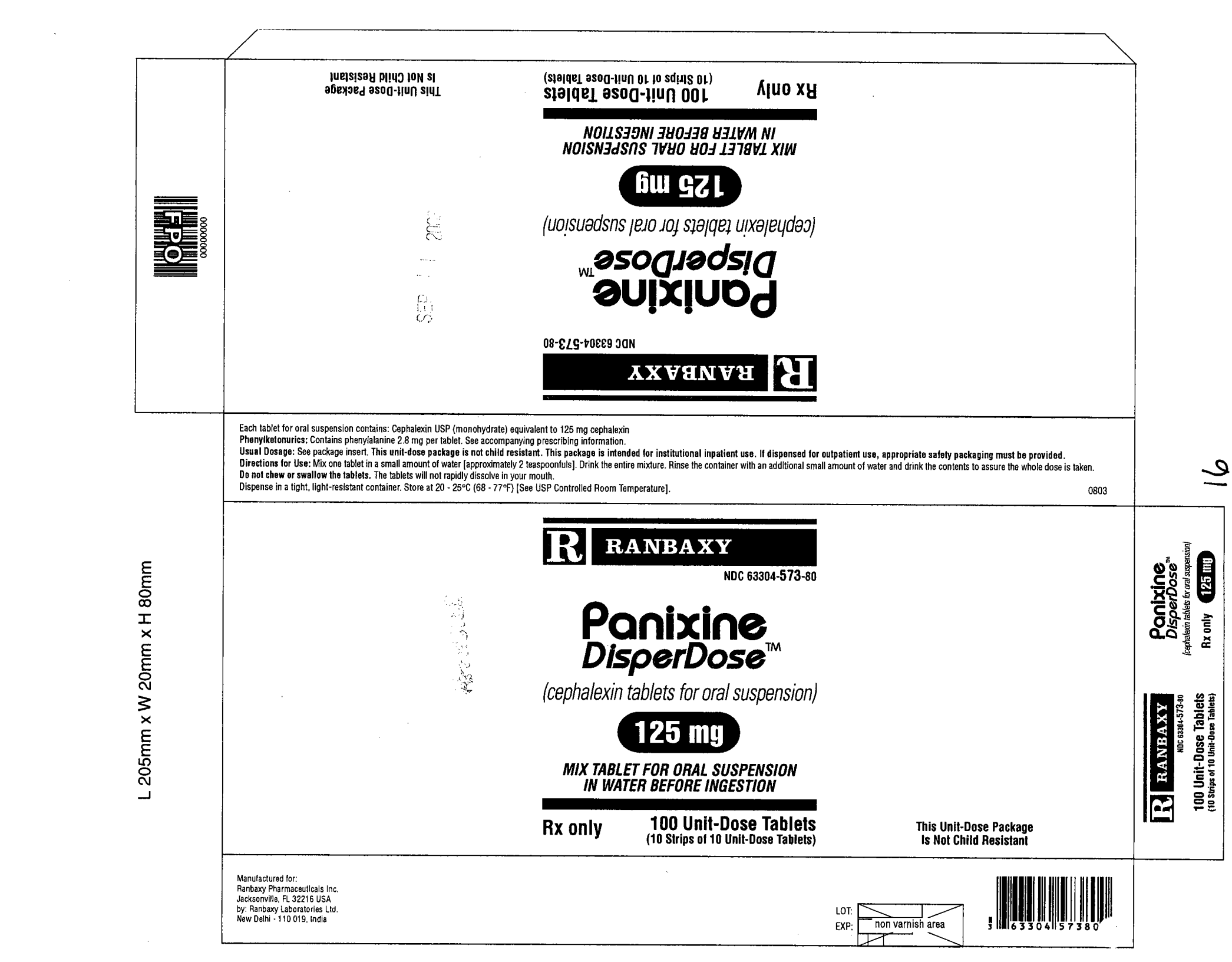
10's Blister Card
Width 74mm x Height 105mm



41mm x 86mm


PHYSICIAN SAMPLE: NOT FOR SALE
Panixine
DisperDose™
(cephalexin tablet for oral suspension)
Rx only
125 mg
MIX IN WATER
Contains 2.8 mg phenylalanine
Manufactured by:
Ranbaxy Laboratories Limited
New Delhi - 110 019, India
LOT:
EXP:
PHYSICIAN SAMPLE: NOT FOR SALE
Panixine
DisperDose™
(cephalexin tablet for oral suspension)
Rx only
125 mg
MIX IN WATER
Contains 2.8 mg phenylalanine
Manufactured by:
Ranbaxy Laboratories Limited
New Delhi - 110 019, India
LOT:
EXP:


H 3 11/16" x D 7/8" x W 3 1/16"
RANBAXY
NDC 63304-573-26
2 Unit-Dose Tablets
(1 Strip of 2 Unit-Dose Tablets)
Panixine DisperDose™
(cephalexin tablets for oral suspension)
Rx only 125 mg
PHYSICIAN SAMPLE: NOT FOR SALE
RANBAXY
NDC 63304-573-26
Panixine DisperDose™
(cephalexin tablets for oral suspension)
125 mg
MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION
Rx only
2 Unit-Dose Tablets
(1 Strip of 2 Unit-Dose Tablets)
APPROVED
PHYSICIAN SAMPLE: NOT FOR SALE
RANBAXY
Panixine DisperDose™
(cephalexin tablets for oral suspension)
125 mg
Rx only
Each tablet for oral suspension contains: Cephalexin USP (monohydrate) equivalent to 125 mg cephalexin
Phenylketonurics: Contains phenylalanine 2.8 mg per tablet. See accompanying prescribing information.
Usual Dosage: See package insert. This unit-dose package is not child resistant. This package is intended for institutional inpatient use. If dispensed for outpatient use, appropriate safety packaging must be provided.
Directions for Use: Mix one tablet in a small amount of water [approximately 2 teaspoonfuls]. Drink the entire mixture. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken. Do not chew or swallow the tablets. The tablets will not rapidly dissolve in your mouth.
Dispense in a tight, light-resistant container.
Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].
0803
Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32216 USA
by: Ranbaxy Laboratories Limited
New Delhi -110 019, India
FPO
00000000
LOT:
EXP:
non varnish area
63304 57326 8
7-1



Each tablet for oral suspension contains: Cephalexin USP (monohydrate) equivalent to 125 mg cephalexin
Phenylketonurics: Contains phenylalanine 2.8 mg per tablet. See accompanying prescribing information.
Usual Dosage: See package insert. **This unit-dose package is not child resistant. This package is intended for institutional inpatient use. If dispensed for outpatient use, appropriate safety packaging must be provided.**
Directions for Use: Mix one tablet in a small amount of water [approximately 2 teaspoonfuls]. Drink the entire mixture. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken.
Do not chew or swallow the tablets. The tablets will not rapidly dissolve in your mouth.
Dispense in a tight, light-resistant container. Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].
0803

RANBAXY
NDC 63304-573-80

Panixine DisperDose™
(cephalexin tablets for oral suspension)
125 mg
MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION
Rx only
100 Unit-Dose Tablets
(10 Strips of 10 Unit-Dose Tablets)
This Unit-Dose Package Is Not Child Resistant

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32216 USA
by: Ranbaxy Laboratories Ltd.
New Delhi - 110 019, India

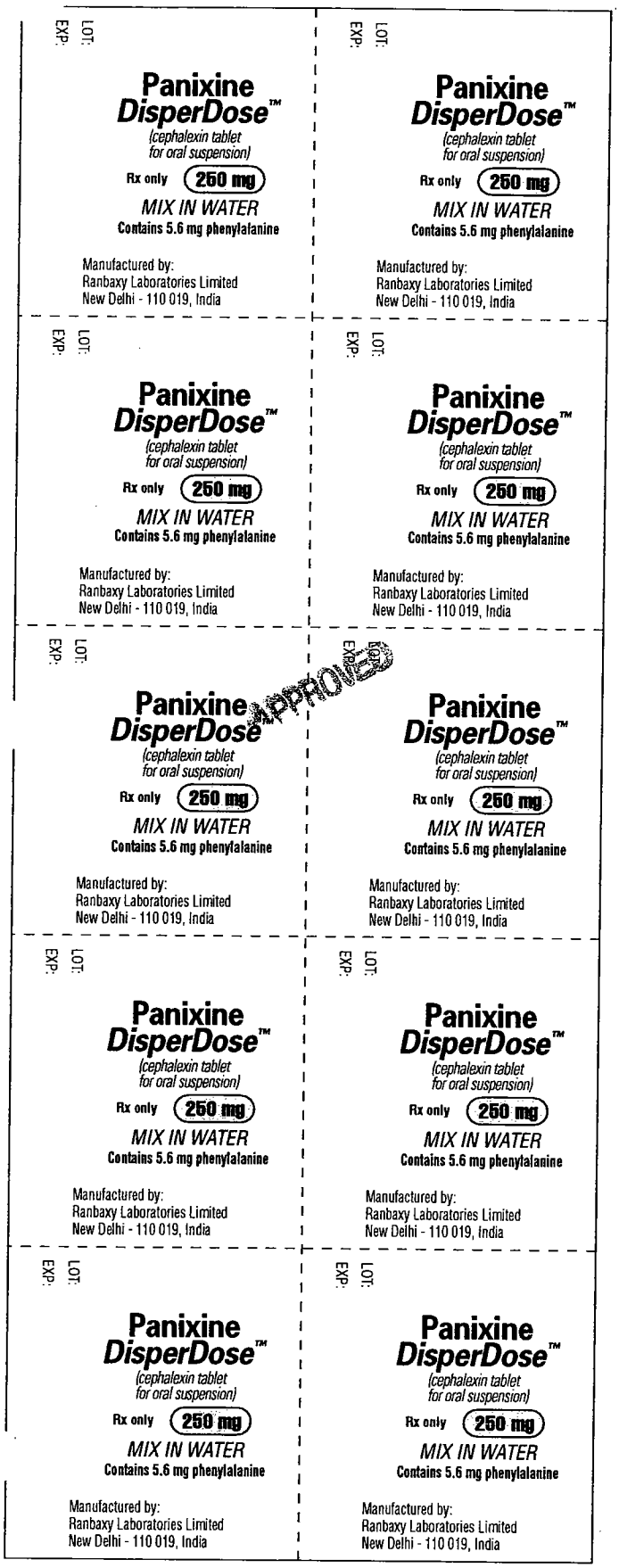
LOT:
EXP:
non varnish area

3 63304 57380

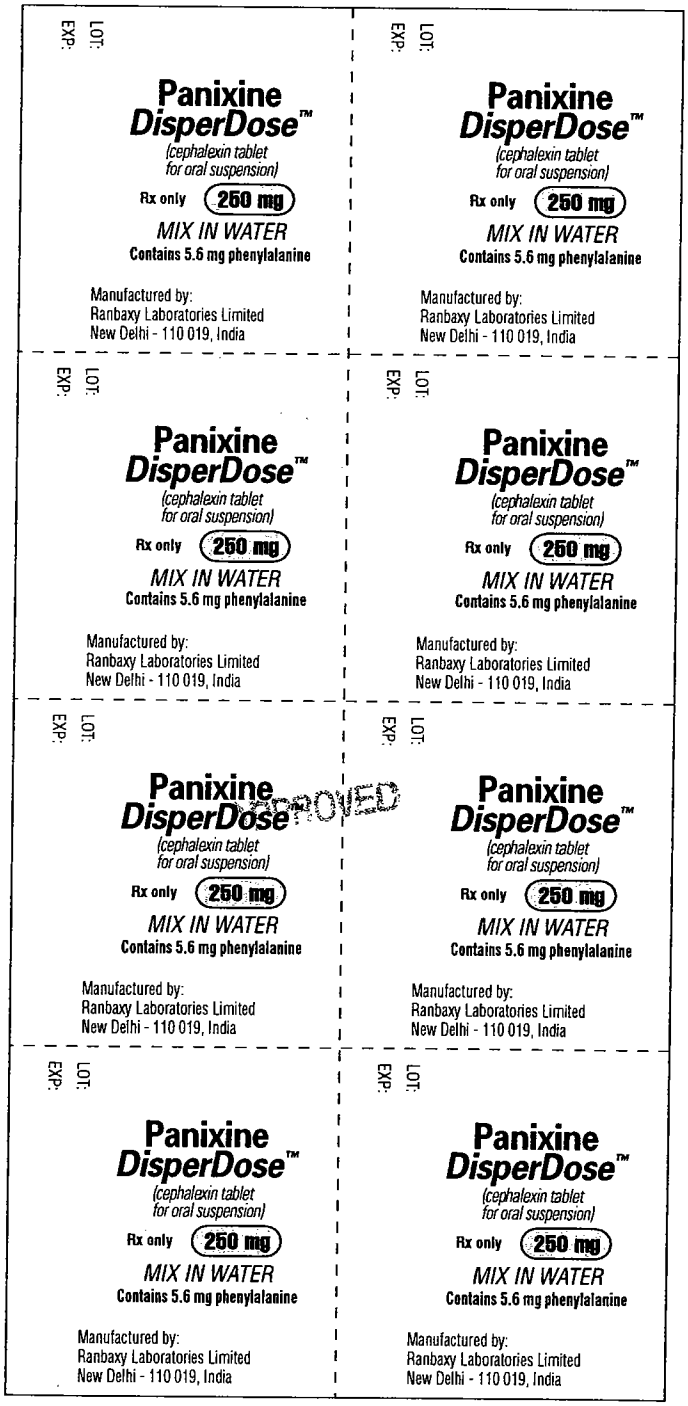
Panixine DisperDose™
(cephalexin tablets for oral suspension)
Rx only 125 mg
RANBAXY
NDC 63304-573-80
100 Unit-Dose Tablets
(10 Strips of 10 Unit-Dose Tablets)

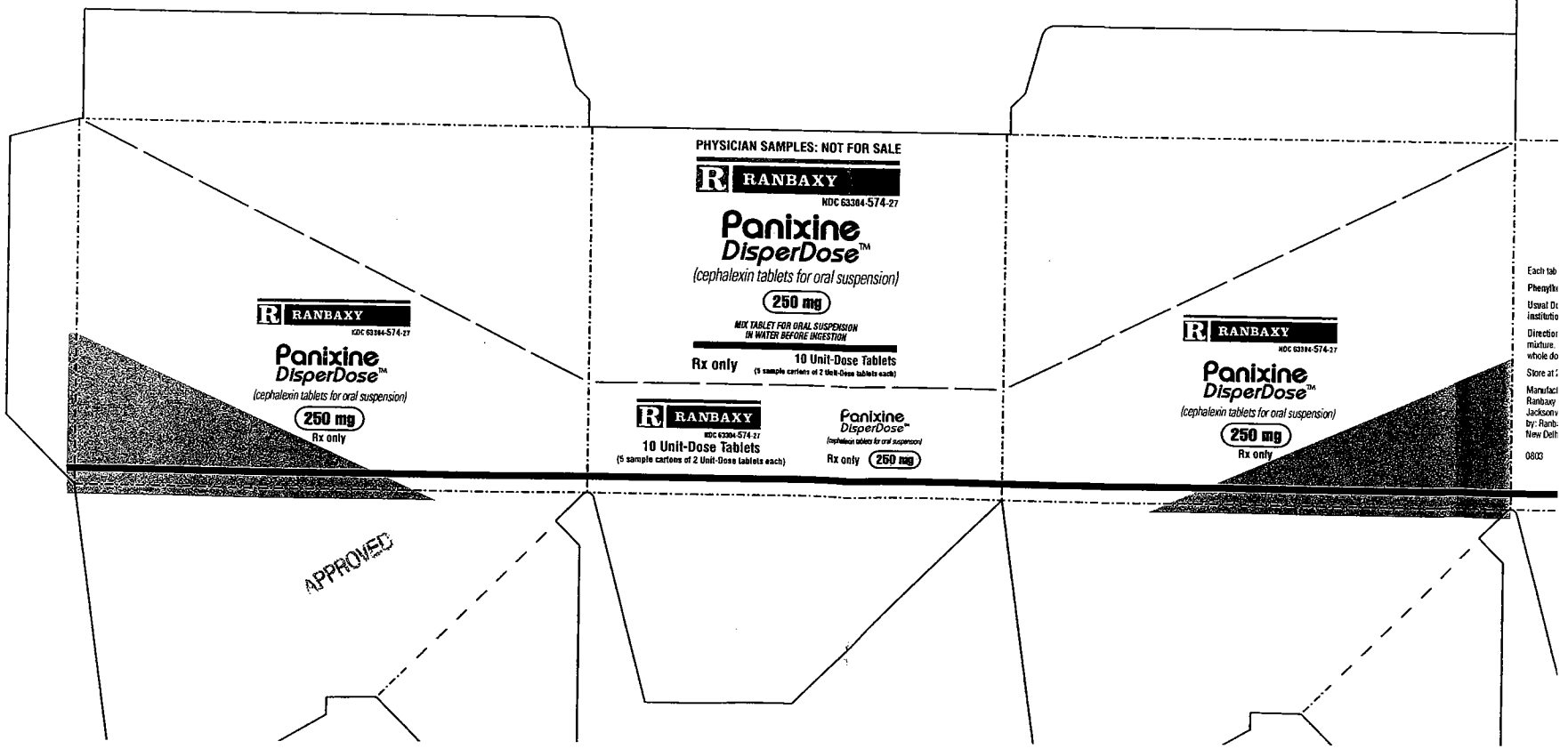
L 205mm x W 20mm x H 80mm

10's Strip Pack
Width 88mm x Height 230mm



8's Strip Pack
Width 88mm x Height 184mm




PHYSICIAN SAMPLES: NOT FOR SALE
RANBAXY
NDC 63304-574-27
Panixine DisperDose™
(cephalexin tablets for oral suspension)
250 mg
MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION
Rx only
10 Unit-Dose Tablets
(5 sample cartons of 2 Unit-Dose tablets each)
RANBAXY
NDC 63304-574-27
Panixine DisperDose™
(cephalexin tablets for oral suspension)
250 mg
Rx only
RANBAXY
NDC 63304-574-27
10 Unit-Dose Tablets
(5 sample cartons of 2 Unit-Dose tablets each)
Panixine DisperDose™
(cephalexin tablets for oral suspension)
Rx only 250 mg
RANBAXY
NDC 63304-574-27
Panixine DisperDose™
(cephalexin tablets for oral suspension)
250 mg
Rx only
APPROVED

L 164mm x W 30mm x H 80mm

RANBAXY

NDC 63304-573-42

Panixine DisperDose™

(cephalexin tablets for oral suspension)

125 mg

MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only **40 Unit-Dose Tablets** (5 Strips of 8 Unit-Dose Tablets)

This Unit-Dose Package is Not Child Resistant

APPROVED

Each tablet for oral suspension contains: Cephalexin USP (monohydrate) equivalent to 125 mg cephalexin

Phenylketonurics: Contains phenylalanine 2.8 mg per tablet See accompanying prescribing information.

Usual Dosage: See package insert. **This unit-dose package is not child resistant. This package is intended for institutional inpatient use. If dispensed for outpatient use, appropriate safety packaging must be provided.**

Directions for Use: Mix one tablet in a small amount of water (approximately 2 teaspoonfuls). Drink the entire mixture. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken. **Do not chew or swallow the tablets.** The tablets will not rapidly dissolve in your mouth.

Dispense in a tight, light-resistant container.

Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature]. 0603

RANBAXY

NDC 63304-573-42

Panixine DisperDose™

(cephalexin tablets for oral suspension)

125 mg

MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only 40 Unit-Dose Tablets (5 Strips of 8 Unit-Dose Tablets) This Unit-Dose Package is Not Child Resistant

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32216 USA
by: Ranbaxy Laboratories Ltd
New Delhi - 110 019, India

63304 573 42

non-varnish area

LOT:
EXP:

00000000

FPO

RANBAXY

NDC 63304-573-42

Panixine DisperDose™

(cephalexin tablets for oral suspension)

125 mg

Rx only 40 Unit-Dose Tablets (5 Strips of 8 Unit-Dose Tablets)

250 mg 8's Strip Box
L 188mm x W 38mm x H 92mm

RANBAXY

NDC 63304-574-42

Panixine DisperDose™

(cephalexin tablets for oral suspension)

250 mg

MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only **40 Unit-Dose Tablets** (5 Strips of 8 Unit-Dose Tablets)

This Unit-Dose Package Is Not Child Resistant

FPO

Each tablet for oral suspension contains: Cephalexin USP (monohydrate) equivalent to 250 mg cephalexin

Phenylketonurics: Contains phenylalanine 5.6 mg per tablet. See accompanying prescribing information.

