

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203195Orig1s000**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SUPRAX<sup>®</sup> safely and effectively. See full prescribing information for SUPRAX<sup>®</sup>.

Suprax<sup>®</sup> (cefixime) Tablets USP, 400 mg

Suprax<sup>®</sup> (cefixime) Capsules, 400 mg

Suprax<sup>®</sup> (cefixime) for Oral Suspension USP, 100 mg/5 mL

Suprax<sup>®</sup> (cefixime) for Oral Suspension USP, 200 mg/5 mL

### For oral administration

Initial U.S. Approval 1986

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Suprax and other antibacterial drugs, Suprax should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.

### INDICATIONS AND USAGE

Suprax (cefixime) is a cephalosporin antibiotic indicated for

- Uncomplicated Urinary Tract Infections (1.1)
- Otitis Media (1.2)
- Pharyngitis and Tonsillitis (1.3)
- Acute Exacerbations of Chronic Bronchitis (1.4)
- Uncomplicated Gonorrhea (cervical/urethral) (1.5)

### DOSAGE AND ADMINISTRATION

- Adults: 400 mg daily (2.1)
- Children: 8 mg/kg/day (2.2)

### DOSAGE FORMS AND STRENGTHS

- Film-coated Tablets: 400 mg (3)
- Capsules: 400 mg (3)
- Oral Suspension 100 mg/5 mL and 200 mg/5 mL (3)

### CONTRAINDICATIONS

- Contraindicated in patients with known allergy to cefixime or other cephalosporins. (4)

### WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions including shock and fatalities have been reported with cefixime. Discontinue use if a reaction occurs. (5.1)
- *Clostridium difficile* associated diarrhea: Evaluate if diarrhea occurs. (5.2)

### ADVERSE REACTIONS

Most common adverse reactions are gastrointestinal such as diarrhea (16%), nausea (7%), loose stools (6%), abdominal pain (3%), dyspepsia (3%), and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharma at 1-800-399-2561 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Elevated carbamazepine levels have been reported in postmarketing experience when cefixime is administered concomitantly. (7.1)
- Increased prothrombin time, with or without clinical bleeding, has been reported when cefixime is administered concomitantly with warfarin and anticoagulants. (7.2)

### USE IN SPECIFIC POPULATIONS

- Pregnancy: Cefixime should be used during pregnancy only if clearly needed. (8.1)
- Nursing Mothers: Consideration should be given to discontinuing nursing temporarily during treatment with cefixime. (8.3)
- Children: Efficacy and safety in infants aged less than six months have not been established. (8.4)
- Geriatric Use: Clinical studies did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. (8.5)
- Renal Impairment: Cefixime may be administered in the presence of impaired renal function. Dose adjustment is required in patients whose creatinine clearance is less than 60 mL/min. (8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2012

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

- 1.1 Uncomplicated Urinary Tract Infections
- 1.2 Otitis Media
- 1.3 Pharyngitis and Tonsillitis
- 1.4 Acute Exacerbations of Chronic Bronchitis
- 1.5 Uncomplicated Gonorrhea (cervical/urethral)

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Adults
- 2.2 Pediatric Patients (6 months or older)
- 2.3 Renal Impairment
- 2.4 Reconstitution Directions for Oral Suspension

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Hypersensitivity Reactions
- 5.2 *Clostridium difficile*-Associated Diarrhea
- 5.3 Dose Adjustment in Renal Impairment
- 5.4 Coagulation Effects
- 5.5 Development of Drug-Resistant Bacteria

### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Post-marketing Experience

### 7 DRUG INTERACTIONS

- 7.1 Carbamazepine
- 7.2 Warfarin and Anticoagulants
- 7.3 Drug/Laboratory Test Interactions

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 14 CLINICAL STUDIES

Organism

### 15 REFERENCES

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

- 17.1 Information for Patients

\* Sections or subsections omitted from the full prescribing information are not listed

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

To reduce the development of drug resistant bacteria and maintain the effectiveness of Suprax (cefixime) and other antibacterial drugs, Suprax should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antimicrobial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Suprax (cefixime) is a cephalosporin antibacterial indicated in the treatment of adults and pediatric patients six months of age or older with the following infections when caused by susceptible isolates of the designated bacteria:

#### 1.1 Uncomplicated Urinary Tract Infections

Uncomplicated Urinary Tract Infections caused by *Escherichia coli* and *Proteus mirabilis*.