Usual Dosage: See package insert. **This unit-dose package is not child resistant. This package is intended for institutional inpatient use. If dispensed for outpatient use, appropriate safety packaging must be provided.**

Directions for Use: Mix one tablet in a small amount of water [approximately 2 teaspoonfuls]. Drink the entire mixture. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken. **Do not chew or swallow the tablets.** The tablets will not rapidly dissolve in your mouth.

Dispense in a tight, light-resistant container

Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature].

0803

Manufactur
Ranbaxy Ph
Jacksonville
by: Ranbaxy
New Delhi -

RANBAXY

NDC 63304-574-42

Panixine DisperDose™

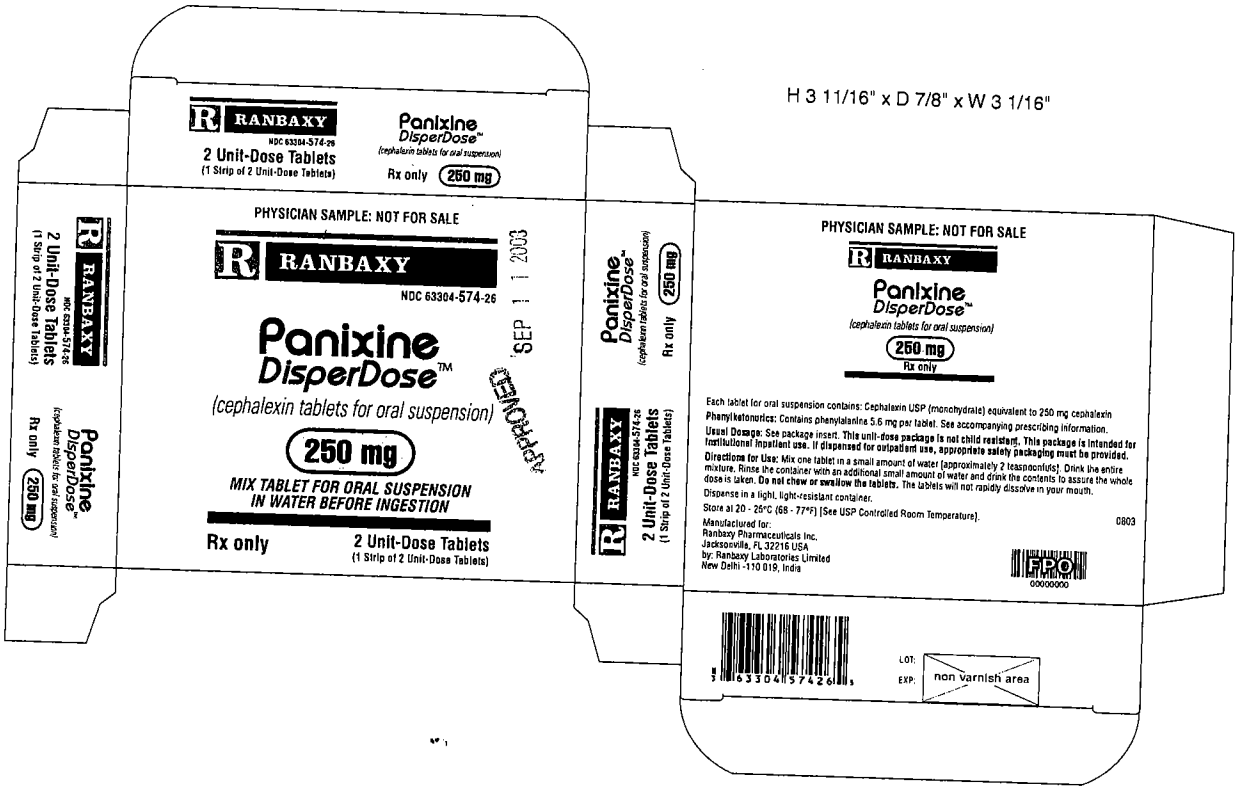
(cephalexin tablets for oral suspension)

250 mg

MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION

Rx only **40 Unit-Dose Tablets** (5 Strips of 8 Unit-Dose Tablets)

This Unit-Dose Package Is Not Child Resistant



H 3 11/16" x D 7/8" x W 3 1/16"

27

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-100

CSO LABELING REVIEW(S)

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-100 Date of Submission: August 6, 2003

Applicant's Name: Ranbaxy Pharmaceuticals Inc.

Established Name: Cephalexin Tablets for Oral Suspension, 125 mg and 250 mg

Proposed Proprietary Name: Panixine DisperDose

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes
125 mg
Container Labels: 20s and 100s
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1].
Blister Unit Dose Carton Labeling: 40s (5 x 8s) and 100s (10 x 10)
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1].
Strip Unit Dose Carton Labeling: 40s (5 x 8s) and 100s (10 x 10)
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1].
Physician Sample Strip Unit Dose Carton Labeling: 1 x 2s and 10s (5 x 2s)
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1].
Physician Sample Strip Unit Dose Labels: 2s
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1].
Blister Unit Dose Labels: 8s and 10s
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1].
Strip Unit Dose Labels: 8s and 10s
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1].
250 mg
Container Labels: 20s and 100s
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1].
Blister Unit Dose Carton Labeling: 40s (5 x 8s) and 100s (10 x 10)
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1].
Strip Unit Dose Carton Labeling: 40s (5 x 8s) and 100s (10 x 10)
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1].
Physician Sample Strip Unit Dose Carton Labeling: 1 x 2s and 10s (5 x 2s)
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1].
Physician Sample Strip Unit Dose Labels: 2s
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1].
Blister Unit Dose Labels: 8s and 10s
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1].
Strip Unit Dose Labels: 8s and 10s
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1].

Patient Information Sheet:
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1]
Professional Package Insert Labeling:
Satisfactory in FPL as of August 6, 2003 submission [Vol 4.1 - rev 8-03 - 50294140].
Revisions needed post-approval: **See third page.**

BASIS OF APPROVAL:
Was this approval based upon a petition? Yes
What is the RLD on the 356(h) form: Keflex Oral Suspension
NDA Number: 50-406
NDA Drug Name: Keflex (cephalexin) Oral Suspension
NDA Firm: Eli Lilly and Company
Date of Approval of NDA Insert and supplement #: 5/15/96 (S-012)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Basis of Approval for the Carton Labeling: side-by-sides
Other Comments

Labeling Deficiencies: **[TO BE MADE AFTER APPROVAL OF THIS APPLICATION]**

1. INSERT

   a. DOSAGE AND ADMINISTRATION

      i. Revise the first paragraph to read, "...orally after mixture in water".

      ii. Delete the title "Cephalexin Tablets For Oral Suspension" from both tables.

      iii. First table – Fourth column

      Print "1/2 to 1 tablet" on the same line.

      iv. Second table – Last column

      Revise "1 tablet bid" to read "1/2 to 1 tablet bid"

      v. Delete the paragraph, "For ¼ ... section".

Please revise your insert labeling, as instructed above, and in final print.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25		X	
Is this name different than that used in the Orange Book?*Cephalexin tablets	*		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present? DMETS has found the name Panixine DisperDose acceptable.		X	
Has the name been forwarded to DMETS? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified?	X		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?	X		
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been			

adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	X		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		**X**	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTE TO BIO. REVIEWER:

The firm revised the CLINICAL PHARMACOLOGY section to include some of the pharmacokinetic data of their [redacted] tablet dosage form. Is this information accurate?

> Following a dose of Ranbaxy's [redacted] tablets, equivalent to 500 mg of cephalexin, the average peak serum level of 15.25 mcg/mL was obtained at 1 hour. Following a dose of conventional cephalexin suspension equivalent to 500 mg of cephalexin, the average peak serum level of 14.67 mcg/mL was obtained a 1 hour. Measurable levels were present 6 hours after administration [redacted]

NOTE TO THE CHEMIST

The firm revised their "DOSAGE AND ADMINISTRATION/Directions for [redacted] tablets" section to read, "[redacted] drink the entire dispersion. Do not chew or swallow the tablets. [redacted]

Did Ranbaxy provide data to support their revision? [Note, previously the firm recommended, "[redacted]

This change in dispersion volume is ok, since a suspension and not a solution is formed. [This is same answer as Ruth did for 65-080].

Yanping

NOTE TO THE CHEMIST [From previous review]

1. In the PRECAUTIONS section, Ranbaxy indicates that their 125 mg and 250 mg [redacted] tablets contains phenylalanine 2.8 mg and 5.6 mg, respectively. Is this accurate?

2. Did Ranbaxy provide data to support their statement, "..[redacted]

3. The firm has proposed [redacted] container labels. Although we do not approve [redacted] container labels, do you have any guidelines for storage recommendations of [redacted] containers, or is what they printed sufficient?

4. The firm indicates that their unit-dose blister packages are child-resistant.
   - Is this information accurate?
   - If so, is the blister child-resistant or carton?

5. The firm included "[redacted]" in your list of components on page 2414b, however, it is not listed as an inactive ingredients. Should "[redacted] be listed as an inactive ingredient?

FOR THE RECORD: (portions taken from previous review)

1. Keflex® (cephalexin) pulvules® NDA 50-405/S-090 and oral suspension NDA 50-406/S-012, Approved May 15, 1996.

2. There are no patents or exclusivities for this drug product.

3. Manufacturer:

   Ranbaxy, India. [B1.1, p. 2535]

4. Package Size:

   RLD/pulvules 250 mg– 20s and 100s
   RLD/pulvules 500 mg- 20s and 100s
   RLD/suspension 125 mg/5 mL –100 mL
   RLD/suspension 250 mg/5 mL – 100 mL

ANDA
125 mg –20s, 100s
- blister packs 40s, 100s
- strip packs 40s, 100s
- sample packs 2s, 10s (5 x 2s)
250 mg – 20s, 100s
- blister packs 40s, 100s
- strip packs 40s, 100s
- sample packs 2s, 10s (5 x 2s)

5. Storage/dispensing recommendations

Store at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container.

6. Container/Closure:

ANDA
125 mg –20s, 100s
- high density, white, round with CRC
- blister packs 40s, 100s
- child-resistant laminate/paper/ /aluminum foil/ film clear
- strip packs 40s, 100s
- /aluminum foil/ laminate
- sample packs 2s, 10s (5 x 2s)

250 mg –20s, 100s
- high density, white, round with CRC
- blister packs 40s, 100s
- child-resistant laminate/paper/ aluminum foil/ film clear
- strip packs 40s, 100s
- /aluminum foil/ laminate
- sample packs 2s, 10s (5 x 2s)

[Vol. B1.3, p.3002]

7. The list of inactives in the DESCRIPTION section is consistent with the firm's components and composition statement. [However, see comment under DESCRIPTION]. [Vol. B1.1, p.2414]

8. The firm's physical description of each tablet in the HOW SUPPLIED section is consistent with their finished dosage form statements, except the flavor. [See comment under HOW SUPPLIED]. [Vol. B1.3, p.3534, 3512]

9. Patient Package Insert

a. An Office decision was made to request Ranbaxy's ANDA 65-080 to provide a "Patient Information Sheet" with "Directions for Use" instead of a " The text for the "Directions for Use" was reviewed by Dr. Hixon in response to the Labeling Consult. An agreement was made to replace

b. This decision applies to Ranbaxy's ANDA 65-100.

c. DMETS was previously forwarded a copy the firm's proposed PPI and had the following comments:

PATIENT INFORMATION

Revise the statement [redacted]

Revise the WARNINGS section so that it uses language that is easily understood by the layperson.

[NOTE: DMETS also requested that the firm provide separate instructions for the patient in a response to our previous labeling consult].
We will not forward DMETS comments to Ranbaxy due to the Office decision that the firm to provide a "Patient Information Sheet" instead of a PPI.

10. DOSAGE AND ADMINISTRATION section

The updated text requested in this review is from Dr. Hixon's response to the Labeling Consult for ANDA 65-080. [See consult response to Ranbaxy's ANDA 65-080].

11. The labeling review of the firm's December 11, 2002, submission was based on decisions made in a meeting on June 10, 2003, between OGD and the Office of Counter-Terrorism and Pediatric Drug Development (HFD-950). See labeling revisions below and related e-mails in the file folder.

The following decisions effects the labeling:

- Cephalexin and cefaclor are to be scored.
- Update the bolded statements "... for informational purposes ... to reflect with the 1/2 tablet wording.
- Amount of water: 2 teaspoonfuls
- Include the statement, " [redacted]

Keep the statement " [redacted]

12. DMETS does not recommend the use of the proposed proprietary name " [redacted] However, DMETS has not objections to the use of the proprietary name Panixine DisperDose. The firm was informed of the above decisions on 6/16/03.

Date of Review: August 19, 2003 Date of Submission: August 6, 2003

Primary Reviewer: Jacqueline Council, Pharm.D. Date:
Q. Vezza for J. Council 8/22/03

Team Leader: Captain Lillie Golson Date:
Lil Golson 8/22/03

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cc: ANDA: 65-100
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
aev/8/21/03|V:\FIRMSNZ\RANBAXY\LTRS&REV\65100.APL
Review

A 3.1

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-100

Date of Submission: December 11, 2002

Applicant's Name: Ranbaxy Pharmaceuticals Inc.

Established Name: Cephalexin Tablets for Oral Suspension, 125 mg and 250 mg

Proposed Proprietary Name: Panixine DisperDose

Labeling Deficiencies:

1. General Comment

   Upon further review and in consultation with the Office of Counter-Terrorism and Pediatric Drug Development (HFD-950), please further revise your labels and labeling as instructed below.

2. CONTAINER:

   a. 125 mg – 20s and 100s
      250 mg - 20s and 100s

      i. Front panel

         Revise the text, " [redacted] to read "MIX TABLET FOR ORAL SUSPENSION IN WATER BEFORE INGESTION".

      ii. Right side panel

         Revise the "Directions for Use" to read:

         Mix one tablet in a small amount of water [approximately 2 teaspoonfuls]. Drink the entire mixture. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken. Do not chew or swallow the tablets. The tablets will not rapidly dissolve in your mouth.

      iii. Revise your storage temperature recommendation to read: "Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature]".

   b. Blister: 125 mg and 250 mg

      i. Revise " [redacted] " to read " [redacted]

      ii. Improve the clarity of your "Manufactured by...." statement.

[redacted] to read as follows:

*CERTAIN DOSES FOR PEDIATRIC PATIENTS MAY NOT BE OBTAINABLE BY TAKING A WHOLE OR HALF TABLET. THEREFORE, CEPHALEXIN ORAL SUSPENSION MAY BE BETTER SUITED FOR DOSES IN THE PEDIATRIC POPULATION".

c. HOW SUPPLIED

i. Describe the score of your tablet.

ii. Revise your storage temperature recommendation to read: "Store at 20 - 25°C (68 - 77°F) [See USP Controlled Room Temperature]".

iii. See comment under DESCRIPTION.

d. PATIENT INFORMATION SHEET

PATIENT'S DIRECTIONS FOR USE

Mix one [redacted] tablet in water before you take it.

1. Remove one tablet from the bottle or unit dose pack.
2. Place the tablet in a small amount of water (approximately 2 teaspoonfuls).
3. Swirl or stir until thoroughly mixed.
4. Drink the mixture immediately after mixing. (The mixture is light yellow colored and has a fruity flavor.)
5. Be sure to drink the entire mixture.
6. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken.

DO NOT CHEW or SWALLOW the [redacted] Tablets [redacted] tablets whole. The tablets will not rapidly dissolve in your mouth.

Take all of the medicine as recommended by your doctor or other health care provider.

Do not mix [redacted] Tablets f [redacted] with any liquid other than water.

Please revise your container labels and insert labeling, as instructed above, and in final print or draft if you prefer.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -
http://www.fda.gov/cder/cdernew/listserv.html

c. Strip unit pack: 125 mg and 250 mg

Revise "[redacted] to read "[redacted]

d. Sample:

Revise "[redacted]" to read "[redacted]

3. CARTON:

a. 40s and 100s unit dose blisters

See comments under CONTAINER.

b. 40s and 100s unit dose strips

See comments under CONTAINER.

c. 10s unit dose – Physician Samples

See comments under CONTAINER.

4. INSERT

a. DESCRIPTION: Please clarify the flavor of this product (i.e., fruit flavor or peppermint.

b. DOSAGE AND ADMINISTRATION

i. Directions for Cephalexin Tablets for Oral Suspension:

Revise this subsection to read as follows.

Mix one tablet in a small amount of water [approximately 2 teaspoonfuls]. Drink the entire mixture. Rinse the container with an additional small amount of water and drink the contents to assure the whole dose is taken. Do not chew or swallow the tablets. The tablets will not rapidly dissolve in your mouth.

ii. Since your tablets will be scored, you may delete the statement, '[redacted]

ii. Pediatric Patients

A) Dosage Tables

Revise accordingly to reflect your scored tablet. For example: "1/2 tablet" instead of "[redacted]

D) Revise the asterisk statement, "*[redacted]

[redacted]

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25		X	
Is this name different than that used in the Orange Book?*Cephalexin tablets	*		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to DMETS? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified? *The proposed names were found to be unacceptable. DMETS comments are in this review.	*		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?	X		
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs			

Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	x		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	x		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		**X**	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTE TO BIO. REVIEWER:

The firm revised the CLINICAL PHARMACOLOGY section to include some of the pharmacokinetic data of their dispersible tablet dosage form. Is this information accurate?

> Following a dose of Ranbaxy's ' [redacted] tablets, equivalent to 500 mg of cephalexin, the average peak serum level of 15.25 mcg/mL was obtained at 1 hour. Following a dose of conventional cephalexin suspension equivalent to 500 mg of cephalexin, the average peak serum level of 14.67 mcg/mL was obtained a 1 hour. Measurable levels were present 6 hours after administration of Ranbaxy's [redacted]

NOTE TO THE CHEMIST

The firm revised their "DOSAGE AND ADMINISTRATION/Directions for [redacted] tablets" section to read, " [redacted] Do not chew or swallow the tablets. [redacted]

> Did Ranbaxy provide data to support their revision? [Note, previously the firm recommended, ' [redacted]

This change in dispersion volume is ok, since a suspension and not a solution is formed. [This is same answer as Ruth did for 65-080].

Yanping

NOTE TO THE CHEMIST [From previous review]

1. In the PRECAUTIONS section, Ranbaxy indicates that their 125 mg and 250 mg [redacted] tablets contains phenylalanine 2.8 mg and 5.6 mg, respectively. Is this accurate?

2. Did Ranbaxy provide data to support their statement, "... [redacted]

3. The firm has proposed [redacted] container labels. Although we do not approve [redacted] container labels, do you have any guidelines for storage recommendations of [redacted] containers, or is what they printed sufficient?

4. The firm indicates that their unit-dose blister packages are child-resistant.
   - Is this information accurate?
   - If so, is the blister child-resistant or carton?

5. The firm included " [redacted] in your list of components on page 2414b, however, it is not listed as an inactive ingredients. Should ' [redacted] ' be listed as an inactive ingredient?

FOR THE RECORD:

1. Keflex® (cephalexin) pulvules® NDA 50-405/S-090 and oral suspension NDA 50-406/S-012, Approved May 15, 1996.

2. There are no patents or exclusivities for this drug product.

3. Manufacturer:

   Ranbaxy, India.
   [B1.1, p. 2535]

4. Package Size:

   RLD/pulvules 250 mg– 20s and 100s
   RLD/pulvules 500 mg- 20s and 100s
   RLD/suspension 125 mg/5 mL –100 mL
   RLD/suspension 250 mg/5 mL – 100 mL

   ANDA
   125 mg –20s, 100s
   - blister packs 40s, 100s
   - strip packs 40s, 100s
   250 mg – 20s, 100s
   - blister packs 40s, 100s
   - strip packs 40s, 100s

5. Storage/dispensing recommendations

   Store at controlled room temperature 15o to 30oC (59o to 86oF)(see USP). Dispense in a tight, light-resistant container.

6. Container/Closure:

   ANDA
   125 mg –20s, 100s
   - high density, white, round with CRC
   - blister packs 40s, 100s
   - child-resistant laminate/paper/ aluminum foil/ r film clear
   - strip packs 40s, 100s
   - aluminum foil/ laminate
   250 mg –20s, 100s
   - high density, white, round with CRC
   - blister packs 40s, 100s
   - child-resistant laminate/paper/ /aluminum foil/ film clear
   - strip packs 40s, 100s
   aluminum foil/ laminate

   [Vol. B1.3, p.3002]

7. The list of inactives in the DESCRIPTION section is consistent with the firm's components and composition statement. [However, see comment under DESCRIPTION]. [Vol. B1.1, p.2414]

8. The firm's physical description of each dispersible tablet in the HOW SUPPLIED section is consistent with their finished dosage form statements, except the flavor. [See comment under HOW SUPPLIED].
[Vol. B1.3, p.3534, 3512]

9. Patient Package Insert

   a. An Office decision was made to request Ranbaxy's ANDA 65-080 to provide a "Patient Information Sheet" with "Directions for Use" instead of a " ". The text for the "Directions for Use" was reviewed by Dr. Hixon in response to the Labeling Consult. An agreement was made to replace

   b. This decision applies to Ranbaxy's ANDA 65-100.

   c. DMETS was previously forwarded a copy the firm's proposed PPI and had the following comments:

      PATIENT INFORMATION

      Revise the statement. "

      Revise the WARNINGS section so that it uses language that is easily understood by the layperson.