#### 1.2 Otitis Media

Otitis Media caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pyogenes*. (Efficacy for *Streptococcus pyogenes* in this organ system was studied in fewer than 10 infections.)

Note: For patients with otitis media caused by *Streptococcus pneumoniae*, overall response was approximately 10% lower for cefixime than for the comparator. [See **CLINICAL STUDIES (14)**]

#### 1.3 Pharyngitis and Tonsillitis

Pharyngitis and Tonsillitis caused by *Streptococcus pyogenes*. (Note: Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* infections. Suprax is generally effective in the eradication of *Streptococcus pyogenes* from the nasopharynx; however, data establishing the efficacy of Suprax in the subsequent prevention of rheumatic fever is not available.)

#### 1.4 Acute Exacerbations of Chronic Bronchitis

Acute Exacerbations of Chronic Bronchitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*.

#### 1.5 Uncomplicated Gonorrhea (cervical/urethral)

Uncomplicated Gonorrhea (cervical/urethral) caused by *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing isolates).

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Adults

The recommended dose of cefixime is 400 mg daily. This may be given as a 400 mg tablet or capsule daily or the 400 mg tablet may be split and given as one half tablet every 12 hours. For the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended. The capsule and tablet may be administered without regard to food.

In the treatment of infections due to *Streptococcus pyogenes*, a therapeutic dosage of cefixime should be administered for at least 10 days.

### 2.2 Pediatric Patients (6 months or older)

The recommended dose is 8 mg/kg/day of the suspension. This may be administered as a single daily dose or may be given in two divided doses, as 4 mg/kg every 12 hours.

PEDIATRIC DOSAGE CHART			
		100 mg/5 mL	200 mg/5 mL
Patient Weight (kg)	Dose/Day (mg)	Dose/Day (mL)	Dose/Day (mL)
5 to 6.2	50	2.5	1.25
6.3 to 12.5	100	5	2.5
12.6 to 18.8	150	7.5	3.75
18.9 to 25	200	10	5
25.1 to 31.3	250	12.5	6.25
31.4 to 37.5	300	15	7.5
37.6 to 43.8	350	17.5	8.75
43.9 to 50	400	20	10

Children weighing more than 50 kg or older than 12 years should be treated with the recommended adult dose.

Otitis media should be treated with the suspension. Clinical trials of otitis media were conducted with the suspension, and the suspension results in higher peak blood levels than the tablet when administered at the same dose.

Therefore, the tablet or capsule should not be substituted for the suspension in the treatment of otitis media. [See **CLINICAL PHARMACOLOGY (12.3)**]

In the treatment of infections due to *Streptococcus pyogenes*, a therapeutic dosage of cefixime should be administered for at least 10 days.

### 2.3 Renal Impairment

Suprax may be administered in the presence of impaired renal function. Normal dose and schedule may be employed in patients with creatinine clearances of 60 mL/min or greater. Patients whose clearance is between 21 and 60 mL/min or patients who are on renal hemodialysis may be given 6.5 ml of Suprax<sup>®</sup> for Oral Suspension (200 mg/5 mL) daily or 13 ml of Suprax<sup>®</sup> for Oral Suspension (100 mg/5 mL) daily. Patients whose clearance is 20 mL/min or less, or patients who are on continuous ambulatory peritoneal dialysis may be given 200 mg daily (i.e. half of the 400 mg tablet). Neither hemodialysis nor peritoneal dialysis removes significant amounts of drug from the body.

### 2.4 Reconstitution Directions for Oral Suspension

Strength	Bottle Size	Reconstitution Directions
100 mg/5 mL and 200 mg/5 mL	100 mL	To reconstitute, suspend with <b>68 mL water</b> . Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.
100 mg/5 mL and 200 mg/5 mL	75 mL	To reconstitute, suspend with <b>51 mL water</b> . Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.
100 mg/5 mL and 200 mg/5 mL	50 mL	To reconstitute, suspend with <b>34 mL water</b> . Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.
200 mg/5 mL	37.5 mL	To reconstitute, suspend with <b>26 mL water</b> . Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.
200 mg/5 mL	25 mL	To reconstitute, suspend with <b>17 mL water</b> . Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.

After reconstitution, the suspension may be kept for 14 days either at room temperature, or under refrigeration, without significant loss of potency. Keep tightly closed. Shake well before using. Discard unused portion after 14 days.

### 3 DOSAGE FORMS AND STRENGTHS

Suprax is available for oral administration in the following dosage forms and strengths:

- Film-coated tablets provide 400 mg of cefixime as trihydrate. These are white to off-white, film-coated, capsule shaped tablets with beveled edges and a divided score line on each side. The tablet is debossed with “SUPRAX” across one side and “LUPIN” across the other side.
- Capsules provide 400 mg of cefixime as trihydrate. These are size “00EL” capsules with dark brown cap and dark brown body with “LU” on the cap and “U43” on the body in white ink. Capsules contain white to yellowish white granular powder.
- Powder for oral suspension, when reconstituted, provides either 100 mg/5 mL or 200 mg/5 mL of cefixime as trihydrate. The powder has an off white to pale yellow color and is strawberry flavored.

### 4 CONTRAINDICATIONS

Suprax (cefixime) is contraindicated in patients with known allergy to cefixime or other cephalosporins.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Hypersensitivity Reactions

Anaphylactic/anaphylactoid reactions (including shock and fatalities) have been reported with the use of cefixime.

Before therapy with Suprax is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins, or other drugs. If this product is to be given to penicillin-sensitive patients, caution should be exercised because cross hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Suprax occurs, discontinue the drug.

#### 5.2 *Clostridium difficile*-Associated Diarrhea

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Suprax, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

### **5.3 Dose Adjustment in Renal Impairment**

The dose of Suprax should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD). Patients on dialysis should be monitored carefully [See **DOSAGE AND ADMINISTRATION (2)**].

### **5.4 Coagulation Effects**

Cephalosporins, including Suprax, may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

### **5.5 Development of Drug-Resistant Bacteria**

Prescribing Suprax (cefixime) in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

## **6 ADVERSE REACTIONS**

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most commonly seen adverse reactions in U.S. trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the twice daily or the once daily regimen. Five percent (5%) of patients in the U.S. clinical trials discontinued therapy because of drug-related adverse reactions. Individual adverse reactions included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 4%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to the incidence seen in adult patients receiving tablets.

### **6.2 Post-marketing Experience**

The following adverse reactions have been reported following the use of cefixime. Incidence rates were less than 1 in 50 (less than 2%).

### ***Gastrointestinal***

Several cases of documented pseudomembranous colitis were identified in clinical trials. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

### ***Hypersensitivity Reactions***

Anaphylactic/anaphylactoid reactions (including shock and fatalities), skin rashes, urticaria, drug fever, pruritus, angioedema, and facial edema. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness-like reactions have been reported.

### ***Hepatic***

Transient elevations in SGPT, SGOT, alkaline phosphatase, hepatitis, jaundice.

### ***Renal***

Transient elevations in BUN or creatinine, acute renal failure.

### ***Central Nervous System***

Headaches, dizziness, seizures.

### ***Hemic and Lymphatic System***

Transient thrombocytopenia, leukopenia, neutropenia, prolongation in prothrombin time, elevated LDH, pancytopenia, agranulocytosis, and eosinophilia.

### ***Abnormal Laboratory Tests***

Hyperbilirubinemia.

### ***Other Adverse Reactions***

Genital pruritus, vaginitis, candidiasis, toxic epidermal necrolysis.