      [NOTE: DMETS also requested that the firm provide separate instructions for the patient in a response to our previous labeling consult].
      We will not forward DMETS comments to Ranbaxy due to the Office decision that the firm to provide a "Patient Information Sheet" instead of a PPI.

10. DOSAGE AND ADMINISTRATION section

    The updated text requested in this review is from Dr. Hixon's response to the Labeling Consult for ANDA 65-080.
    [See consult response to Ranbaxy's ANDA 65-080].

11. The labeling review of the firm's December 11, 2002, submission was based on decisions made in a meeting on June 10, 2003, between OGD and the Office of Counter-Terrorism and Pediatric Drug Development (HFD-950). See labeling revisions below and related e-mails in the file folder.

    The following decisions effects the labeling:

    - Cephalexin and cefaclor are to be scored.
    - Update the bolded statements "... for informational purposes ... to reflect with the 1/2 tablet wording.
    - Amount of water: 2 teaspoonfuls
    - Include the statement, "

    Keep the statement "

12. DMETS does not recommend the use of the proposed proprietary name However, DMETS has not objections to the use of the proprietary name Panixine DisperDose.
    The firm was informed of the above decisions on 6/16/03.

Date of Review: 7/11/03

Date of Submission: 12/11/02

Primary Reviewer:
Jacqueline Council, Pharm.D.

Date: 7-21-03

Team Leader:
Captain Lillie Golson

Date: 7/25/03

cc: ANDA: 65-100
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-100

Date of Submission: November 11, 2002

Applicant's Name: Ranbaxy Pharmaceuticals Inc.

Established Name: Cephalexin Tablets for Oral Suspension, 125 mg and 250 mg

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Labeling Deficiencies:

General Comment

Your proposed proprietary names [redacted] Panixine™ DisperDose™ and [redacted]™ have been forwarded to the Office of Drug Safety/Division of Medication Errors and Technical Support [DMETS] for their review and comment. We will inform you of their findings when available.

Please note that DMETS only accepts two proposed names at a time. If neither name is found to be acceptable we will then forward your third choice, unless you advise us differently. Please be advised that labels and labeling bearing the proposed name will need to be provided.

We will not ask for labels and labeling in final print until we receive input on the acceptability of these proposals.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25		X	
Is this name different than that used in the Orange Book?*Cephalexin tablets	*		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to DMETS? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified? *The proposed names were found to be unacceptable. DMETS comments are in this review.	*		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?	X		
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been		X	

adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	x		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	x		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		**X**	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. Keflex® (cephalexin) pulvules® NDA 50-405/S-090 and oral suspension NDA 50-406/S-012, Approved May 15, 1996.

2. There are no patents or exclusivities for this drug product.

3. Manufacturer:

   Ranbaxy, India.
   [B1.1, p. 2535]

4. Package Size:

   RLD/pulvules 250 mg– 20s and 100s
   RLD/pulvules 500 mg- 20s and 100s
   RLD/suspension 125 mg/5 mL –100 mL
   RLD/suspension 250 mg/5 mL – 100 mL

   ANDA
   125 mg –20s, 100s
   - blister packs 40s, 100s
   - strip packs 40s, 100s
   250 mg – 20s, 100s
   - blister packs 40s, 100s
   - strip packs 40s, 100s

5. Storage/dispensing recommendations

   Store at controlled room temperature 15o to 30oC (59o to 86oF)(see USP).
   Dispense in a tight, light-resistant container.

6. Container/Closure:

   ANDA
   125 mg –20s, 100s
   - high density, white, round with CRC
   - blister packs 40s, 100s
   - child-resistant laminate/paper/ aluminum foil/ film clear
   - strip packs 40s, 100s
   /aluminum foil/ laminate
   250 mg –20s, 100s
   - high density, white, round with CRC
   - blister packs 40s, 100s
   - child-resistant laminate/paper/ /aluminum foil/ film clear
   - strip packs 40s, 100s
   - aluminum foil/ laminate

   [Vol. B1.3, p.3002]

7. The list of inactives in the DESCRIPTION section is consistent with the firm's components and composition statement. [However, see comment under DESCRIPTION].
[Vol. B1.1, p.2414]

8. The firm's physical description of each [redacted] tablet in the HOW SUPPLIED section is consistent with their finished dosage form statements, except the flavor. [See comment under HOW SUPPLIED].
[Vol. B1.3, p.3534, 3512]

9. Patient Package Insert

   a. An Office decision was made to request Ranbaxy's ANDA 65-080 to provide a "Patient Information Sheet" with "Directions for Use" instead of a "[redacted]
   The text for the "Directions for Use" was reviewed by Dr. Hixon in response to the Labeling Consult. An agreement was made to replace "..[redacted]

   b. This decision applies to Ranbaxy's ANDA 65-100.

   c. DMETS was previously forwarded a copy the firm's proposed PPI and had the following comments:

      PATIENT INFORMATION

      Revise the statement, "[redacted]

      Revise the WARNINGS section so that it uses language that is easily understood by the layperson.

      [NOTE: DMETS also requested that the firm provide separate instructions for the patient in a response to our previous labeling consult].
      We will not forward DMETS comments to Ranbaxy due to the Office decision that the firm to provide a "Patient Information Sheet" instead of a PPI.

10. DOSAGE AND ADMINISTRATION section

    The updated text requested in this review is from Dr. Hixon's response to the Labeling Consult for ANDA 65-080.
    [See consult response to Ranbaxy's ANDA 65-080].

11. A consult regarding the labeling for this ANDA is pending review by the Office of Pediatric Drug Development and Program Initiatives. [Sent January 2003] Therefore, the firm's labeling submitted 12/11/02 will be delayed at this time, pending the consult response.

12. NOTE: The firm indicates the following in their 12/11/02 amendment:

    Upon closer review we have noticed that we had provided an inaccurate response to the Agency's question 2.a.ii from the Agency's May 1, 2002 deficiency. In our response dated June 13, 2002, we incorrectly said the larger unit-dose strips were packaged in a child resistant package. This was incorrect. The larger unit dose strips are a non-child resistant package and the smaller unit-dose blisters are a child resistant package. Please note, we have revised all unit-dose packages to clearly illustrate which package are child resistant and which packages are non child resistance.

Date of Review: 1/13/03

Date of Submission: 11/11/02

Primary Reviewer:
Jacqueline Council, Pharm.D. Date: 1/30/02

Team Leader:
Captain Lillie Golson

Date: 1/30/03

cc: ANDA: 65-100
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
V:\FIRMSNZ\RANBAXY\LTRS&REV\65100na4.l.doc
Review

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 65-100

Date of Submission: June 13, 2002

Applicant's Name: Ranbaxy Pharmaceuticals Inc.

Established Name: Cephalexin Tablets for Oral Suspension, 125 mg and 250 mg

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Labeling Deficiencies:

1. General Comment

The Office of Drug Safety/Division of Medication Errors and Technical Support [DMETS] has reviewed your proposed proprietary names, " " and " " DMETS does not recommend the use of these names for the following reasons:

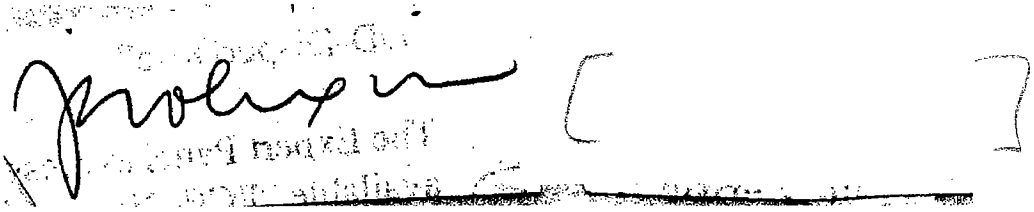
The products considered to have the greatest potential for name confusion with " ", were Prolixin, Robaxin, Eulexin, Raloxifene, Rocephin, Rituxan, and Skelaxin. The products considered to have the greatest potential for name confusion with " " were Duricef, Risperdal, and Dispermox.

- Look-alike/Sound-alike Names

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that " " can be confused with Prolixin, Robaxin, and Rocephin. Positive findings included a response of " ", 2 responses of "Robaxin DD", and a response of "Robaxin". A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. In addition, one participant in the written outpatient study responded with "Robaxisall" and the another participant provided the interpretation "Rocefin". The marketed products, Robaxisal and Rocephin, are a near match. The majority of interpretations from the verbal and written prescription studies were phonetic/misspelled interpretations of the drug name " "

Prolixin (fluphenazine) is indicated for the management of manifestations of psychotic disorders; esterified formulations (enanthate and decanoate) are indicated for patients requiring prolonged and parenteral neuroleptic therapy (e.g., chronic schizophrenics). The recommended adult oral dosage is 0.5 to 10 mg/day initially in divided doses administered at 6 to 8 hour intervals. When symptoms are controlled, the dose can be reduced to a maintenance dose of 1 to 5 mg, often given as a single daily dose. In general, the parenteral dose is approximately 1/3 to ½ the oral dose. *Prolixin* and the proposed proprietary name may look similar when written and sound similar when spoken. In fact, one study participant interpreted the written inpatient prescription as "Prolixin DD". A positive finding in a study with a relatively small number of participants is highly significant and predictive of confusion between these two products

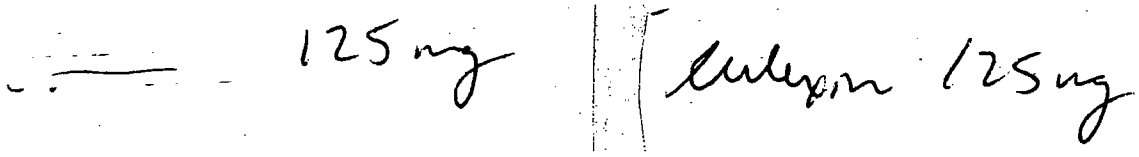
in the marketplace. Common look-alike characteristics for the two names include, similarities in the letters "P" and "R", and the shared letters, "o", "l", "x", "i", and "n" (see writing sample below). The names also share sound-alike characteristics. Each name has 3 syllables. Because of the common "ro", the first syllable of each name sounds very similar, ("Pro" vs. "Ro"). The last syllables, ("lixin" vs. "lexin") are virtually indistinguishable. The drug products have other similarities. Prolixin and [redacted], are both available as tablets for oral administration and may have a common dosing regimen of every 6 hours. Although the products do not have a strength in common, the 250 mg [redacted], dose could be mistaken for the 2.5 mg Prolixin dose, especially if the latter dose were written with a terminal "0" and if the decimal point lacks prominence. If Prolixin was given instead of [redacted] the patient's infection would not be adequately treated. The patient would also be exposed to risk of Neuroleptic Malignant Syndrome as well as unnecessary side effects such as dyskinesias, drowsiness, and other unwanted anticholinergic effects. If [redacted] was given rather than Prolixin, the patients mental illness might not be controlled and he/she would be at risk if they had allergies to a cephalosporin.



Robaxin (Methocarbamol) Tablets and Injection is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The recommended adult oral dosage is 6 grams a day for the first 48 to 72 hours of treatment. For severe conditions 8 grams a day may be administered. Thereafter, the dosage can usually be reduced to approximately 4 grams a day. The tablets are given in 4 divided doses. *Robaxin* and [redacted] may look similar when written and sound similar when spoken. When written, the only discernable difference between the two names is the letters in the middle of the name ("ba" vs. "le"). The "b" and the "l" are similar in appearance in that they both have a looping upstroke. Also, the "b" looks very much like the "le" in general shape (see writing sample on page 17). The similarities between the written names caused confusion for the participants of the written study. Study participants interpreted [redacted] as "Robaxin" (twice), "Robaxin DD", "Robexin DD", and "Robixin DD". The names sound very much alike as well, again, differing only by the middle of the name ("ba" vs. "le"). [redacted] and Robaxin also share other similarities. Both are tablets which can be given four times daily. In addition, Robaxin is available in a 500 mg tablet. It is possible for a prescription to be written for 500 mg of [redacted] (two 250 mg tablets) which overlaps with the 500 mg strength of Robaxin. It is also possible for the 750 mg Robaxin strength and 250 mg [redacted] strength to be confused since "750" and "250" may look similar.

Eulexin (Flutamide Capsules) is indicated for use in combination with LHRH agonists for the management of locally confined Stage B_2-C and Stage D_2 metastatic carcinoma of the prostate. The recommended adult dosage is 2 capsules 3 times a day at 8-hour intervals for a total daily dose of 750 mg. *Eulexin* and [redacted] may sound similar when spoken and look similar when written. Each name has 3 syllables. The last syllable in each word, "[redacted] is identical. If the first syllable is not clearly annunciated, the two

names may be confused. The two names look very similar when scripted (see writing sample below). The lower case "r" may look like an "e" and the lower case "o" may look like a "u" and vice versa. If the "o" is not completed closed, it may look like a "u" and the left and right upstrokes of the "u" could come close together resembling an "o". In addition to the sound-alike, look-alike properties, the two drug products share other similarities. Both are capsules for oral administration and each is available as 125 mg. If Eulexin was given instead of [redacted] the patient's infection would not be adequately treated. Also, there have been postmarketing reports of hospitalization and rarely death due to liver failure in patients taking Eulexin. The patient would also be exposed to risk of liver damage as well as unnecessary side effects such as hot flashes, impotence, and loss of libido.



Rocephin (Ceftriaxone for Injection) is indicated for the treatment of the following infections when caused by susceptible organisms: lower respiratory tract infections, acute bacterial otitis media, urinary tract infections, uncomplicated gonorrhea, pelvic inflammatory disease, bacterial septicemia, bone and joint infections, intra-abdominal infections, and surgical prophylaxis. The recommended adult dosage is 1 to 2 grams given once a day (or in equally divided doses twice a day) depending on the type and severity of infection. The total daily dose should not exceed 4 grams. *Rocephin* and [redacted] may sound similar when spoken. The names each have 3 syllables. The first syllables of each name are identical ("Ro"). The second syllables, "ce" vs. [redacted], contain the short "e" sound. The last syllables, "phin" vs. [redacted] combine the similar sounding voiceless fricatives* "ph" and "x" with the identical "in". Although, Rocephin and [redacted] lack convincing look-alike properties, a study participant interpreted the written inpatient prescription as "Rocefin", which is phonetically identical to Rocephin. Although "Rocefin" is not a drug product, it is conceivable for a selection error to take place if a pharmacist associates "Rocefin" with Rocephin. These two drug products have other common features. Both are antibiotics that can be given twice a day. The products also share a common strength of 250 mg. Although the products are available in different dosage forms, tablets vs. injection, it is conceivable that they may be confused for one another in a hospital setting. Postmarketing experience has shown errors between Celebrex *tablets* and Cerebyx *injection.* Because of the similarities in these products and the positive study finding, there is cause for concern that they be confused if [redacted] were introduced in the marketplace. Confusion of these two cephalosporins could result in treatment failure due to lack of susceptibility or incorrect dosing and could lead to resistance.

- Modifier

With regard to the modifier "DD" in " [redacted] , DMETS does not recommend using the modifier "DD" in conjunction with the proprietary name since it can be misinterpreted as a medical abbreviation "OD" (right eye) and "QD" (once a day). If the pharmacist interprets the dosing directions as "once a day", the patient may be under dosed if the patient was supposed to take it 2 or 3 times a day. Respondents from the written study conducted by ODS for the proposed name [redacted] (ANDA 65-080), interpreted "DD" as "DO", "AD", "DP", and "AP". "DD" could also be interpreted as "double dose", which could lead to an overdose of the medication. Also, using "DD" and "DisperDose" together is redundant. In the study conducted by ODS, 11 of 45 respondents (24 %) who correctly identified [redacted] did not include the modifier "DD" in their interpretation. Since some prescribers may write a prescription for [redacted] instead of [redacted], the confusion between [redacted] and the above proprietary names would increase. The likelihood that a prescriber may omit "DD" is high because the "DD" is not being used to differentiate [redacted] from a different product.

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* A good reference for phonetic terminology can be found at: http://www.unil.ch/ling/phonetique/api-eng.html

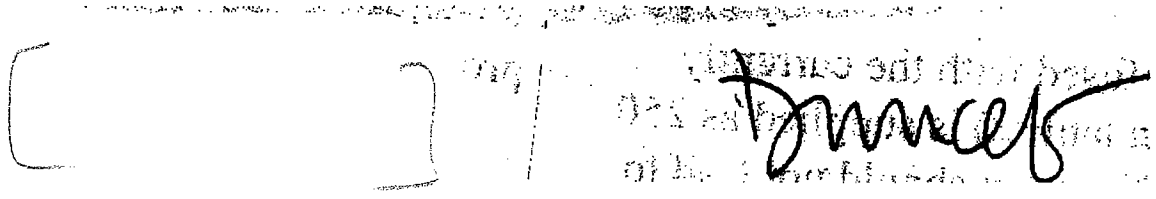
Reference is made to comments in Ranbaxy Pharmaceutical's letter of February 13, 2002, to ANDA 65-080 concerning the use of the modifier "DD" with the proposed proprietary name " [redacted] . Those comments are addressed here because of the inclusion of the "DD" modifier in the proposed name, [redacted]. The modifier "DD" was included in each of the studies for the name [redacted]. When asked to identify the drug name [redacted], 28 of 108 respondents (26 %) did not include the "DD". The omission of "DD" in the study responses raises two concerns. First, that the omission of "DD" by study participants is predictive of the omission of "DD" if a product with this name were to be ordered. Also, the omission of "DD" in the study responses shows a lack of attention to the suffix and diminishes the credence of the sponsor's contention that, "...the addition of the "DD" suffix further distinguishes the marks and avoids any risk of medication error." The fact that study participants identified incorrect medications (Robaxin and Prolixin) when looking at an order for [redacted] contradicts the concept that the use of "DD" would distinguish the products.

Ranbaxy states that, "Clearly, the abbreviation "DD" is not a medical abbreviation." This fact may not be immediately clear to the health practitioner. The reality is that confusion of abbreviations used in ordering medications is both long standing and well documented. The table at this web site summarizes misinterpretations of commonly used abbreviations: http://www.ismp.org/MSAarticles/specialissuetable.html

Ranbaxy states that "DD" will only be a problem if the letters are misread. This scenario is entirely possible as evidenced by the study for [redacted] . In that case, one study participant misread the "DD" as "ll" and returned a response of "Robaxisall". Another participant returned a similar response, "Rolexinall". The finding of misinterpretation of "DD" in a study with such a small number of respondents (108) is highly significant and is predictive of errors if the product were to be marketed as [redacted] In this regard, Ranbaxy's contention that the risk of confusion of "DD" with other letters including "QD" and "OD" is "extremely low" is without merit.

[redacted]

Duricef (Cefadroxil Monohydrate, USP) is indicated for the treatment of patients with infection caused by susceptible strains of the designated organisms in the following diseases: urinary tract infections caused by *E. coli, P. mirabilis,* and *Klebsiella* species; skin and skin structure infections caused by staphylococci and/or streptococci; and pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes* (Group A beta-hemolytic streptococci). Duricef is available as 1 g tablets, 500 mg capsules, and 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL oral suspension. The recommended adult dosage is 1 g to 2 g a day in one or two divided doses. *Duricef* and [redacted] may look similar when written and sound similar when spoken. The names share the letters "D", "r", and "cef" (see writing sample below). These two drug products have other common features. Both products are antibiotics which are available in solid oral dosage forms and both can be given twice a day. The products also share a common strengths of 125 mg and 250 mg. Confusion of these two cephalosporins could result in treatment failure due to lack of susceptibility or incorrect dosing and could lead to resistance.



The tradename "Dispermox" has been proposed by Ranbaxy Laboratories Limited in ANDA 65-080 and was not found to be objectionable by ODS in a review conducted in December of 2001. Dispermox (Amoxicillin Tablets, 200 mg and 400 mg) is indicated for the treatment of infections due to susceptible (only β-lactamase-negative) strains of many gram-positive and gram-negative microorganisms. Dispermox is to be supplied as a 200 mg and 400 mg tablet. The recommended adult dosage is 200 mg or 400 mg twice daily

or three times daily. *Dispermox* and [redacted] may sound similar when spoken. The drug products also look similar because of similarities in trade dress in the labeling submitted, because of similar statements regarding the dissolution of the tablets, and because of common warnings to phenylketonurics. It is important to note that amongst the responses to studies of written [redacted] prescriptions, one respondent provided "Disperox" as an interpretation. "Disperox" is very similar to Dispermox. Although both products are antibiotics, incorrect product selection due to name confusion could lead to treatment failure and/or promotion of anti-microbial resistance.