### ***Adverse Reactions Reported for Cephalosporin-class Drugs***

Allergic reactions, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, and colitis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. [See **DOSAGE AND ADMINISTRATION (2)** and **OVERDOSAGE (10)**] If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

## **7 DRUG INTERACTIONS**

### **7.1 Carbamazepine**

Elevated carbamazepine levels have been reported in postmarketing experience when cefixime is administered concomitantly. Drug monitoring may be of assistance in detecting alterations in carbamazepine plasma concentrations.

## **7.2 Warfarin and Anticoagulants**

Increased prothrombin time, with or without clinical bleeding, has been reported when cefixime is administered concomitantly.

## **7.3 Drug/Laboratory Test Interactions**

A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

The administration of cefixime may result in a false-positive reaction for glucose in the urine using Clinitest<sup>®\*\*</sup>, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix<sup>®\*\*</sup> or TesTape<sup>®\*\*</sup>) be used. A false-positive direct Coombs test has been reported during treatment with other cephalosporins; therefore, it should be recognized that a positive Coombs test may be due to the drug.

\*\* Clinitest<sup>®</sup> and Clinistix<sup>®</sup> are registered trademarks of Ames Division, Miles Laboratories, Inc. Tes-Tape<sup>®</sup> is a registered trademark of Eli Lilly and Company.

# **8 USE IN SPECIFIC POPULATIONS**

## **8.1 Pregnancy**

Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 40 times the human dose and have revealed no evidence of harm to the fetus due to cefixime. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

## **8.2 Labor and Delivery**

Cefixime has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

## **8.3 Nursing Mothers**

It is not known whether cefixime is excreted in human milk. Consideration should be given to discontinuing nursing temporarily during treatment with this drug.

## **8.4 Pediatric Use**

Safety and effectiveness of cefixime in children aged less than six months old have not been established. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in the pediatric patients receiving the suspension, was comparable to the incidence seen in adult patients receiving tablets.

## 8.5 Geriatric Use

Clinical studies did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. A pharmacokinetic study in the elderly detected differences in pharmacokinetic parameters [See **CLINICAL PHARMACOLOGY (12.2)**]. These differences were small and do not indicate a need for dosage adjustment of the drug in the elderly.

## 8.6 Renal Impairment

The dose of cefixime should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD). Patients on dialysis should be monitored carefully [See **DOSAGE AND ADMINISTRATION (2.3)**].

## 10 OVERDOSAGE

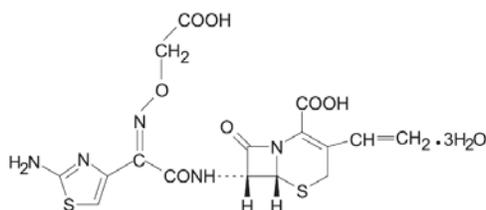
Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of cefixime did not differ from the profile seen in patients treated at the recommended doses.

## 11 DESCRIPTION

Cefixime is a semisynthetic, cephalosporin antibacterial for oral administration. Chemically, it is (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, 7<sup>2</sup>-(*Z*)-[*O*-(carboxy methyl) oxime] trihydrate.

Molecular weight = 507.50 as the trihydrate. Chemical Formula is C<sub>16</sub>H<sub>15</sub>N<sub>5</sub>O<sub>7</sub>S<sub>2</sub>·3H<sub>2</sub>O

The structural formula for cefixime is:



- Inactive ingredients contained in the 400 mg tablets are: dibasic calcium phosphate, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, titanium dioxide and triacetin.
- Inactive ingredients contained in the 400 mg capsules are: colloidal silicon dioxide, crospovidone, low substituted hydroxy propyl cellulose, magnesium stearate and mannitol. The capsule shell contains the following inactive ingredients: ferric oxide black, ferric oxide red, gelatin, potassium hydroxide, propylene glycol, shellac, sodium lauryl sulfate and titanium dioxide.
- Inactive ingredients contained in the powder for oral suspension are: colloidal silicon dioxide, strawberry flavor, sodium benzoate, sucrose, and xanthan gum.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Cefixime is a semisynthetic cephalosporin antibacterial drug [see **Microbiology** (12.4)].