In addition to the above examples, ODS also has concerns with the use of the prefix, "Disper" in the proposed tradename. We note that you have proposed the labeling statement "DisperDose™" to reference your dispersible dosage form. There is a currently marketed erythromycin product which utilizes the dosage form descriptor "*Dispertab*". The introduction of proprietary names Dispermox and Dispercef increases the chance of confusion with dosage forms DisperDose and Dispertab. In the study for Dispercef, many aberrations of names with the prefix "Disper" were amongst the responses. In the written studies, responses included, *Disperyl, Disperox, Dispersof* (3 responses), *Dispernof, Dispercof, Disperay, Dispericef*, and *Dispercy* (3 responses). In the verbal studies, responses included *Disperseph, Dispercept* (4 responses), *Dispersef,* and *Disperceft.* In every case, the prefix, "Disper" was correctly identified, whereas the suffix was subject to variability. Because of the likelihood for variations in interpretations for names with the "disper" prefix, it is prudent not to introduce a greater chance of error by the proliferation of its use.

In addition, DMETS reviewed the container labels, carton and insert labeling of [redacted]". DMETS has focused on safety issues relating to possible medication errors and has identified several areas of possible improvement, which might minimize potential user error.

- UNIT DOSE CARTON (10's)

  Please include a Phenylalanine statement as seen on your container labels.

- PROFESSIONAL INSERT LABELING (PRECAUTIONS - Information for Patients)

Reference patient information reprinted at the end of the insert. We refer you to 21 CFR 201.57(f)(2) for guidance.

2. CONTAINER:

a. 125 mg – 20s and 100s
250 mg - 20s and 100s

i. Front panel

Differentiate the text, [redacted] ... INGESTION" from the other bolded text on the front panel by using bold italic print and/or a different color. In addition, revise [redacted] to read "TABLET FOR ORAL SUSPENSION".

ii. Right side panel

Revise "Directions" to read as follows:

Directions for Use

[redacted] one tablet [redacted] drink the entire mixture. [redacted] Do not chew or swallow the tablets. The tablets will not rapidly dissolve in your mouth.

b. Blister: 125 mg and 250 mg

We encourage you to decrease the prominence of the "Manufactured by:..." statement and add the text "Dissolve in water" and "Phenyketonurics:..".

c. Strip unit pack: 125 mg and 250 mg

We encourage you to decrease the prominence of the "Manufactured by:..." statement and add the text "Dissolve in water".

d. Sample:

We have no further comments at this time.

3. CARTON:

a. 40s and 100s unit dose blisters

See comments 1(a)(i and ii) under CONTAINER.

b. 40s and 100s unit dose strips

See comments 1(a)(i and ii) under CONTAINER.

c. 10s unit dose – Physician Samples

See comments 1(a)(i and ii) under CONTAINER.

4. INSERT

a. CLINICAL PHARMACOLOGY/Human Pharmacology

Delete the extra spaces appearing between the first and second sentences.

b. PRECAUTIONS (Information for Patients)

Delete the paragraph, "[redacted]..." as previously requested.

c. DOSAGE AND ADMINISTRATION

i. Directions for Cephalexin Tablets for Oral Suspension:

Revise this subsection to read as follows.

[redacted] one tablet in [redacted] drink the entire mixture. [redacted]. Do not chew or swallow the tablets. The tablets will not rapidly dissolve in your mouth.

ii. Pediatric Patients

A) Revise the first dosage table read as follows:

Child's Weight	**Cephalexin Suspension 125 mg/5 mL**	**Cephalexin Suspension 250 mg/5 mL**	**Cephalexin Tablets for Oral Suspension 125 mg***	**Cephalexin Tablets for Oral Suspension 250 mg***
10 kg (22 kg)	...	...	[redacted]* to 1 tablet q.i.d.	
...				[redacted]* to 1 tablet q.i.d.
...				

B) Relocate the word "or" to appear in the center between the tablets, instead of on the side of the tables.

C) There are numerous errors in both tables for the administration of Cephalexin Suspension. Please correct.

D) Revise your asterisk statement to read, "*

iii. After further review we request that you provide a "Patient Information Sheet" with "Directions for Use" instead of a "Patient Package Insert".

PATIENT'S DIRECTIONS FOR USE

Dissolve the Cephalexin Tablets for Oral Suspension in water before you take it.

1. Remove one tablet from the bottle
2. Place the tablet in
3. Swirl or stir until
4. Drink the mixture immediately after mixing. (The mixture is light yellow colored and has a fruity flavor.)
5. Be sure to drink the entire mixture.
6. Rinse the
7.

DO NOT CHEW or SWALLOW the Cephalexin Tablets for Oral Suspension whole. The tablets will not rapidly dissolve in your mouth.

Take all of the medicine as recommended by your doctor or other health care provider.

Do not mix with any liquid other than water.

vi. HOW SUPPLIED

Revise " to read "unit dose pack".

Please revise your container labels and insert labeling, as instructed above, and in final print or draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 25		X	
Is this name different than that used in the Orange Book?*Cephalexin tablets	*		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to DMETS? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified? *The proposed names were found to be unacceptable. DMETS comments are in this review.	*		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?	X		
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the			

FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	x		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	x		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		**X**	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

APPEARS THIS WAY
ON ORIGINAL

NOTE TO BIO. REVIEWER:

The firm revised the CLINICAL PHARMACOLOGY section to include some of the pharmacokinetic data of their [redacted] tablet dosage form. Is this information accurate?

> Following a dose of Ranbaxy's [redacted] tablets, equivalent to 500 mg of cephalexin, the average peak serum level of 15.25 mcg/mL was obtained at 1 hour. Following a dose of conventional cephalexin suspension equivalent to 500 mg of cephalexin, the average peak serum level of 14.67 mcg/mL was obtained a 1 hour. Measurable levels were present 6 hours after administration of Ranbaxy's [redacted]

NOTE TO THE CHEMIST

The firm revised their "DOSAGE AND ADMINISTRATION/Directions for [redacted] tablets" section to read, [redacted] Do not chew or swallow the tablets. [redacted]

> Did Ranbaxy provide data to support their revision? [Note, previously the firm recommended, " [redacted]

This change in dispersion volume is ok, since a suspension and not a solution is formed. [This is same answer as Ruth did for 65-080].

Yanping

NOTE TO THE CHEMIST [From previous review]

1. In the PRECAUTIONS section, Ranbaxy indicates that their 125 mg and 250 mg [redacted] tablets contains phenylalanine 2.8 mg and 5.6 mg, respectively. Is this accurate?

2. Did Ranbaxy provide data to support their statement, ". [redacted] tablets for a uniform dispersion when dispersed in 2 to 4 ounces [1/4 – 1/2] of water"?

3. The firm has proposed [redacted] container labels. Although we do not approve [redacted] container labels, do you have any guidelines for storage recommendations of [redacted] containers, or is what they printed sufficient?

4. The firm indicates that their unit-dose blister packages are child-resistant.
   - Is this information accurate?
   - If so, is the blister child-resistant or carton?

5. The firm included " [redacted] " in your list of components on page 2414b, however, it is not listed as an inactive ingredients. Should " [redacted] be listed as an inactive ingredient?

FOR THE RECORD:

1. Keflex® (cephalexin) pulvules® NDA 50-405/S-090 and oral suspension NDA 50-406/S-012, Approved May 15, 1996.

2. There are no patents or exclusivities for this drug product.

3. Manufacturer:

   Ranbaxy, India.
   [B1.1, p. 2535]

4. Package Size:

   RLD/pulvules 250 mg– 20s and 100s
   RLD/pulvules 500 mg- 20s and 100s
   RLD/suspension 125 mg/5 mL –100 mL
   RLD/suspension 250 mg/5 mL – 100 mL

   ANDA
   125 mg –20s, 100s
   - blister packs 40s, 100s
   - strip packs 40s, 100s
   250 mg – 20s, 100s
   - blister packs 40s, 100s
   - strip packs 40s, 100s

5. Storage/dispensing recommendations

   Store at controlled room temperature 15o to 30oC (59o to 86oF)(see USP).
   Dispense in a tight, light-resistant container.

6. Container/Closure:

   ANDA
   125 mg –20s, 100s
   - high density, white, round with CRC
   - blister packs 40s, 100s
   - child-resistant laminate/paper/ aluminum foil/ film clear
   - strip packs 40s, 100s
   aluminum foil/ laminate
   250 mg –20s, 100s
   - high density, white, round with CRC
   - blister packs 40s, 100s
   - child-resistant laminate/paper/ /aluminum foil/
   - strip packs 40s, 100s
   aluminum foil/ laminate

   [Vol. B1.3, p.3002]

7. The list of inactives in the DESCRIPTION section is consistent with the firm's components and composition statement. [However, see comment under DESCRIPTION].
   [Vol. B1.1, p.2414]

8. The firm's physical description of each [redacted] tablet in the HOW SUPPLIED section is consistent with their finished dosage form statements, except the flavor. [See comment under HOW SUPPLIED].
[Vol. B1.3, p.3534, 3512]

9. Patient Package Insert

a. An Office decision was made to request Ranbaxy's ANDA 65-080 to provide a "Patient Information Sheet" with "Directions for Use" instead of a "[redacted]
The text for the "Directions for Use" was reviewed by Dr. Hixon in response to the Labeling Consult. An agreement was made to replace ".[redacted]

b. This decision applies to Ranbaxy's ANDA 65-100.

c. DMETS was previously forwarded a copy the firm's proposed PPI and had the following comments:

PATIENT INFORMATION

Revise the statement, "[redacted]

Revise the WARNINGS section so that it uses language that is easily understood by the layperson.

[NOTE: DMETS also requested that the firm provide separate instructions for the patient in a response to our previous labeling consult].
We will not forward DMETS comments to Ranbaxy due to the Office decision that the firm to provide a "Patient Information Sheet" instead of a PPI.

10. DOSAGE AND ADMINISTRATION section

The updated text requested in this review is from Dr. Hixon's response to the Labeling Consult for ANDA 65-080.
[See consult response to Ranbaxy's ANDA 65-080].

Date of Review: 7/11/02 [updated 10/7/02]

Date of Submission: 613/02

Primary Reviewer:
Jacqueline Council, Pharm.D. Date:
Jacqueline Council Pharm

Acting Team Leader:
Captain Lillie Golson Date: 10/11/02

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cc: ANDA: 65-100
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
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Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	65-100
Date of Submission:	- January 9, 2002 - March 12, 2002
Applicant's Name:	Ranbaxy Pharmaceuticals Inc.
Established Name:	Cephalexin Tablets [redacted] 125 mg and 250 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. The Office of Drug Safety [ODS] does not object to the use of the name "DisperDose", for your proposed " [redacted] dosage formulation. However, ODS does not recommend the use of your proposed proprietary name" [redacted] for the reasons listed below.

      i. [redacted]

      In reviewing the proposed name, " [redacted] the primary concerns were related to one look-alike and sound-alike name that already exists in the U.S. marketplace: *Sporanox*. We conducted prescription studies to simulate the prescription ordering process in order to detect potential medication errors. Our study did not confirm confusion between " [redacted] and "Sporanox." ***However, one participant from the outpatient written study commented the proposed name looks similar to Sporanox.***

      One participant from the written study commented that the proposed name looks similar to Sporanox. Not only does the proposed product [redacted] and the currently marketed product, "Sporanox", share the same prefix, "Spor," but the endings [redacted] and "ox" sound and look alike too (see below). Moreover, Sporanox (itraconazole), an anti-fungal agent, and the Sporidex share overlapping dosage form (oral) and dosing interval (BID). Although the strengths do not overlap, a "5" of "250 mg" could be misinterpreted as "0" when scripted. Therefore, a prescription for "Sporanox 200 mg BID" could be misinterpreted as " [redacted] 250 mg BID" (see below). The omission of Sporanox could be detrimental in patients with life-threatening fungal infections. The inadvertent ingestion of Sporanox could result in serious hepatotoxicity. In addition, post-marketing experience with the drug products, "Serzone" and "Seroquel," has demonstrated that having *different suffixes does not eliminate* the potential for error. As of November 2001, the Agency has received twenty-three (23) medication error reports involving Serzone and Seroquel. Lastly, the addition of the modifier DD will not make it look less like Sporanox, because the proposed product, [redacted] DD, and Sporanox share too many similarities as mentioned above. Moreover, 30 of 52 (58%) respondents of the written studies did not provide a modifier with the proposed name, [redacted]

Sporanox 200mg BID

BID

b. "DD"

In order to express the dosage formulation, dispersible tablets, the modifier "DD", which is interpreted as "DisperDose," was added to the proposed name, Sporidex. However, this modifier, "DD", is misleading for the following reasons:

Although the modifier, "DD," may have been intended to represent the "DisperDose" version of [redacted], this implication is not obvious due to the misinterpretation of the modifier, "DD" as "double dose." Furthermore, the modifier "DD" could be misinterpreted as "OD" (right eye) or "QD" (once daily) when scripted. In fact, one respondent from the written study provided "QD" as an interpretation instead of "DD." This error could lead to inadequate dosing of Sporidex. Other interpretations in the studies were "AD" (right ear), "RD" (renal disease), and "BD." The "BD" could be misinterpreted as "BID" and lead to inadequate dosing of [redacted] in some instances.

Currently, no approved prescription drug product that contains the modifier, "DD" in its proprietary name exists in the current market place. Consequently, health professionals are not familiar with the modifier, "DD," and may not interpret the modifier, "DD", as "DisperDose."

c. Your proposed proprietary names "[redacted]™ and "[redacted]™" have been forwarded to the Office of Drug Safety for their review and comment. We will inform you of their findings when available. We will not ask for labels and labeling in final print until we receive input on the acceptability of these proposals.

d. We acknowledge your comment that your drug product does not comply with the USP monograph for Cephalexin Tablets. We recommend that you contact the USP regarding your "proposed dosage form" and "established name". Please keep our office apprised of recommendations from the USP including recommendations regarding the established name of your drug product.

e. We received the samples of your unit-dose blisters and strips. We have no further comment at this time.

2. CONTAINER:

a. General Comments

i. We acknowledge your statement informing us that you have submitted child resistant strip packs in attachment 4. However, attachment 4 contains a patient package insert and carton labeling. Please submit in your next amendment.

ii. Please clarify which of your package configurations are child resistant, the "smaller size unit-dose blisters" or the "larger unit-dose strips"?

iii. We recommend relocating "DisperDose" to appear next to the proprietary name, [(e.g., proprietary name (DisperDose)].

3. CARTON:

See comments under CONTAINER.

4. INSERT

a. PRECAUTIONS (Information for Patients)

i. We acknowledge the addition of the text, "[redacted]" in this subsection. This text is not in the insert labeling of the reference listed drug. Please delete.

ii. Include a statement indicating that your "patient package insert" is located at the end of your insert labeling. We refer your 21 CFR 201.57(f)(2).

b. DOSAGE AND ADMINISTRATION (Pediatric Patients)

i. Relocate and properly align "Cephalexin [redacted]Tablets" to appear as the heading immediately above the [redacted] tablets administration column.

ii. Revise your dosage table to appear in a similar format as the reference listed drug.

For example:

Child's Weight	Cephalexin Suspension 125 mg/5 mL	Cephalexin Suspension 250 mg/5 mL	Dispersible Tablets 125 mg	[redacted] Tablets 250 mg
10 kg (22 kg)	... qid	...	...	...
...				
...				

Child's Weight	Cephalexin Suspension 125 mg/5 mL	Cephalexin Suspension 250 mg/5 mL	Dispersible Tablets 125 mg	[redacted] Tablets 250 mg
10 kg (22 kg)	... bid	...	...	...
...				
...				

iii. Dosage Table

- Include all dosage and administration information for each strength of the suspension dosage form
- Include only the administration information appropriate for your 125 mg and 250 mg ——— tablet dosage form

c. Patient Package Insert

Your proposed Patient Package Insert for your other dispersible tablet dosage form, [ANDA 65-080] was forwarded to the Division of Anti-Infective Drug Products for review and comment. We have no further comments on your proposed Patient Package Insert at this time.

Please revise your container labels and insert labeling, as instructed above, and submit 4 draft copies of each. We will not request final printed labeling until resolution of your proposed proprietary and established name issues have been resolved.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?	X		
Has the name been forwarded to OPDRA? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified? *to be sent	*		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?	X		
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	x		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	x		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be			

used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTE TO BIO. REVIEWER:

The firm revised the CLINICAL PHARMACOLOGY section to include some of the pharmacokinetic data of their [redacted] tablet dosage form. Is this information accurate?

> Following a dose of Ranbaxy's [redacted] tablets, equivalent to 500 mg of cephalexin, the average peak serum level of 15.25 mcg/mL was obtained at 1 hour. Following a dose of conventional cephalexin suspension equivalent to 500 mg of cephalexin, the average peak serum level of 14.67 mcg/mL was obtained a 1 hour. Measurable levels were present 6 hours after administration of Ranbaxy's [redacted]

NOTE TO THE CHEMIST

The firm revised their "DOSAGE AND ADMINISTRATION/Directions for [redacted] tablets" section to read, [redacted] Do not chew or swallow the tablets. [redacted]

> Did Ranbaxy provide data to support their revision? [Note, previously the firm recommended, " [redacted]

NOTE TO THE CHEMIST [From previous review]

1. In the PRECAUTIONS section, Ranbaxy indicates that their 125 mg and 250 mg [redacted] tablets contains phenylalanine 2.8 mg and 5.6 mg, respectively. Is this accurate?

2. Did Ranbaxy provide data to support their statement, ". [redacted]

3. The firm has proposed [redacted] container labels. Although we do not approve [redacted] container labels, do you have any guidelines for storage recommendations of [redacted] containers, or is what they printed sufficient?

4. The firm indicates that their unit-dose blister packages are child-resistant.
   - Is this information accurate?
   - If so, is the blister child-resistant or carton?

5. The firm included " [redacted] " in your list of components on page 2414b, however, it is not listed as an inactive ingredients. Should " [redacted] " be listed as an inactive ingredient?

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD:

1. Keflex® (cephalexin) pulvules® NDA 50-405/S-090 and oral suspension NDA 50-406/S-012, Approved May 15, 1996.

2. There are no patents or exclusivities for this drug product.

3. Manufacturer:

   Ranbaxy, India.
   [B1.1, p. 2535]

4. Package Size:

   RLD/pulvules 250 mg– 20s and 100s
   RLD/pulvules 500 mg- 20s and 100s
   RLD/suspension 125 mg/5 mL –100 mL
   RLD/suspension 250 mg/5 mL – 100 mL

   ANDA
   125 mg –20s, 100s
   - blister packs 40s, 100s
   - strip packs 40s, 100s
   250 mg – 20s, 100s
   - blister packs 40s, 100s
   - strip packs 40s, 100s

5. Storage/dispensing recommendations

   Store at controlled room temperature [redacted] (see USP).
   Dispense in a tight, light-resistant container.

6. Container/Closure:

   ANDA
   125 mg –20s, 100s
   - high density, white, round with CRC
   - blister packs 40s, 100s
   - child-resistant laminate/paper/[redacted] aluminum foil/ [redacted] film clear
   - strip packs 40s, 100s
   [redacted] aluminum foil [redacted] laminate
   250 mg –20s, 100s
   - high density, white, round with CRC
   - blister packs 40s, 100s
   - child-resistant laminate/paper/[redacted] aluminum foil/ [redacted] film clear
   - strip packs 40s, 100s
   [redacted] /aluminum foil/ [redacted] laminate

   [Vol. B1.3, p.3002]

7. The list of inactives in the DESCRIPTION section is consistent with the firm's components and composition statement. [However, see comment under DESCRIPTION].
   [Vol. B1.1, p.2414]

8. The firm's physical description of each [redacted] tablet in the HOW SUPPLIED section is consistent with their finished dosage form statements, except the flavor. [See comment under HOW SUPPLIED].
   [Vol. B1.3, p.3534, 3512]

9. Labeling Comments

- We note that you have proposed two different types of unit dose packaging (blisters and strips). In addition, we note that the size of your labels of your unit-dose strips is significantly larger than your unit dose blisters. Are you intending to target a specific market with each package configuration and size? Please comment on your marketing intent and provide an explanation of the difference in packaging size of your blister and strip.

  Firm's response: The child resistant blister pack and strip pack have been developed for direct marketing whereas the non child resistant strip pack is meant for dispensing in hospitals.

- Once your [redacted] tablet is dispersed in water, how do you refer to the mixture, [i.e., mixture or suspension]?

  Firm's response: We refer to the mixture as dispersion

- We note that you indicate that your drug product will not disperse in the mouth if inadvertently swallowed whole. Have the effects of inadvertent chewing been also studied?

  Firm's response: The recommended mode of administration of [redacted] tablets is by dispersing in a quantity of water. If a tablet is inadvertently swallowed whole, the tablet will form a soft mass, which will disintegrate with moisture. The tablet does not swell and will not case difficulty in swallowing if there is exposure to small amount of moisture. If the cephalexin [redacted] tablet is inadvertently chewed it will form a soft mass.

- Can your [redacted] tablets be administered with alternate liquids for pediatric patients, i.e. ... in formula, milk, fruit juice, water, ginger ale or cold drinks?

  Firm's response: Since no studies have been performed with the [redacted] tablet administrated with alternate liquids, only the recommendation of dispersion in water is included in the directions.

Date of Review: April 22, 2002

Date of Submission: January 9, 2002
March 12, 2002

Primary Reviewer:
Jacqueline Council, Pharm.D.

Date: 4-29-02

Acting Team Leader:
Captain Lillie Golson

Date: 4/29/02

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cc: ANDA: 65-100
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
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Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	65-100
Date of Submission:	July 19, 2001
Applicant's Name:	Ranbaxy Pharmaceuticals Inc.
Established Name:	Cephalexin Tablets [redacted], 125 mg and 250 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   a. Your proposed proprietary name ([redacted]) and your dose form trademark (DisperDose™) have been forwarded to the Office of Post-Marketing Drug Risk Assessment for their review and comment. We will inform you of their findings when available. We will not ask for labels and labeling in final print until we receive input on the acceptability of these proposals.

   b. We note that no product is currently marketed nor is there a USP monograph with the established name that you have proposed with this application. Does your drug product meet the USP monograph for Cephalexin Tablets? If so, please revise labels and labeling accordingly. If not please present data to support the concept that this product does not meet the monograph and should therefore have a new established name.

   c. In your next amendment submit 4 [redacted] tablets in unit dose blisters, 4 [redacted] tablets in unit dose strips and 4 [redacted] tablets in a container and/or bag.

2. CONTAINER:

   a. General Comment

      We note that you have proposed two different types of unit dose packaging (blisters and strips). In addition, we note that the size of your labels of your unit-dose strips is significantly larger than your unit dose blisters. Are you intending to target a specific market with each package configuration and size? Please comment on your marketing intent and provide an explanation of the difference in packaging size of your blister and strip.

   b. 125 mg – 20s and 100s
      250 mg - 20s and 100s

      i. Relocate the text "Phenylketonurics..." to appear immediately following the, [redacted] tablet contains..." statement. [If sufficient space is not available, relocate your "Manufactured for..." and "Manufactured by..." statements to other side panel].

      ii. Include directions for administration of your [redacted] tablets.

   c. Blister: 125 mg and 250 mg

      Revise " [redacted] to read "tablet".

   d. Strip unit pack: 125 mg and 250 mg

ii. Revise "[redacted]" to read "tablet".

e. Sample:

We do not approve sample container labels. However, we recommend the following revisions:

Revise "[redacted]" to read "**PHYSICIAN SAMPLE**".

f. [redacted] container label:

We do not approve [redacted] container labels. However, we recommend the following revisions:

i. We encourage the inclusion of your proposed proprietary name.

ii. We encourage you to increase the prominence of the storage recommendations.

iii. We encourage you to include the recommended conditions of relative humidity.

iv. We note that your "CAUTION:... " statement indicates that the [redacted] tablets are for "manufacturing or processing". Please comment on how the dispersible tablets are to be further manufactured or modify this statement for accuracy.

v. We encourage the inclusion of your "Manufactured for: ..." statement as seen on your carton and insert labeling.

3. CARTON:

a. General Comment

Relocate the statement "**THIS UNIT DOSE PACKAGE IS NOT CHILD-RESISTANT"** to appear on the side panel in bold upper case print following the "USUAL DOSAGE: ..." statement on your non-child resistant cartons.

b. 40s and 100s unit dose blisters

See comment 2(a)(ii) under CONTAINER.

c. Sample

See comment 2(d) under CONTAINER.

4. INSERT

a. GENERAL COMMENT

Your ANDA was accepted for filling with an approved petition for a "[redacted] tablet" dosage form, therefore you may propose labeling revisions that are specific to the [redacted] tablet dosage form.

b. DESCRIPTION

i. We note that your included [redacted] in your list of components on page 2414b, however, it is not listed as an inactive ingredients. Please comment and/or revise.

ii. Revise the molecular weight to read, "365.41". We refer you to USP 24.

c. CLINICAL PHARMACOLOGY (Human Pharmacology)

i. Revise this section to include your drug product specific pharmacokinetic data.

ii. First paragraph –

... administration. It has been reported that following doses of cephalexin 250 mg, 500 mg and 1 g, ... at 1 hour. Following doses of *cephalexin [illegible] tablets* of 125 mg and 250 mg ... _____(*NOTE: include your [illegible] tablet data*). In addition, it has been reported that measurable levels were present 6 hours after administration of cephalexin. Measurable levels were present ____(*NOTE: include your [illegible] tablets data*) after administration of *cephalexin [illegible] tablets.*

d. DOSAGE AND ADMINISTRATION

i. General Comments

A) Since your drug product can not provide all doses possible for the reference listed drug, add an explanatory statement. We offer the following as an example:

All recommended dosages for cephalexin are included in this section for informational purposes only. The 125 mg [illegible] tablet is appropriate only for a 125 mg dose and the 250 mg [illegible] tablet is appropriate only for a 250 mg dose.

If you prefer, you may propose another statement.

B) Once your dispersible tablet is dispersed in water, how do you refer to the mixture, [i.e. dispersed mixture or suspension]?

ii. Revise to read, "Cephalexin [illegible] tablets are administered orally after complete dispersion in water".

iii. Revise [illegible] to read "**Directions for [illegible] Tablets**".

iv. We note that you indicate that your drug product will not disperse in the mouth if inadvertently swallowed whole. Have the effects of inadvertent chewing been also studied?

v. Pediatric Patients

A) We note that you indicate that ¼ or ½ or your [illegible] tablets should be administered for certain pediatric doses. Are your [illegible] tablets appropriately scored to provide a ¼ or ½ [illegible] tablet dose? If so. provide an additional subsection titled "**Directions for [illegible] Tablets for Pediatric Patients".** [NOTE: instructions should include information on breaking the tablet and whether a smaller volume of water is to be used for dispersion].

B) Can your [illegible] tablets be administered with alternate liquids for pediatric patients, i.e. ... in formula, milk, fruit juice, water, ginger ale or cold drinks?

C) Table

Revise "[illegible]" to read "[illegible] tablets".

e. HOW SUPPLIED

i. See comment 4(b)(i).

ii. Indicate that your tablets are "unscored".

iii. We encourage you to include a "Dispense in..." statement.

iv. Revise "[redacted]" to read "capsule shaped".

Please revise your container labels and insert labeling, as instructed above, and submit 4 draft copies of each. In addition, submit 4 dispersible tablets in unit dose blisters, 4 dispersible tablets in unit dose strips and 4 dispersible tablets in a container and/or bag. We will not request final printed labeling until resolution of your proposed proprietary and established name issues have been resolved.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?	X		
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.	X		
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?	X		
Has the name been forwarded to OPDRA? YES If so, what were the recommendations? If the name was unacceptable, has the firm been notified? *to be sent	*		
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?	X		
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	x		
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	x		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

APPEARS THIS WAY
ON ORIGINAL

NOTE TO THE CHEMIST

1. In the PRECAUTIONS section, Ranbaxy indicates that their 125 mg and 250 mg [redacted] tablets contains phenylalanine 2.8 mg and 5.6 mg, respectively. Is this accurate?

2. Did Ranbaxy provide data to support their statement, "..[redacted]

3. The firm has proposed [redacted] container labels. Although we do not approve [redacted] container labels, do you have any guidelines for storage recommendations of [redacted] containers, or is what they printed sufficient?

4. The firm indicates that their unit-dose blister packages are child-resistant.
   - Is this information accurate?
   - If so, is the blister child-resistant or carton?

5. The included " [redacted] " in your list of components on page 2414b, however, it is not listed as an inactive ingredients. Should " [redacted] be listed as an inactive ingredient?

OK per REA 11/26/01

FOR THE RECORD:

1. Keflex® (cephalexin) pulvules® NDA 50-405/S-090 and oral suspension NDA 50-406/S-012, Approved May 15, 1996.

2. There are no patents or exclusivities for this drug product.

3. Manufacturer:

   Ranbaxy, India.
   [B1.1, p. 2535]

4. Package Size:

   RLD/pulvules 250 mg– 20s and 100s
   RLD/pulvules 500 mg- 20s and 100s
   RLD/suspension 125 mg/5 mL –100 mL
   RLD/suspension 250 mg/5 mL – 100 mL

   ANDA
   125 mg –20s, 100s
   - blister packs 40s, 100s
   - strip packs 40s, 100s
   250 mg – 20s, 100s
   - blister packs 40s, 100s
   - strip packs 40s, 100s

5. Storage/dispensing recommendations

   Store at controlled room temperature [redacted] (see USP).
   Dispense in a tight, light-resistant container.

6. Container/Closure:

   ANDA
   125 mg –20s, 100s
   - high density, white, round with CRC
   - blister packs 40s, 100s
   - child-resistant laminate/paper/[redacted]/aluminum foil/[redacted], film clear
   - strip packs 40s, 100s
   - [redacted] aluminum foil/[redacted] laminate
   250 mg –20s, 100s
   - high density, white, round with CRC
   - blister packs 40s, 100s
   - child-resistant laminate/paper/[redacted]/aluminum foil/[redacted] film clear
   - strip packs 40s, 100s
   - [redacted] aluminum foil/[redacted] laminate

   [Vol. B1.3, p.3002]

7. The list of inactives in the DESCRIPTION section is consistent with the firm's components and composition statement. [However, see comment under DESCRIPTION].
   [Vol. B1.1, p.2414]

8. The firm's physical description of each dispersible tablet in the HOW SUPPLIED section is consistent with their finished dosage form statements, except the flavor. [See comment under HOW SUPPLIED].
   [Vol. B1.3, p.3534, 3512]

Date of Review: 9/10/01

Date of Submission: 7/19/01

Primary Reviewer:
Jacqueline Council, Pharm.D.

Date: 9-13-01

Team Leader:

Date: 9/14/01

cc: ANDA: 65-100
DUP/DIVISION FILE
HFD-613/JCouncil/CHoppes (no cc)
V:\FIRMSNZ\RANBAXY\LTRS&REV\65100na1.l.doc
Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-100

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. [redacted]

2. **ANDA # 65-100**

3. **NAME AND ADDRESS OF APPLICANT:**
Ranbaxy Laboratories Limited
Sector 18
Udyog Vihar Industrial Area
Gurgaon-122 011 India

US Agent
Shirley Ternyik
Ranbaxy Pharmaceuticals Inc.
600 College Road East
Princeton, NJ 08540

4. **LEGAL BASIS FOR SUBMISSION:**
RLD: Keflex® (NDA #62-117, Eli Lilly)
Patent certification and exclusively statement are provided on p. 12.

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Cephalexin [redacted] Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

8. **AMENDMENTS AND OTHER DATES:**
Ranbaxy Laboratories Limited
7-19-2001 Submission of ANDA

FDA:
8-23-2001 Acknowledgment (acceptable for filing 7/25/01)

10. **PHARMACOLOGICAL CATEGORY:** Antibacteriac

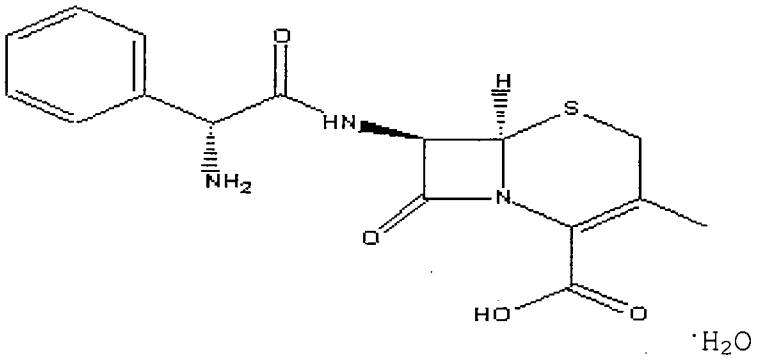
11. **Rx or OTC:** R_x

12. **RELATED IND/NDA/DMF(s):**
Under #37 in this review.

13. **DOSAGE FORM**: Tablets (Dispersible)

14. **POTENCIES**: 125 mg and 250 mg

15. **CHEMICAL NAME AND STRUCTURE**:
5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(aminophenylacetyl)amino]-3-methyl-8-oxo,monohydrate, [6R-[$6\alpha, 7\beta(R^*)$]]
Empirical formula of $C_{16}H_{17}N_3O_4S.H_2O$
Molecular weight 365.41.



CAS: 23325-78-2 (Monohydrate)

16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:
- EERs: issued on 8/23/01
- DMF(" status: adequate (7/2/01)
- Labeling review: 1st round—Deficiencies (9/13/01)
- Bio-review: 250 mg is bioequivalent to RLD; The waiver of *in vivo* bioequivalence study for 125 mg is granted (9/7/01)
- MV: pending
- CMC deficiencies under item 38.

18. **CONCLUSIONS AND RECOMMENDATIONS**:
Not Approvable (~~MINOR~~)
FAX

19. **REVIEWER**: Yanping Pan Yaping Pan **DATE COMPLETED**: 11/9/01

Redacted 34

Page(s) of trade secret and /or confidential commercial information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.2**

2. **ANDA # 65-100**

3. **NAME AND ADDRESS OF APPLICANT:**
Ranbaxy Laboratories Limited
Sector 18
Udyog Vihar Industrial Area
Gurgaon-122 011 India

US Agent
Abha Pant
Ranbaxy Pharmaceuticals Inc.
600 College Road East
Princeton, NJ 08540

4. **LEGAL BASIS FOR SUBMISSION:**
RLD: Keflex® (NDA #62-117, Eli Lilly)
Patent certification and exclusively statement are provided on p. 12.

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Cephalexin [redacted] Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**
Ranbaxy Laboratories Limited
7-19-2001 Submission of ANDA
1-9-2002 Minor Amendment
1-11-2002 Amendment to 1-9-2002 Amendment

FDA:
8-23-2001 Acknowledgment (acceptable for filing 7/25/01)
12-12-2001 CR#1

10. **PHARMACOLOGICAL CATEGORY:** Antibacterial

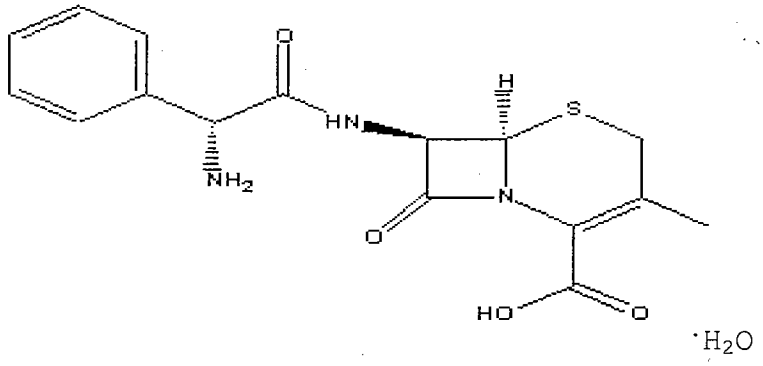
11. **Rx or OTC:** R_x

12. **RELATED IND/NDA/DMF(s):**
Under #37 in this review.

13. **DOSAGE FORM:** Tablets (Dispersible)

14. **POTENCIES:** 125 mg and 250 mg

15. **CHEMICAL NAME AND STRUCTURE:**
5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(aminophenylacetyl)amino]-3-methyl-8-oxo,monohydrate, [6R-[$6_\alpha, 7_\beta(R^*)$]]
Empirical formula of $C_{16}H_{17}N_3O_4S.H_2O$
Molecular weight 365.41.



CAS: 23325-78-2 (Monohydrate)

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**
- EERs: Acceptable (12/21/01)
- DMF(# ——— status: adequate (2/5/02)
- Labeling review: 1st round—Deficiencies (9/13/01)
- Bio-review: 250 mg is bioequivalent to RLD; The waiver of *in vivo* bioequivalence study for 125 mg is granted (9/7/01)
- MV: sent out 2/5/02

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Approvable; pending acceptable labeling

19. **REVIEWER:** Yanping Pan
DATE COMPLETED: 2/5/02

Redacted 37

Page(s) of trade secret and /or confidential commercial information

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.3**

2. **ANDA # 65-100**

3. **NAME AND ADDRESS OF APPLICANT:**
Ranbaxy Laboratories Limited
Sector 18
Udyog Vihar Industrial Area
Gurgaon-122 011 India

US Agent
Abha Pant
Ranbaxy Pharmaceuticals Inc.
600 College Road East
Princeton, NJ 08540

4. **LEGAL BASIS FOR SUBMISSION:**
RLD: Keflex® (NDA #62-117, Eli Lilly)
Patent certification and exclusively statement are provided on p. 12.

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** N/A

7. **NONPROPRIETARY NAME:** Cephalexin [redacted] Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**
Ranbaxy Laboratories Limited

7-19-2001	Submission of ANDA
1-9-2002	Minor Amendment
1-11-2002	Amendment to 1-9-2002 Amendment
6-13-2002	Labeling Amendment

FDA:

8-23-2001	Acknowledgment (acceptable for filing 7/25/01)

10. **PHARMACOLOGICAL CATEGORY:** Antibacterial

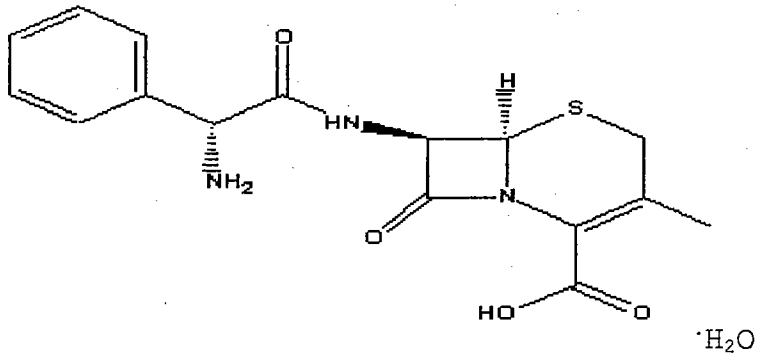
11. **Rx or OTC:** R_x

12. **RELATED IND/NDA/DMF(s):**
Under #37 in this review.

13. **DOSAGE FORM:** Tablets (Dispersible)

14. **POTENCIES:** 125 mg and 250 mg

15. **CHEMICAL NAME AND STRUCTURE:**
5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(aminophenylacetyl)amino]-3-methyl-8-oxo,monohydrate, [6R-[6α,7β(R*)]]
Empirical formula of $C_{16}H_{17}N_3O_4S.H_2O$
Molecular weight 365.41.



CAS: 23325-78-2 (Monohydrate)

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**
- EERs: Acceptable (12/21/01)
- DMF(s) status: adequate (7/25/02)
- Labeling review: Deficient
- Bio-review: 250 mg is bioequivalent to RLD; The waiver of *in vivo* bioequivalence study for 125 mg is granted (9/7/01)
- MV: sent out 2/5/02

18. **CONCLUSIONS AND RECOMMENDATIONS:**
Approvable; pending acceptable labeling

19. **REVIEWER:** Yanping Pan

DATE COMPLETED: 7/25/02

Redacted 37

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. **CHEMISTRY REVIEW NO.3a**

2. **ANDA # 65-100**

3. **NAME AND ADDRESS OF APPLICANT:**
Ranbaxy Laboratories Limited
Sector 18
Udyog Vihar Industrial Area
Gurgaon-122 011 India

US Agent
Abha Pant
Ranbaxy Pharmaceuticals Inc.
600 College Road East
Princeton, NJ 08540

4. **LEGAL BASIS FOR SUBMISSION:**
RLD: Keflex® (NDA #62-117, Eli Lilly)
Patent certification and exclusively statement are provided on p. 12.