### 12.3 Pharmacokinetics

Suprax tablets and suspension, given orally, are about 40% to 50% absorbed whether administered with or without food; however, time to maximal absorption is increased approximately 0.8 hours when administered with food. A single 200 mg tablet of cefixime produces an average peak serum concentration of approximately 2 mcg/mL (range 1 to 4 mcg/mL); a single 400 mg tablet produces an average peak concentration of approximately 3.7 mcg/mL (range 1.3 to 7.7 mcg/mL). The oral suspension produces average peak concentrations approximately 25% to 50% higher than the tablets, when tested in normal *adult* volunteers. Two hundred and 400 mg doses of oral suspension produce average peak concentrations of 3 mcg/mL (range 1 to 4.5 mcg/mL) and 4.6 mcg/mL (range 1.9 to 7.7 mcg/mL), respectively, when tested in normal *adult* volunteers. The area under the time versus concentration curve (AUC) is greater by approximately 10% to 25% with the oral suspension than with the tablet after doses of 100 to 400 mg, when tested in normal *adult* volunteers. This increased absorption should be taken into consideration if the oral suspension is to be substituted for the tablet. Because of the lack of bioequivalence, tablets should not be substituted for oral suspension in the treatment of otitis media [See **DOSAGE AND ADMINISTRATION** (2)]. Cross-over studies of tablet versus suspension have not been performed in children.

The 400 mg capsule is bioequivalent to the 400 mg tablet under fasting conditions. However, food reduces the absorption following administration of the capsule by approximately 15% based on AUC and 25% based on  $C_{max}$ .

Peak serum concentrations occur between 2 and 6 hours following oral administration of a single 200 mg tablet, a single 400 mg tablet or 400 mg of cefixime suspension. Peak serum concentrations occur between 2 and 5 hours following a single administration of 200 mg of suspension. Peak serum concentrations occur between 3 and 8 hours following oral administration of a single 400 mg capsule.

#### *Distribution*

Serum protein binding is concentration independent with a bound fraction of approximately 65%. In a multiple dose study conducted with a research formulation which is less bioavailable than the tablet or suspension, there was little accumulation of drug in serum or urine after dosing for 14 days. Adequate data on CSF levels of cefixime are not available.

### ***Metabolism and Excretion***

There is no evidence of metabolism of cefixime *in vivo*. Approximately 50% of the absorbed dose is excreted unchanged in the urine in 24 hours. In animal studies, it was noted that cefixime is also excreted in the bile in excess of 10% of the administered dose. The serum half-life of cefixime in healthy subjects is independent of dosage form and averages 3 to 4 hours but may range up to 9 hours in some normal volunteers.

### ***Special Populations***

**Geriatrics:** Average AUCs at steady state in elderly patients are approximately 40% higher than average AUCs in other healthy adults. Differences in the pharmacokinetic parameters between 12 young and 12 elderly subjects who received 400 mg of cefixime once daily for 5 days are summarized as follows:

<b>Pharmacokinetic Parameters (mean ± SD) for Cefixime in Both Young &amp; Elderly Subjects</b>		
<b>Pharmacokinetic parameter</b>	<b>Young</b>	<b>Elderly</b>
C <sub>max</sub> (mg/L)	4.74 ± 1.43	5.68 ± 1.83
T <sub>max</sub> (h)*	3.9 ± 0.3	4.3 ± 0.6
AUC (mg h/L)*	34.9 ± 12.2	49.5 ± 19.1
T <sub>½</sub> (h)*	3.5 ± 0.6	4.2 ± 0.4
C <sub>ave</sub> (mg/L)*	1.42 ± 0.50	1.99 ± 0.75
*Difference between age groups was significant. (p<0.05)		

However, these increases were not clinically significant [See **DOSAGE AND ADMINISTRATION (2)**].

**Renal Impairment:** In subjects with moderate impairment of renal function (20 to 40 mL/min creatinine clearance), the average serum half-life of cefixime is prolonged to 6.4 hours. In severe renal impairment (5 to 20 mL/min creatinine clearance), the half-life increased to an average of 11.5 hours. The drug is not cleared significantly from the blood by hemodialysis or peritoneal dialysis. However, a study indicated that with doses of 400 mg, patients undergoing hemodialysis have similar blood profiles as subjects with creatinine clearances of 21 to 60 mL/min.