5. **SUPPLEMENT(s):** N/A

6. **PROPRIETARY NAME:** Panixine™

7. **NONPROPRIETARY NAME:** Cephalexin Tablets for Oral Suspension

8. **SUPPLEMENT(s) PROVIDE(s) FOR:** N/A

9. **AMENDMENTS AND OTHER DATES:**
Ranbaxy Laboratories Limited

7-19-2001	Submission of ANDA
1-9-2002	Minor Amendment
1-11-2002	Amendment to 1-9-2002 Amendment
6-13-2002	Labeling Amendment
7-3-2003	**Telephone Amendment (subject this review)**
9-4-2003	**Telephone Amendment (subject this review)**

10. **PHARMACOLOGICAL CATEGORY:** Antibacterial

11. **Rx or OTC:** R_x

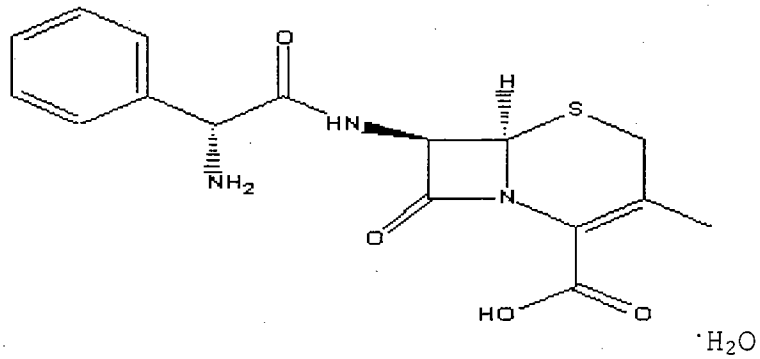
12. **RELATED IND/NDA/DMF(s):**

Under #37 in this review.

13. **DOSAGE FORM**: Tablets (Dispersible)

14. **POTENCIES**: 125 mg and 250 mg

15. **CHEMICAL NAME AND STRUCTURE**:
5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[(aminophenylacetyl)amino]-3-methyl-8-oxo,monohydrate, [6R-[6α,7β(R*)]]
Empirical formula of $C_{16}H_{17}N_3O_4S.H_2O$
Molecular weight 365.41.



CAS: 23325-78-2 (Monohydrate)

16. **RECORDS AND REPORTS**: N/A

17. **COMMENTS**:

X EERs: Acceptable (12/21/01)

X DMF(, status: adequate (5/29/03)

X Labeling review: Deficient

X Bio-review: 250 mg is bioequivalent to RLD; The waiver of *in vivo* bioequivalence study for 125 mg is granted (9/7/01)

X MV: sent out 2/5/02

Note from CR#3a:
Concerns about the volume of water needed for complete dispersion of the tablet and complete delivery of the dose, and the associated labeling, have been the subject of many communications within the office and with the firm. It was agreed that the firm would be asked to determine the percent label claim of dose delivered to the subject when the tablet

is dispersed in 10 mL (~2 teaspoons) of water and administered, followed by a rinse of 5-10 mL. If the response was greater than 95%, then the following labeling recommendation would be made, "dispersed in approximately 2 teaspoons, and rinsed with approximately the same volume."

In the telephone call (6/25/03) the Agency requested Ranbaxy to provide additional data in order to determine the percent of the label claim for the dose delivered to a subject when a tablet is dispersed in 10 mL's of water .

In response to our request (6/25/03 TeleCon), the firm provided data on tablets dispersed in 10 mL and 15 mL of water (7/3/03 Telephone Amendment). The dispersion was discarded, and the residual contents sticking to the container were assayed. Twenty tablets of each strength were assayed. The average and range of the results are summarized in the table below.

Strength	Dispersion in 10 mL/ assay of residue left after discarding the dispersion	Dispersion in 15 mL/ assay of residue left after discarding the dispersion
125 mg	Avg: 1.00% Range: [redacted]	Avg: 0.60% Range: [redacted]
250 mg	Avg: 1.10% Range: [redacted]	Avg: 0.70% Range: [redacted]

The amount of residue is small, and the data supports the labeling instructions, "dispersed in approximately 2 teaspoons, and rinsed with approximately the same volume." Acceptable.

In addition, the agency requested Ranbaxy to provide a signed commitment to provide the following information in "Supplement-Expedited Review Requested" submission:

a) Executed batch records reflecting the manufacture of scored tablets and complete Certificate of Analysis (COA) for each batch
b) A dissolution profile comparing the differing scored configurations for both strengths, and
c) The revised master manufacturing batch records, certificates of analysis, and specification sheets as well as the description of the drug products in the

package inserts to accurately reflect the description of the drug products.

This commitment is provided in attachment 2 (7/3/03 Telephone Amendment).

Note from CR#3a:

In the telephone call (9/4/03), the Agent requested Ranbaxy to tighten the specification for Friability in line with USP <1216> to NMT [redacted] for release and add this test and specification into stability protocol.

In response to our request (9/4/03 TeleCon), the firm provided revised release and stability specification to include spec. for Friability NMT [redacted] The firm also commits to perform Friability test for all future stability batches with limit NMT [redacted] (9/4/03 Telephone Amendment).

18. CONCLUSIONS AND RECOMMENDATIONS:
Approvable; pending acceptable labeling

19. REVIEWER: Yanping Pan

DATE COMPLETED: 7/21/03, revise 9/4/03

APPEARS THIS WAY
ON ORIGINAL

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Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-100

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 65-100 SPONSOR :Ranbaxy Laboratories Limited

DRUG AND DOSAGE FORM : Cephalexin Dispersible Tablets, 125 mg and 250 mg

STRENGTH(S) : 125 mg and 250 mg

TYPES OF STUDIES : STF X STP STM OTHER X

CLINICAL STUDY SITE(S) : ———

ANALYTICAL SITE(S) : ———

STUDY SUMMARY: In single-dose fasting BE study, Cephalexin Dispersible Tablets, 250 mg, was shown to be bioequivalent to Keflex[R] for Oral Suspension, 250 mg/5ml. A waiver for the 125 mg strength is granted.

Formulation is acceptable.

DISSOLUTION : acceptable

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic ____ New facility ____ For cause ____ other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Carol Y. Kim BRANCH : 3

INITIAL : CYK DATE : 9/7/01

TEAM LEADER : Barbara M. Davit BRANCH : 3

INITIAL : BMD DATE : 9/7/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 9/13/01

Cephalexin [redacted] Tablets
125 mg and 250 mg
ANDA 65-100
Reviewer: Carol Y. Kim
V:\firmsnz\ranbaxy\ltrs&rev\65100stf.701

Ranbaxy Laboratories Limited
Gurgaon, India
Submission Date: 7/19/01

Review of a Bioavailability Study and Dissolution Data

I. Introduction

First Generic: Yes

Indication: For treatment of infections

Contents of Submission:

- Fasting BE: 250 mg
- Waiver request: 125 mg
- *In vitro* dissolution data: 125 mg and 250 mg

RLD: Keflex[R] (Cephalexin, USP) for Oral Suspension, 250 mg/5 ml, manufactured by Eli Lilly (NDA# 62117, March 27, 1978)

Recommended Dose: 250 mg Q6 hours or 500 mg Q12 hours

II. Background

1. 6/13/00: Suitability Petition, #99P-5451/CP1, was approved for the change in dosage form from Keflex[R] (Cephalexin) for Oral Suspension, 125 mg/5 ml, 250 mg/5 ml and 500 mg/5 ml, to [redacted] tablets. See attachment # 1 for details.

2. 2/1/01: #00-261 (Addendum): Control Correspondence submitted by Ranbaxy, Cephalexin [redacted] Tablets

The DBE recommended the following *in vivo* bioavailability studies:

a. Fasting BA study on 500 mg [redacted] Tablets using Keflex[R] Capsule, 500 mg (Eli Lilly, NDA# 50-405) as the RLD;

OR

b. Fasting BA study on 500 mg [redacted] Tablets using Keflex[R] Suspension, 100 mg/ml (Eli Lilly, NDA# 62-117) as the RLD;

c. A waiver may be requested for the 250 mg and 125 mg strength [redacted] Tablets.

The DBE concluded that a bioavailability study under fed conditions will not be requested for Cephalexin [redacted] Tablets.

3. 3/13/01: #01-090: Control Correspondence submitted by Ranbaxy, Cephalexin [redacted] Tablets

In response to a request regarding the dissolution method for Cephalexin [redacted] Tablets, 125 mg and 250 mg, the DBE recommended that Ranbaxy develop a suitable dissolution method for their products.

III. Pharmacokinetics

Cephalexin is acid-stable and is rapidly absorbed after oral administration. The half-life of cephalexin is 0.9 hours. Orally administered doses of 250 mg 500 mg, and 1000 mg result in average peak blood levels of approximately 9, 18, and 32 ug/ml, respectively, obtained at1 hour after administration.

IV. Study No. 01146: Randomized, 2-Way Crossover, Comparative Bioavailability Study comparing Ranbaxy's Cephalexin [redacted] Tablets, 250mg (2 X 250 mg), and Eli Lilly's Cephalexin for Oral Suspension, 250 mg/5ml (2 X 5ml), in Healthy Volunteers Under Fasting Conditions

Study Information

Clinical Facility:	[redacted]
Principal Investigator:	[redacted]
Clinical Study Dates:	Period 1: 3/28/01 Period 2: 3/31/01
Analytical Facility:	[redacted]
Analytical Director:	[redacted]
Analytical Study Dates:	4/2/01-4/29/01
Storage Period:	No > 32 days at -80°C

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Cephalexin [redacted] Tablet	Cephalexin for Oral Suspension
Manufacturer:	Ranbaxy	Eli Lilly
Manufacture Date:	2/01	N/A
Expiration Date:	1/03	2/02
ANDA Batch Size:	[redacted]	-
Full Batch Size:	[redacted]	-
Batch/Lot Number:	1115059	3AS64A

Strength:	250 mg	250 mg/5ml
Dosage Form:	1 Tablet ([redacted]	Suspension
Dose Administered*:	2 tablets (500 mg)	10 ml (500 mg)
Study Condition:	Fasting	Fasting
Length of Fasting:	10 hours pre-dosing 4 hours post-dosing	10 hours pre-dosing 4 hours post-dosing

[redacted] tablet doses: Two tablets were dispersed in 20 ml of water and approximately after 1 minute, swirled vigorously before oral administration. Any remaining contents in the dispensing cup were rinsed with additional 20 ml of water and administered. The last sequence was repeated two times. The remaining 160 ml of water was transferred in the dispensing cup and ingested. Thus, a total of 240 ml of water was administered.

* Suspension doses: Prior to dispensing, each bottle was gently shaken approximately 30 times for approximately thirty seconds. The suspension was transferred into an adequately sized glass beaker. The glass beaker was swirled four times before submerging a 20-ml Slip Tip syringe into each suspension and drawing 10 ml of suspension. The syringe was gently tapped to remove all air bubbles. The excess suspension was expelled until a total of 10 ml of suspension remains in the syringe. The prepared suspension was administered directly into the mouth and swallowed. The syringe was filled with 10 ml of water and administered directly into the mouth and swallowed. This sequence was repeated for a total of three times. Following drug administration and rinses, the remaining 210 ml of water was ingested. Thus, a total of 240 ml of water was administered.

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Washout Period:**	3 days
No. of Treatments:	2	**Center**	single

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	38
Route of Administration:	Oral	**No. of Subjects Completing:**	35
		No. of Subjects Plasma Analyzed:	34 (the first 34/38 who completed)
		No. of Dropouts:	3
		Sex(es) Included:	32 Males + 6 Females
		Age:	18-55 years
		Healthy Volunteers Only:	Y
		No. of Adverse Events:	16

Inclusion/Exclusion Criteria:	Vol. 1.3 (p. 496-498)
Housing:	The night before dosing until after the 8 hour blood draw
Blood Sampling:	0, 0.167, 0.333, 0.5, 0.667, 0.833, 1.0, 1.25, 1.50, 1.75, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, and 8.0 hours post dose
Volume:	7 ml

Study Results

1) Clinical

Demographic Data (all randomized patients)

Subj	Race*				Sex		Age Group (Yr.)		Height (in)		Weight (lbs.)	
Total	Asian	Black	Caucasian	Hispanic	Male	Female	18-40	41-65	Mean	Range	Mean	Range
38	0	0	38	0	32	6	24	14	69	63-74	157	116-194

A: Asian, B: Black, C: Caucasian, H: Hispanic, NA: Native American,

Adverse Events: -Total- 16 adverse events in association to the study drug
-7 events (4 subjects)-treatment A, drug related
-9 events (5 subjects)-treatment B, drug related
-The most common adverse events were a mild abdominal cramp and dizziness. (vol. 1.2, p. 162-165)

Vomiting Episodes

Subject #	Time after post-dose	Period	Comments
24	5 hours 23 minutes	I	Included in the final analysis since vomiting occurred after 2 times median Tmax
36	4 minutes; 1 hour and 7 minutes	II	Excluded from the final analysis

Dropouts:

Subject #	Comments	Replacement	Excluded from the final analysis
#1	Withdrew from the study due to personal reasons in period II	No	Yes
#36	Withdrawn from the study due to vomiting episode in period II	No	Yes
#38	Withdrew from the study due to personal reasons in period I	No	Yes

Protocol Deviations: Minor sampling deviations were noted.

2) Analytical (Not to be Released Under FOI)

Redacted _____

Page(s) of trade secret and /or confidential commercial information

SPECIFICITY:

[redacted]

Conclusion: The analytical method is acceptable.

3) Pharmacokinetic/Statistical Analysis

Mean Cephalexin plasma levels of 34 subjects are summarized in Table 1.

Table 1

Mean(CV) Plasma Concentrations of Cephalexin (ng/ml)

Test=Ranbaxy's Cephalexin [redacted] Tablets, 250 mg, Dose Administered=2 tablets, fasting
Reference=Cephalexin for Oral Suspension, 250 mg/5 ml, Dose Administered=10 ml, fasting

Time (hours)	Test	%CV	Reference	%CV	Ratio (T/R)*
0	0	0	0	0	-
0.167	1746.65	82.73	2143.12	93.35	0.82
0.333	10407.72	43.33	10179.46	52.20	1.02
0.5	17064.52	27.10	17047.45	31.99	1.00
0.667	19282.73	14.78	18611.48	25.12	1.04
0.833	17712.16	13.56	16818.54	23.50	1.05
1.0	15246.66	15.95	14672.38	21.36	1.04
1.25	11840.61	19.10	11580.26	23.13	1.02
1.50	9080.27	20.81	8896.81	23.61	1.02
1.75	7246.70	24.27	7429.56	27.28	0.98
2.0	5847.19	26.86	6065.58	32.79	0.96
2.50	4000.79	29.13	4330.66	52.59	0.92
3.0	2836.59	34.41	3010.81	43.87	0.94
4.0	1551.77	35.58	1587.63	43.72	0.98
5.0	870.23	34.42	882.99	43.79	0.99
6.0	513.78	36.09	551.28	45.24	0.93
8.0	105.47	148.71	113.84	143.72	0.93

*calculated by the reviewer

Analysis of variance was performed on each pharmacokinetic parameter using SAS PROC GLM. Mean reported pharmacokinetic parameters for cephalexin are shown in Table 2. The Geometric means of the ln-transformed pharmacokinetic parameters, means, and the 90% confidence intervals of test product versus reference product are presented in Table 3.

Table 2
Mean Cephalexin Plasma Pharmacokinetic Parameters

Parameter*	Test Mean	Test %CV	Ref Mean	Ref %CV	T/R Ratio
AUCT	30624.83	16.35	30670.24	17.06	1.00
AUCI	31304.77	16.10	31358.11	16.97	1.00
CMAX	20024.25	14.76	20048.37	17.03	1.00
TMAX	0.66	23.20	0.73	51.16	0.90
KEL	0.55	12.42	0.55	11.56	1.00
THALF	1.28	12.35	1.27	12.38	1.01

*AUCT=ng*hr/ml, AUCI=ng*hr/ml, TMAX=hr, CMAX=ng/ml

Table 3
Geometric Mean ratios and 90% confidence intervals for Cephalexin

	Geometric Means		Geometric Mean	90%CI	
Parameter*	Test	Reference	Ratio (T/R)	Lower 90% CI	Upper 90% CI
LAUC0-inf	30927.3	30972.8	0.99	97.9	101.9
LAUC0-t	30242.7	30289.1	0.99	97.8	101.9
LCmax	19812.7	19752.6	1.00	95.1	105.8

*LAUC0-inf =ng*hr/ml, LAUC0-t=ng*hr/ml, LCMAX=ng/ml

Comments:

1. No significant period, treatment, or sequence effect for cephalexin was noted on LAUCT, LAUCI and LCMAX ($p>0.05$).

2. The pharmacokinetic parameters and 90% confidence intervals re-calculated by the reviewer were in good agreement with the values determined by the firm.

3. The mean (%CV) AUC_T/AUC_I ratios of cephalexin were 0.98 (0.6), range 0.96 to 0.98, and 0.98 (0.6), range 0.97 to 0.99, for test and reference, respectively.

4. The 90% confidence intervals of ln-transformed AUCT, AUCI, and CMAX for cephalexin are all within 80-125% range.

Conclusion: The study is acceptable.

Table 4: Root Mean Square Error (MSE) for ln-transformed AUCT and Cmax

Cephalexin	fasting	
	ln AUCT	ln CMAX
MSE, Test & Reference	0.0502400	0.1307243

V. Dissolution (Not to be released under FOI)

The firm submitted dissolution data for Cephalexin Tablets ([redacted] , 250 mg and 125 mg, obtained using the following conditions:

Apparatus: II
Speeds: 25 and 50 rpm
Media: water, 0.01 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, pH 7.5 phosphate buffer

However, Ranbaxy indicated that the USP 24 Apparatus I (basket) at 100 rpm in 900 ml of water will be used for the routine quality control and stability analysis of Cephalexin [redacted] Tablets. Since Apparatus I (basket) can not be used for dissolution studies of the suspension formulation, Apparatus II (paddle) was selected at a lower speed.

Firm's Proposed method for quality control and stability analysis

Method of dissolution	Apparatus I (basket)
Speed	100 rpm
No. of Units Tested	12
Media Tested	Water
Temperature	37°C
Volume	900 ml
Assay Methodology	[redacted]
Specification	NLT [redacted] (Q) of labeled amount of cephalexin in 30 minutes
Reference Products	Keflex[R] for Oral Suspension, 250 mg/5 ml and 125 mg/5 ml

Results of In Vitro Dissolution Profile Summary for Cephalexin [redacted] Tablets, 250 and 125 mg vs. Cephalexin for Oral Suspension (Eli Lilly), 250 mg/5 ml and 125 mg/5 ml.