## 12.4 Microbiology

### Mechanism of Action

Bactericidal action of cefixime results from inhibition of cell-wall synthesis.

Cefixime has been shown to be active against most isolates of the following bacteria both in vitro and in clinical infections [see **INDICATIONS AND USAGE (1)**]:

#### Gram-positive bacteria

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

#### Gram-negative bacteria

*Haemophilus influenzae*

*Moraxella catarrhalis*

*Escherichia coli*

*Proteus mirabilis*

*Neisseria gonorrhoeae*

The following in vitro data are available, but their clinical significance is unknown. Suprax exhibits in vitro MICs of 1 mcg/mL or less against most ( $\geq 90\%$ ) isolates of the following bacteria; however, the safety and effectiveness of Suprax in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

#### Gram-positive bacteria

*Streptococcus agalactiae*

#### Gram-negative bacteria

*Haemophilus parainfluenzae*

*Proteus vulgaris*

*Klebsiella pneumoniae*

*Klebsiella oxytoca*

*Pasteurella multocida*

*Providencia* species

*Salmonella* species

*Shigella* species

*Citrobacter amalonaticus*

*Citrobacter diversus*

*Serratia marcescens*

### ***Susceptibility Tests Methods***

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drugs used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

***Dilution Techniques:*** Quantitative methods are used to determine the minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using standardized test methods<sup>1,2</sup> (broth, and/or agar). The MIC values should be interpreted according to the criteria in Table 1.

***Diffusion Techniques:*** Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using standardized method.<sup>2,3</sup> This procedure uses paper disks impregnated with 5 mcg of cefixime to test the susceptibility of bacteria to cefixime. The disk diffusion interpretive criteria are provided in Table 1.

**Table 1: Susceptibility interpretive criteria for cefixime**

Pathogen	Minimum Inhibitory Concentrations (mcg/ml)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
<i>Neisseria gonorrhoeae</i>	≤ 0.25	- <sup>a</sup>	-	≥ 31	-	-
<i>H. influenzae</i>	≤ 1	-	-	≥ 21	-	-
<i>E. coli</i> and <i>P. mirabilis</i>	≤ 1	2	≥ 4	≥ 19	16 - 18	≤ 15

<sup>a</sup> Insufficient information is available to determine Intermediate or Resistant interpretive criteria

A report of “Susceptible” indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentration at the infection site necessary to inhibit growth of the pathogen. A report of “Intermediate” indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated. 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 the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

### ***Quality Control***

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.<sup>1,2,3</sup> The standard cefixime powder should provide the following range of MIC values provided in Table 2. For the diffusion technique using the 5-mcg cefixime disk the criteria provided in Table 2 should be achieved.

**Table 2: Acceptable Quality Control Ranges for Susceptibility Testing**

Quality Control Organisms	Minimum Inhibitory Concentrations (mcg/ml)	Disk Diffusion (zone diameters in mm)
<i>E. coli</i> ATCC 25922	0.25 - 1	23 - 27
<i>S. aureus</i> ATCC 29213	8 - 32	--
<i>H. influenzae</i> ATCC 49247	0.12-1	25-33
<i>N. gonorrhoeae</i> ATCC 49226	0.004 - 0.03	37 - 45

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies in animals to evaluate carcinogenic potential have not been conducted. Cefixime did not cause point mutations in bacteria or mammalian cells, DNA damage, or chromosome damage in vitro and did not exhibit clastogenic potential in vivo in the mouse micronucleus test. In rats, fertility and reproductive performance were not affected by cefixime at doses up to 25 times the adult therapeutic dose.

## 14 CLINICAL STUDIES

Comparative clinical trials of otitis media were conducted in nearly 400 children between the ages of 6 months to 10 years. *Streptococcus pneumoniae* was isolated from 47% of the patients, *Haemophilus influenzae* from 34%, *Moraxella catarrhalis* from 15% and *S. pyogenes* from 4%.