250 mg vs. 250 mg/5 ml (50 RPM)

50 RPM, Water, 900 ml						
Cephalexin Tablets ([redacted] , 250 mg Test Lot # 1115059 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 250 mg/5 ml; Reference Lot #: 3AS64A Exp: 2/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	92	[redacted]	1.8	97	[redacted]	1.9
10	94	[redacted]	2.0	98	[redacted]	1.7
15	95	[redacted]	1.1	98	[redacted]	2.2
20	96	[redacted]	1.9	99	[redacted]	1.8
30	96	[redacted]	1.7	100	[redacted]	1.9

50 RPM, 0.01 N HCl, 900 ml						
Cephalexin Tablets ( ), 250 mg Test Lot # 1115059 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 250 mg/5 ml; Reference Lot #: 3AS64A Exp: 2/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	93		2.9	92		2.7
10	95		2.1	96		2.6
15	97		2.1	98		1.9
20	97		2.0	99		1.0
30	99		1.9	99		1.1

50 RPM, pH 4.5, 900 ml						
Cephalexin Tablets , 250 mg Test Lot # 1115059 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 250 mg/5 ml; Reference Lot #: 3AS64A Exp: 2/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	91		3.3	96		1.7
10	95		2.3	99		1.2
15	96		2.1	99		0.8
20	98		1.9	100		1.0
30	98		2.1	101		0.9

50 RPM, pH 6.8, 900 ml						
Cephalexin Tablets), 250 mg Test Lot # 1115059 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 250 mg/5 ml; Reference Lot #: 3AS64A Exp: 2/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	89		5.0	95		1.3
10	92		4.1	95		1.3
15	91		4.0	96		1.2
20	91		4.0	96		1.1
30	92		3.5	96		1.0

50 RPM, pH 7.5, 900 ml						
Cephalexin Tablets [redacted], 250 mg Test Lot # 1115059 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 250 mg/5 ml; Reference Lot #: 3AS64A Exp: 2/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	90	[redacted]	2.9	94	[redacted]	1.7
10	94	[redacted]	3.7	96	[redacted]	1.8
15	95	[redacted]	3.2	97	[redacted]	1.6
20	95	[redacted]	3.0	99	[redacted]	1.7
30	95	[redacted]	2.9	101	[redacted]	1.1

125 mg vs. 125 mg/5 ml (50 RPM)

50 RPM, Water, 900 ml						
Cephalexin Tablets [redacted], 125 mg Test Lot # 1115061 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 125 mg/5 ml; Reference Lot #: 3AS60B Exp: 1/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	95	[redacted]	2.5	88	[redacted]	3.4
10	98	[redacted]	2.0	91	[redacted]	3.8
15	99	[redacted]	1.8	92	[redacted]	3.1
20	99	[redacted]	1.5	93	[redacted]	2.5
30	100	[redacted]	1.5	94	[redacted]	2.7

50 RPM, 0.01 N HCl, 900 ml						
Cephalexin Tablets [redacted] 125 mg Test Lot # 1115061 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 125 mg/5 ml; Reference Lot #: 3AS60B Exp: 1/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	96	[redacted]	1.9	92	[redacted]	2.1
10	98	[redacted]	1.8	94	[redacted]	2.0
15	99	[redacted]	1.4	96	[redacted]	1.8
20	100	[redacted]	2.5	98	[redacted]	1.8
30	101	[redacted]	2.1	100	[redacted]	1.2

50 RPM, pH 4.5, 900 ml						
Cephalexin Tablets ([redacted], 125 mg Test Lot # 1115061 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 125 mg/5 ml; Reference Lot #: 3AS60B Exp: 1/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	96	[redacted]	2.8	94	[redacted]	2.1
10	99	[redacted]	1.7	97	[redacted]	1.2
15	100	[redacted]	0.8	99	[redacted]	1.1
20	99	[redacted]	1.9	100	[redacted]	1.0
30	100	[redacted]	1.2	101	[redacted]	0.8

50 RPM, pH 6.8, 900 ml						
Cephalexin Tablets [redacted], 125 mg Test Lot # 1115061 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 125 mg/5 ml; Reference Lot #: 3AS60B Exp: 1/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	91	[redacted]	4.0	93	[redacted]	1.8
10	94	[redacted]	3.3	93	[redacted]	1.4
15	98	[redacted]	2.5	95	[redacted]	1.4
20	98	[redacted]	2.6	96	[redacted]	1.8
30	99	[redacted]	2.4	97	[redacted]	3.2

50 RPM, pH 7.5, 900 ml						
Cephalexin Tablets ([redacted], 125 mg Test Lot # 1115061 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 125 mg/5 ml; Reference Lot #: 3AS60B Exp: 1/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	89	[redacted]	2.1	89	[redacted]	3.1
10	90	[redacted]	2.6	95	[redacted]	2.7
15	90	[redacted]	1.6	98	[redacted]	1.7
20	90	[redacted]	2.2	100	[redacted]	1.2
30	93	[redacted]	3.7	101	[redacted]	1.1

See attachment #2 for 250 mg vs. 250 mg/5 ml (25 RPM) and 125 mg vs. 125 mg/5 ml (25 RPM)

Dissolution testing site: not reported

Comments

The firm proposed Apparatus I (basket) at 100 rpm in 900 ml water as the dissolution method for the routine quality control and stability analysis of Cephalexin [redacted]

Tablets. However, after reviewing all submitted dissolution data, the DBE recommends the following dissolution method and specifications for Cephalexin [redacted] Tablets:

Method: Apparatus II (paddle)
Speed: 50 rpm
Medium: water
Volume: 900 ml
Specification: NLT [redacted] (Q) in 15 minutes

VI. Composition of Formulation (not to be released under FOI)

Ingredients	mg/tablet	mg/tablet	%
[redacted]			
Cephalexin anhydrous as cephalexin USP*	125 mg	250 mg	-
Crospovidone NF	[redacted]	[redacted]	[redacted]
Colloidal Silicon Dioxide NF	[redacted]	[redacted]	[redacted]
Povidone USP	[redacted]	[redacted]	[redacted]
D&C Yellow No. 10 Aluminum Lake	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	-
[redacted]			
Mannitol USP	[redacted]		
Microcrystalline Cellulose NF ([redacted])			
Microcrystalline Cellulose NF ([redacted])			
Crospovidone NF			
Aspartame NF			
[redacted] Flavor Peppermint [redacted]			
[redacted] Flavor Fruit Gum [redacted]			
D&C Yellow No. 10 Aluminum Lake			
Colloidal Silicon Dioxide NF			
Magnesium Stearate NF			
Total	**400.0**	**800.0**	**100**

*This quantity is based on 100% assay on anhydrous basis and [redacted] content. The RLD uses monohydrate equivalent 125 mg or 250 mg of cephalexin. The DBE previously accepted anhydrous cephalexin in ANDA #65-081, 3/2/01.
**The quantity of Microcrystalline Cellulose shall be adjusted based on the input of Cephalexin USP to maintain constant batch weight.

DMF # [redacted] contains the composition data for [redacted] Flavor Fruit Gum [redacted] and Flavor Peppermint [redacted] is present in Flavor Fruit Gum [redacted] and Flavor Peppermint [redacted] at [redacted] of the total drug product, respectively. At these concentrations, the amount of [redacted] is within the limits specified by the FDA Inactive Ingredient Guide (1996). All other remaining individual components that make up these two flavors are on the GRAS list with 21 CFR citations and are below [redacted] of the total drug product.

All other remaining inactive ingredients are also within the limits specified by the FDA Inactive Ingredient Guide (1996).

Assay and Content Uniformity

Product	Assay %	Content Uniformity %
Test, Cephalexin Tablets [redacted] 125 mg Lot # 1115061	101.1	101.9 (1.89)
Reference, Cephalexin for Oral Suspension (Eli Lilly), 125 mg/ 5ml Lot # 3AS60B	100.2	94 (2.9)
Test, Cephalexin Tablets [redacted] 250 mg Lot # 1115059	100.1	100.08 (1.61)
Reference, Cephalexin for Oral Suspension (Eli Lilly), 250 mg/ 5ml Lot # 3AS64A	101.6	100 (1.9)

VII. Waiver Request

1. The firm requested a waiver of *in vivo* bioavailability testing for the 125 mg tablets.

2. The lists of active and inactive ingredients in the proposed test formulation, Cephalexin Tablets [redacted], are proportionally similar in 125 mg and 250 mg tablets. The total weight in 250 mg tablet is double the amount present in 125 mg tablet.

VIII. Recommendations

1. The single-dose bioequivalence study, 01146, under fasting conditions, conducted by Ranbaxy Laboratories, Limited, on its Cephalexin [redacted] Tablets, 250 mg, #1115059, comparing it to Keflex^{R} (Cephalexin) for Oral Suspension, 250 mg/5 ml, #3AS64A, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Ranbaxy's Cephalexin [redacted] Tablet, 250 mg, is bioequivalent to the reference product, Keflex^{R} (Cephalexin) for Oral Suspension, 250 mg, manufactured by Eli Lilly.

2. The dissolution method conducted by Ranbaxy on its Cephalexin [redacted] Tablets, 250 mg (lot #1115059), and 125 mg (lot #1115061) is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water at 37°C using USP 24 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

   Not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

4. The waiver of *in vivo* bioequivalence study requirements for the 125 mg tablet of the test product is granted. The formulation of Cephalexin [redacted] Tablet, 125 mg, is proportionally similar to the 250 mg strength of the test product which underwent acceptable bioequivalence testing. The Division of Bioequivalence deems Cephalexin [redacted] Tablets, 125 mg, manufactured by Ranbaxy, to be bioequivalent to Keflex^{R} (Cephalexin) for Oral Suspension, 125 mg, manufactured by Eli Lilly.

The firm should be informed of the above recommendations.

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

BMD 9/6/01

RD INITIALLED BY BDAVIT Barbara M Davit
FT INITIALLED BY BDAVIT

Date: 9/7/01

Concur: Dale P. Conner

Date: 9/13/01

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #65-100 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Cephalexin [redacted] Tablets, 125 mg and 250 mg

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

The following dissolution testing will need to be incorporated into your stability and quality control programs. The dissolution testing should be conducted in 900 ml of water at 37°C using USP 24 Apparatus II (paddle) at 50 rpm. The test should meet the following specifications:

> Not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

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,

Dale P. Conner

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

CC: ANDA #65-100
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer C. Kim
HFD-658/ Bio team leader B. Davit

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Endorsements: (Final with Dates)
HFD-658/ Reviewer C. Kim 9/7/01
HFD-658/ Bio team Leader B. Davit 9/7/01
HFD-658/ Reviewer N. Tran
HFD-650/ S. Mazzella
HFD-650/ D. Conner 9/13/01

BIOEQUIVALENCY - Acceptable Submission date: 7/19/01

ok **1. Fasting Study (STF)** **Strength: 250 mg**
Clinical: [redacted] **Outcome: AC**
Analytical: [redacted]

ok **2. Dissolution Waiver (DIW)** **Strength: 150 mg**
Outcome: AC

Outcome Decision: AC - acceptable

APPEARS THIS WAY
ON ORIGINAL

25 RPM, pH 6.8, 900 ml						
Cephalexin Tablets [redacted], 250 mg Test Lot # 1115059 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 250 mg/5 ml; Reference Lot #: 3AS64A Exp: 2/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	25	[redacted]	5.5	82	[redacted]	4.0
10	33	[redacted]	6.2	84	[redacted]	3.5
15	38	[redacted]	6.1	86	[redacted]	3.1
20	42	[redacted]	5.8	88	[redacted]	3.0
30	47	[redacted]	6.1	90	[redacted]	2.4
45	52	[redacted]	6.0	-		-

25 RPM, pH 7.5, 900 ml						
Cephalexin Tablets [redacted], 250 mg Test Lot # 1115059 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 250 mg/5 ml; Reference Lot #: 3AS64A Exp: 2/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	32	[redacted]	5.0	86	[redacted]	3.1
10	42	[redacted]	5.4	88	[redacted]	3.0
15	49	[redacted]	7.1	90	[redacted]	2.7
20	52	[redacted]	6.4	92	[redacted]	2.6
30	58	[redacted]	6.8	93	[redacted]	1.9
45	62	[redacted]	7.6	-		-

125 mg vs. 125 mg/5 ml (25 RPM)

25 RPM, Water, 900 ml						
Cephalexin Tablets [redacted], 125 mg Test Lot # 1115061 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 125 mg/5 ml; Reference Lot #: 3AS60B Exp: 1/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	38	[redacted]	2.9	93	[redacted]	1.5
10	47	[redacted]	3.6	97	[redacted]	2.5
15	55	[redacted]	5.3	98	[redacted]	2.5
20	60	[redacted]	3.5	97	[redacted]	3.4
30	66	[redacted]	4.2	97	[redacted]	3.2
45	74	[redacted]	2.7	-		-

25 RPM, 0.01 N HCl, 900 ml						
Cephalexin Tablets [redacted], 125 mg Test Lot # 1115061 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 125 mg/5 ml; Reference Lot #: 3AS60B Exp: 1/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	43	[redacted]	6.2	93	[redacted]	2.5
10	54	[redacted]	5.2	95	[redacted]	2.4
15	61	[redacted]	5.4	97	[redacted]	1.3
20	67	[redacted]	6.6	99	[redacted]	0.9
30	73	[redacted]	5.0	100	[redacted]	1.0
45	78	[redacted]	4.7	-	-	-

25 RPM, pH 4.5, 900 ml						
Cephalexin Tablets [redacted] 125 mg Test Lot # 1115061 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 125 mg/5 ml; Reference Lot #: 3AS60B Exp: 1/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	35	[redacted]	3.5	93	[redacted]	2.1
10	43	[redacted]	3.2	94	[redacted]	2.3
15	51	[redacted]	3.9	96	[redacted]	1.6
20	57	[redacted]	4.1	98	[redacted]	1.2
30	63	[redacted]	5.1	99	[redacted]	1.2
45	69	[redacted]	4.2	-		-

25 RPM, pH 6.8, 900 ml						
Cephalexin Tablets [redacted], 125 mg Test Lot # 1115061 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 125 mg/5 ml; Reference Lot #: 3AS60B Exp: 1/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	29	[redacted]	2.6	86	[redacted]	3.3
10	39	[redacted]	2.5	86	[redacted]	3.5
15	47	[redacted]	2.0	87	[redacted]	3.4
20	52	[redacted]	3.2	89	[redacted]	3.0
30	60	[redacted]	3.4	91	[redacted]	2.4
45	66	[redacted]	2.8	-		-

25 RPM, pH 7.5, 900 ml						
Cephalexin Tablets ([redacted]), 125 mg Test Lot # 1115061 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 125 mg/5 ml; Reference Lot #: 3AS60B Exp: 1/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	38	[redacted]	2.5	83	[redacted]	2.8
10	49	[redacted]	3.9	85	[redacted]	2.9
15	56	[redacted]	3.2	87	[redacted]	2.2
20	59	[redacted]	3.3	91	[redacted]	2.5
30	64	[redacted]	4.0	94	[redacted]	2.9
45	69	[redacted]	5.1	-		-

Attachment #2

Additional Dissolution Data using Apparatus II, 25 RPM

250 mg vs. 250 mg/5 ml (25 RPM)

25 RPM, Water, 900 ml						
Cephalexin Tablets [redacted] 250 mg Test Lot # 1115059 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 250 mg/5 ml; Reference Lot #: 3AS64A Exp: 2/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	32	[redacted]	4.4	95	[redacted]	1.9
10	38	[redacted]	4.9	97	[redacted]	1.6
15	42	[redacted]	5.0	97	[redacted]	1.7
20	46	[redacted]	5.4	96	[redacted]	1.9
30	51	[redacted]	5.7	97	[redacted]	1.9
45	59	[redacted]	5.3	-		-

25 RPM, 0.01 N HCl, 900 ml						
Cephalexin Tablets [redacted], 250 mg Test Lot # 1115059 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 250 mg/5 ml; Reference Lot #: 3AS64A Exp: 2/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	35	[redacted]	5.1	88	[redacted]	3.9
10	47	[redacted]	7.5	92	[redacted]	3.1
15	54	[redacted]	8.2	94	[redacted]	3.0
20	58	[redacted]	8.7	97	[redacted]	2.5
30	64	[redacted]	8.1	98	[redacted]	1.8
45	67	[redacted]	8.1	-		-

25 RPM, pH 4.5, 900 ml						
Cephalexin Tablets [redacted], 250 mg Test Lot # 1115059 Exp: 1/03				Cephalexin for Oral Suspension (Eli Lilly) 250 mg/5 ml; Reference Lot #: 3AS64A Exp: 2/02		
Sampling times (min)	Mean (%)	Range (%)	%CV	Mean (%)	Range (%)	%CV
5	31	[redacted]	4.6	90	[redacted]	2.7
10	40	[redacted]	6.5	92	[redacted]	2.0
15	44	[redacted]	6.6	94	[redacted]	1.5
20	48	[redacted]	7.3	96	[redacted]	1.1
30	52	[redacted]	6.5	98	[redacted]	1.2
45	59	[redacted]	8.5	-		-

Redacted 2

Page(s) of trade secret and /or confidential commercial information

Fig. 1: Mean plasma concentrations under fasting conditions (ANDA 65-100)

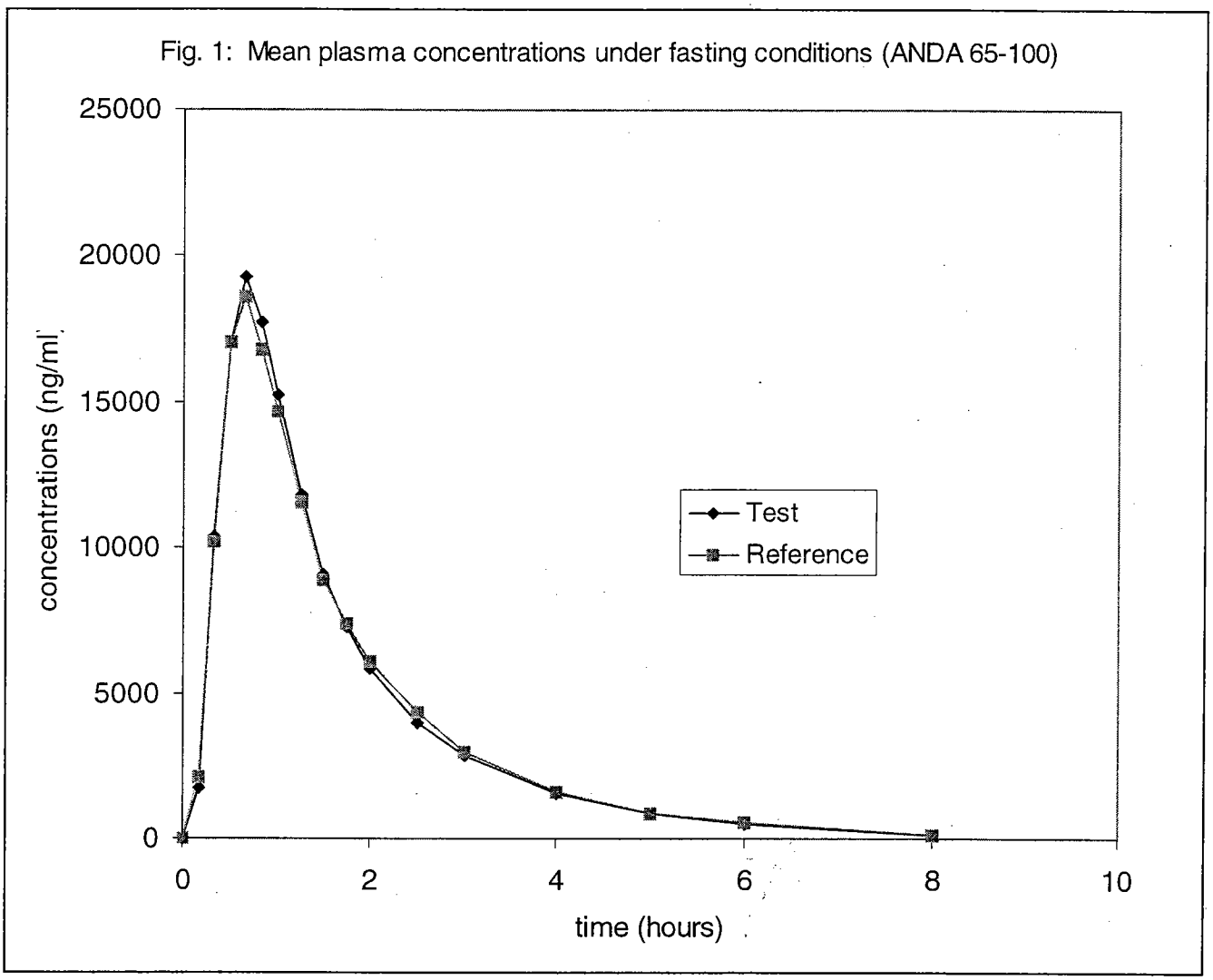
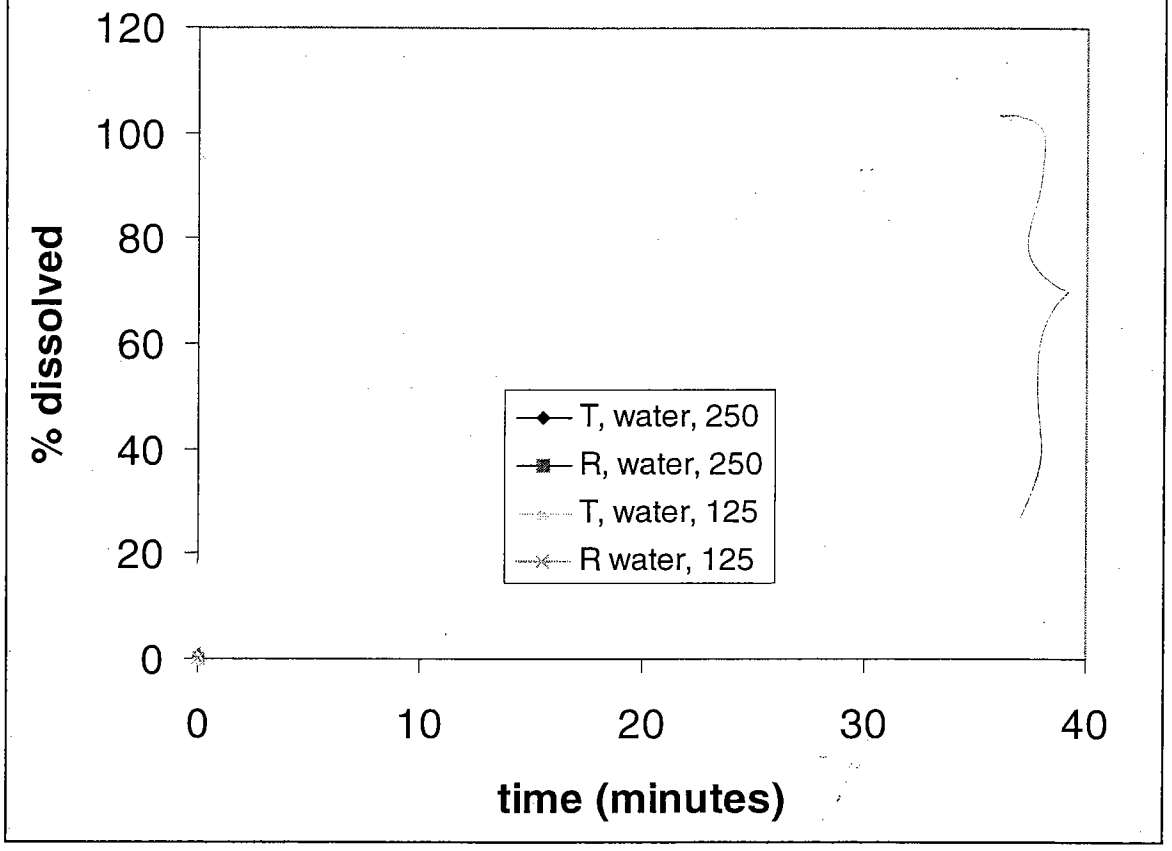


Fig. 2: Dissolution comparison in water, 50 rpm (250 mg and 125 mg), ANDA #65-100



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-100

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

I called Abha Pant at Ranbaxy regarding their pending application for Cephalexin Tablets for Oral Suspension. I said that following a meeting with staff from the Divison of Pediatrics it has been determined that revisions will be needed to the labeling for the product. Also it will be necessary for Ranbaxy to score the tablets in order to provide for dosing of the product to match that of the listed drug Cephalexin for Oral Suspension. Specifically, I requested firm to:

1. Provide data to determine the percent of label claim for dose delivered when tablets are dispersed in 10 mL's (2 teaspoonfuls) of water.
2. Commit to provide for scoring of tablets in a post-approval Supplement-Expedited Review Requested. This should include revised master batch records, executed batch record for scored tablets, COA's, dissolution profile comparing unscored with scored tablets.

This information can be submitted as a Telephone Amendment.

V:\firmsnz\ranbaxy\telecons\65100.001

DATE:

6/25/03

ANDA NUMBER:

65-100

PRODUCT NAME:

Cephalexin Tablets for Oral Suspension

FIRM NAME:

Ranbaxy Laboratories Limited

FIRM REPRESENTATIVE:

Abha Pant

PHONE NUMBER:

609-720-5666

FDA REPRESENTATIVES:

Mark Anderson

SIGNATURES:

Mark Anderson

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65-100

CORRESPONDENCE

RANBAXY
PHARMACEUTICALS INC.

ORIG AMENDMENT
N/Am

September 4, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FAX & UPS OVERNIGHT

TELEPHONE AMENDMENT

Reference: Panixine™ (Cephalexin) Tablets for Oral Suspension, 125 mg and 250 mg
ANDA 65-100

Dear Sir/Madam:

Reference is made to the pending ANDA 65-100 for Panixine™ (Cephalexin) Tablets for Oral Suspension, 125 mg and 250 mg. Reference is also made to the telephone contact of September 4, 2003, in which the Agency had requested Ranbaxy to tighten the specification for Friability in line with USP <1216> to NMT [redacted] for release. In addition, the Agency has requested that this test and specification be incorporated into our stability protocol.

Based on the Agency's request, the revised release specifications as well the revised stability protocol are included on the following pages.

Ranbaxy commits to performing friability for all future stability batches with a limit of NMT [redacted]

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the Office of Generic Drugs for FDA's International Operations Group.

If you have any questions regarding this submission please contact me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky (for)

Scott D. Tomsky
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
SEP 05 2003

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

August 22, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FAX & UPS OVERNIGHT

NEW CORRESP
NC

TELEPHONE AMENDMENT

NDA
MA
9/11/03

Reference: **Panixine™ (Cephalexin) Tablets for Oral Suspension, 125 mg and 250 mg**
ANDA 65-100

Dear Sir/Madam:

Reference is made to the pending ANDA 65-100 for Panixine™ (Cephalexin) Tablets for Oral Suspension, 125 mg and 250 mg. Reference is also made to the telephone contact of August 22, 2003. In the telephone discussion the Agency requested the following revisions be incorporated into the Dosage and Administration section of the package insert prior to commercial distribution:

- in the first sentence of the first paragraph of the Dosage and Administration section revise "[redacted] to read [redacted]
- **delete** the title, "Cephalexin Tablets For Oral Suspension" above the two tables.
- In the first table, column 4, for a 10 kg child weight, revise the alignment of the dosing for ½ to 1 tablet q.i.d so that "**½ to 1 tablet**" fits on the top line as is done for the other doses and q.i.d. is centered underneath.
- In table 2, revise the last column for a 10 kg child weight to read "**½ to 1 tablet**" b.i.d. rather than "[redacted]."
- Remove the statement, "For ¼ and ½ tsp dosing, cephalexin suspension is available from Ranbaxy. See HOW SUPPLIED section." from the first paragraph under the second table.

Ranbaxy hereby commits to make all of the above mentioned revisions to the Package Insert Prior to Commercial Distribution.

If you have any questions regarding this submission please contact me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Regulatory Affairs Associate (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
AUG 25 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

August 6, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

FAX AND UPS

LABELING AMENDMENT
ORIG AMENDMENT
N/AF

Reference: **ANDA 65-100**
Panixine Disperdose™ (Cephalexin Tablets for Oral Suspension)
125 mg and 250 mg

Dear Sir or Madam:

Ranbaxy is providing the labeling response to the above-referenced application as per the Agency's letter dated July 29, 2003.

Included on the following pages are the Agency's deficiency's, as well as, the responses to each deficiency. The questions follow in the same order as they appear in the Agency's letter.

In addition, we are enclosing the revised Dear Pharmacist letter in **attachment 1**, final printed labeling for your review as **attachment 2**, and the side-by-side labeling comparison with all differences annotated by the use of color, in **attachment 3**.

If you have any questions, regarding this supplement, please call me at 609-720-5609, or Abha Pant at 609-720-5666.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
U.S. Agent for Ranbaxy Laboratories Limited

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AUG 07 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

July 3, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FAX & UPS OVERNIGHT

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/Atm

Reference: **Panixine™ (Cephalexin) Tablets for Oral Suspension, 125 mg and 250 mg**
ANDA 65-100

Dear Sir/Madam:

Reference is made to the pending ANDA 65-100 for Panixine™ (Cephalexin) Tablets for Oral Suspension, 125 mg and 250 mg. Reference is also made to the DMETS comments received June 16, 2003 in which the proprietary name Panixine was found acceptable.

Reference is also made to the FDA Telephone contact of June 25, 2003. In the telephone call the Agency requested Ranbaxy to provide additional data in order to determine the percent of the label claim for the dose delivered to a subject when a tablet is dispersed in 10mL's of water.

Based on the Agency's request, each individual tablet was dispersed in the recommended amount of water (10 ml and 15 ml, separately) and the dispersion discarded completely. Assay of residual contents sticking to the container (without rinsing) was done and the data for the same is attached herewith. The testing has been completed on 20 tablets for each strength and is included in **Attachment 1**.

In addition, the Agency requested Ranbaxy to provide a signed commitment to provide the following information in a "Supplement – Expedited Review Requested" submission:

a) Executed batch records reflecting the manufacture of scored tablets and complete Certificate of Analysis (COA) for each batch
b) a dissolution profile comparing the differing scored configurations for both strengths, and
c) the revised master manufacturing batch records, certificates of analysis, and specifications sheets as well as the description of the drug products in the package inserts to accurately reflect the description of the drug products.

This commitment is included in **Attachment 2**.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the Office of Generic Drugs for FDA's International Operations Group.

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JUL 07 2003
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600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

If you have any questions regarding this submission please contact me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

December 11, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FAX & UPS OVERNIGHT

TELEPHONE AMENDMENT
Labeling

ORIG AMENDMENT
N/AF

Reference: Cephalexin Tablets for Oral Suspension 125 mg and 250 mg
ANDA 65-100
Response to Labeling Deficiency Dated October 23, 2002

Dear Sir/Madam:

Reference is made to the pending ANDA 65-100 for Cephalexin Tablets for Oral Suspension 125 mg and 250 mg.

Reference is also made to the labeling facsimile deficiency, dated October 23, 2002, in which Ranbaxy was asked to further revise the labels and the package insert for the above referenced product. Please note, we were requested by the Agency to hold our response until the Agency had a chance to review the labeling for Ranbaxy's ANDA 65-080, Amoxicillin Tablets for Oral Suspension.

Further, Ranbaxy has submitted 3 new names to the Agency in a request for a proprietary name dated November 11, 2002. Please note that throughout the labeling that is being submitted in this response, we have selected one of the names ( ) submitted in the November 11, 2002 request for a proprietary name to illustrate how the labels will be printed and set. If the Agency finds that one of the other names are more acceptable, Ranbaxy commits to simply replace all references to ™ with the Agency accepted proprietary name.

In addition, upon a closer review we have noticed that we had provided an inaccurate response to the Agency's question 2.a.ii from the Agency's May 1, 2002 deficiency. In our response dated June 13, 2002, we incorrectly said the larger unit-dose strips were packaged in a child resistant package. This was incorrect. The larger unit dose strips are a non child resistant package and the smaller unit-dose blisters are a child resistant package. Please note, we have revised all unit-dose packages to clearly illustrate which packages are child resistant and which packages are non child resistant.

Provided on the following pages are the agencies deficiencies followed by Ranbaxy's response. The labels and the package insert have been revised as requested. Four sets of the printed revised labels and package insert are included in **Attachment 3**. To facilitate review we have provided a side-by-side labeling comparison with Ranbaxy's

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revised labeling and previously submitted, with all differences explained and shown with the use of color, in **Attachment 4**.

Please contact the undersigned at 609-720-5633, or Abha Pant at 609-720-5666 if you have any questions regarding this labeling amendment.

Sincerely,

Iris Feliciano

Iris Feliciano
Regulatory Affairs Labeling Specialist (***for***)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

November 11, 2002

N/AF **FAX AND UPS**

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FPL **Request for Acceptance of a Proprietary Name**

RE: Cephalexin Tablets for Oral Suspension, 125 mg and 250 mg
ANDA 65-100

Dear Sir/Madam:

Reference is made to the pending ANDA 65-100 for Cephalexin Tablets for Oral Suspension, 125 mg and 250 mg. Reference is also made to the Agency's labeling comments received October 11, 2002.

At this time Ranbaxy is proposing 3 additional proprietary names for Cephalexin Tablets for Oral Suspension, 125 mg and 250 mg. They are, in order of preference:

1. [redacted]™ (Cephalexin Tablets for Oral Suspension)
2. Panixine™ DisperDose™ (Cephalexin Tablets for Oral Suspension)
3. [redacted]™ (Cephalexin Tablets for Oral Suspension)

We request that these names be forwarded to The Office of Drug Safety/Division of Medication Errors and Technical Support. We have provided a copy of the bottle container labels with the proposed names to facilitate your review.

If further information is necessary, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

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NOV 1 2 2002
OGD / CDER

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

June 13, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

FAX AND UPS

LABELING AMENDMENT
~~ORIG~~ AMENDMENT
N/A M DRAFT

Reference: ANDA 65-100
Cephalexin Tablets For Oral Suspension, 125 mg and 250 mg

Dear Sir or Madam:

Ranbaxy Pharmaceuticals Inc. is providing labeling response to the above-referenced application as per your letter, dated May 1, 2002, received from the Division of Labeling and Program Support Office of Generic Drugs. At that time, Ranbaxy was asked to further revise the Cephalexin [redacted] Tablets.

On May 10, 2002, Mark Anderson left a telephone message informing Ranbaxy of a meeting that transpired with USP and FDA (Gary Buehler was present), and a formal decision was made to pursue the name "cephalexin tablets for oral suspension" versus cephalexin tablets [redacted] for the above referenced application. Ranbaxy Pharmaceuticals has revised the labeling to include "cephalexin tablets for oral suspension" on the additional proprietary names provided in the March 12, 2002 response.

Enclosed please find four (4) draft copies of the labeling for your review as attachment 1. Also enclosed is a side-by-side comparison with all differences annotated by the use of color, as attachment 2.

If you have any questions, regarding this supplement, please call me at 609-720-5633, or Abha Pant at 609-720-5666.

Sincerely,

Iris Feliciano

Iris Feliciano
Regulatory Affairs Labeling Specialist (*for*)
Abha Pant
U.S. Agent for Ranbaxy Laboratories Limited

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JUN 14 2002
OGD / CDER

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

March 12, 2002

ORIG AMENDMENT
N/AF

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

FAX AND UPS

LABELING AMENDMENT

Reference: ANDA 65-100
Cephalexin [redacted] Tablets, 125 mg and 250 mg

Dear Sir or Madam:

Reference is made to our pending Abbreviated New Drug Application, 65-100 for Cephalexin [redacted] Tablets, 125 mg and 250 mg.

Reference is also made to the FDA labeling letter dated December 12, 2001. The questions and responses follow in the same order as in the letter. They are attached.

If you have any questions, regarding this supplement, please call me at 609-720-5617, or Abha Pant at 609-720-5666.

Sincerely,

Patricia S. Strasser
Manager Regulatory Affairs (for)
Abha Pant
U.S. Agent for Ranbaxy Laboratories Limited

RECEIVED
MAR 1 5 2002
OGD / CDER

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

NAE M Anderson 9/15/07

January 10, 2002

NC to FAX

NEW CORRESP

Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish place, Room 150
Rockville, MD 20855

Reference: Cephalexin [redacted] Tablets, 125 mg and 250 mg

Dear Sir/Madam:

Reference is made to the FDA's fax deficiency letter dated December 12, 2001. Within the labeling comments, the FDA requested samples for the different packaging configurations (Question1 c.). These samples and supporting documents in connection with ANDA 65-100 are being supplied.

If you have any questions, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky (for)

Scott D. Tomsky
Regulatory Affairs Associate(for)
Abha Pant
US Agent Ranbaxy Laboratories Limited

CENTER FOR DRUG EVALUATION AND RESEARCH
JAN 11 2002

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

January 9, 2002

Noted. to
Yanping
M Anderson
1/23/02

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and FAX

FAX AMENDMENT

N/FA

DRUG AMENDMENT

Labeling pending

Reference: **ANDA 65-100**
Cephalexin [redacted] Tablets, 125 mg and 250 mg

Dear Sir/Madam:

Reference is made to the pending ANDA 65-100 for Cephalexin [redacted] Tablets, 125 mg and 250 mg submitted July 19, 2001. Reference is also made to the FDA's fax deficiency letter dated December 12, 2001.

The deficiency questions and responses are addressed on the following pages. Please note that due to the fact that the labeling revisions have not been completed yet, we commit to submit an additional labeling amendment as soon as all of the changes have been incorporated into our labeling. However, as requested by the Division of Labeling and Program Support, we have provided the samples of the tablets in the desired packs as described in question 1 c.

Field Copy : We certify that a true copy of the technical section described in 21 CFR 314.95(d)(5) of this submission has been provided to the Office of Generic Drugs for the International Operations Group.

If you have any questions regarding this submission, please call me at (609)-720-5609 or Abha Pant at (609) 720-5666.

Sincerely,

Scott D. Tomsky (for)

Scott D. Tomsky
Regulatory Affairs Associate(for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

ANDA 65-100

AUG 2 3 2001

Ranbaxy Pharmaceuticals Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Shirley Ternyik
600 College Road East
Princeton, NJ 08540

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Cephalexin [redacted] Tablets, 125 mg and 250 mg

DATE OF APPLICATION: July 19, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 25, 2001

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

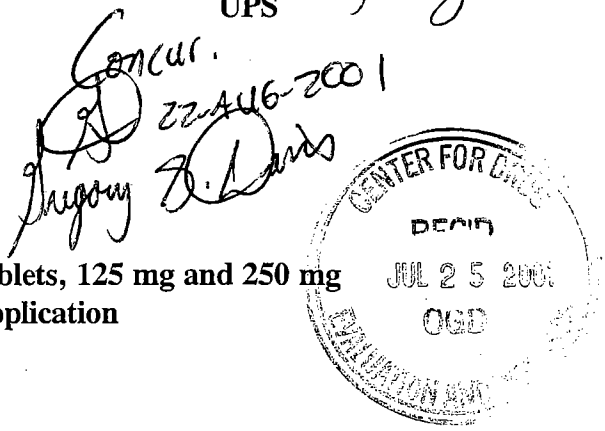
RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-124) 342001-10, Fax: (91-124) 342017, 342030

July 19, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS



Reference: **Cephalexin [redacted] Tablets, 125 mg and 250 mg**
Abbreviated New Drug Application

Dear Sir/Madam:

Ranbaxy Laboratories Limited (RLL) herewith submits an abbreviated new drug application (ANDA) for Cephalexin [redacted] Tablets 125 mg and 250 mg pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

The abbreviated new drug application (ANDA) for Cephalexin [redacted] Tablets 125 mg and 250 mg is based on the approved suitability petition (Docket # 99P-5451/CP-1) dated June 13, 2000. The subject suitability petition requested for a change in the dosage form from [redacted] to [redacted] Tablets. The approved petition permits this change in dosage form under Section 505 (j) (2) (C) of the Federal Food, Drug and Cosmetic Act.

Accordingly, the ANDA refers to the listed drug, Eli Lilly's Keflex® (cephalexin) for Oral Suspension, which is manufactured by Eli Lilly, the holder of ANDA 62-117, and which is listed in the 2001 Approved Drug Products with Therapeutic Equivalence Evaluations, 21rst Edition, (commonly known as the Orange Book), page 3-74.

In the applicant's opinion and to the best of applicant's knowledge, no patent claims have been submitted to the FDA. In addition, the applicant is not aware of any marketing exclusivity.

The drug product manufacturer is Ranbaxy Laboratories Limited. Cephalexin [redacted] Tablets 125 mg and 250 mg, will be manufactured at Ranbaxy Laboratories Limited's FDA registered and inspected Dewas, India facility in accordance with 21 CFR 210 and 211.

The drug product will also be packaged in bulk, bottle, strip and blister packs at the Dewas, India facility.

The manufacturer of the Cephalexin drug substance used to produce the ANDA batches of drug product is Ranbaxy Laboratories Limited, SAS Nagar Mohali, Punjab, India. The Drug Master File (DMF) No [redacted] was filed on September 29, 1989 and was amended on November 17, 2000 for [redacted] material is available and will be provided to the Agency upon request.

The required bioavailability/bioequivalence study was conducted on Ranbaxy's Cephalexin [redacted] Tablets 250 mg and Eli Lilly's Cephalexin for Oral Suspension, 250 mg/5mL by Anapharm Inc., 2050, Boul. Rene-Levesque Quest, Sainte-Foy (Quebec), Canada G1V 2K8. The study indicates that Ranbaxy's Cephalexin [redacted] Tablets 250 mg are bioequivalent to Eli Lilly's Cephalexin for Oral Suspension, 250 mg/5mL. The *in-vitro* dissolution profiles for Ranbaxy's Cephalexin [redacted] Tablets 125 mg & 250 mg are comparable to those of Eli Lilly's Cephalexin for Oral Suspension, 125 mg/5mL and 250 mg/5mL. Therefore, a waiver of *in-vivo* bioavailability/bioequivalence study requirements for Ranbaxy's Cephalexin [redacted] Tablets 125 mg is requested.

Cephalexin [redacted] Tablets 125 mg & 250 mg are stable and a two year expiration dating is requested. The two year expiration dating for these products is supported by one, two and three months accelerated stability data (40°C/75% relative humidity).

The route of administration, indications and usage, active ingredient, potency and labeling (except DESCRIPTION and HOW SUPPLIED sections) for Ranbaxy's Cephalexin [redacted], Tablets 125 mg & 250 mg are the same as those for Keflex® (cephalexin) for Oral Suspension, 125 mg/ 5mL and 250 mg/5mL. Dosage is based on the approved suitability petition.

This ANDA is submitted in nine volumes :

Volume I:	Section I through Section V.
Volume II: through Volume VI	Section VI.
Volume VII:	Section VII through Section XI

Volume VIII:	Section XII through Section XIV
Volume IX:	Section XV through Section XXII

Ranbaxy Laboratories Limited commits to resolve any issues identified in the methods validation process after approval.

Please contact the undersigned at 609-720-5612 if you have any questions regarding this submission.

Field Copy : We certify that a true copy of the technical section described in 21 CFR 314.95(d)(5) of this submission has been provided to the Office of Generic Drugs for the International Operations Group.

Sincerely,

Carol Coveney

Carol Coveney
Regulatory Affairs Associate (for)
Shirley Ternyik
US Agent for Ranbaxy Laboratories Limited.