The overall response rate of *Streptococcus pneumoniae* to cefixime was approximately 10% lower and that of *Haemophilus influenzae* or *Moraxella catarrhalis* approximately 7% higher (12% when beta-lactamase positive isolates of *H. influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg twice a day or 8 mg/kg once a day, or with a comparator. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated 2 to 4 weeks post-treatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *Haemophilus influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the 2 to 4 week follow-up, a total of 30%-31% of patients had evidence of either treatment failure or recurrent disease.

<b>Bacteriological Outcome of Otitis Media at Two to Four Weeks Post-Therapy Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome</b>			
<b>Organism</b>	<b>Cefixime(a) 4 mg/kg BID</b>	<b>Cefixime(a) 8 mg/kg QD</b>	<b>Control(a) drugs</b>
<i>Streptococcus pneumoniae</i>	48/70 (69%)	18/22 (82%)	82/100 (82%)
<i>Haemophilus influenzae</i> beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
<i>Haemophilus influenzae</i> beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1 (b)
<i>Moraxella catarrhalis</i>	26/31 (84%)	5/5	18/24 (75%)
<i>S. pyogenes</i>	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

(a) Number eradicated/number isolated.

(b) An additional 20 beta-lactamase positive isolates of *Haemophilus influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In nineteen of these, the clinical course could be assessed and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

## 15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI) Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically: Approved Standard-9th Edition. CLSI Document M07-A9. CLSI, 950 West Valley Rd., Suite 2500, Wayne, PA 19087, 2012.
2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing 21st Informational Supplement, CLSI document M100-S22, CLSI, 2012.
3. CLSI. Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests. Approved Standard-11<sup>th</sup> Edition, CLSI document M02-A11, 2012.
4. Faulkner RD, Bohaychuk W, Lanc RA, et al.: Pharmacokinetics of cefixime in the young and elderly. *J Antimicrob Chemother* 1988; 21(6): 787-794.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Suprax<sup>®</sup> is available for oral administration in following dosage forms, strengths and packages listed in the table below:

Dosage Form	Strength	Description	Package Size	NDC Code	Storage
Suprax <sup>®</sup> (cefixime) Tablets USP	400 mg	White to off-white, film-coated, capsule shaped tablets with beveled edges and a divided score line on each side, debossed with "SUPRAX" across one side and "LUPIN" across other side containing 400 mg of cefixime as the trihydrate	Bottles of 10 tablets	27437-201-10	Store at 20 to 25°C (68 to 77°F) [See USP Controlled Room Temperature].
			Bottle of 50 tablets	27437-201-08	
			Bottle of 100 tablets	27437-201-01	
Suprax <sup>®</sup> (cefixime) Capsules	400 mg	Size "00EL" capsules with dark brown cap and dark brown body imprinted with "LU" on cap and "U43" on body in white ink containing white to yellowish white granular powder containing 400 mg of cefixime as the trihydrate	Bottle of 50 capsules	27437-208-08	Store at 20 to 25°C (68 to 77°F) [See USP Controlled Room Temperature].
Suprax <sup>®</sup> (cefixime) for Oral Suspension USP	100 mg/5 mL	Off-white to pale yellow colored powder. After reconstitution as directed, each 5 mL of reconstituted suspension contains 100 mg of cefixime as the trihydrate	Bottle of 50 mL	68180-202-03	<u>Prior to reconstitution:</u> Store drug powder at 20 to 25°C (68 to 77°F) [See USP Controlled Room Temperature].  <u>After reconstitution:</u> Store at room temperature or under refrigeration. Keep tightly closed.
			Bottle of 75 mL	68180-202-02	
			Bottle of 100 mL	68180-202-01	
	200 mg/5 mL	Off-white to pale yellow colored powder. After reconstituted as directed, each 5 mL of reconstituted suspension contains 200 mg of cefixime as the trihydrate	Bottle of 25 mL	27437-206-05	
			Bottle of 37.5 mL	27437-206-06	
			Bottle of 50 mL	27437-206-03	
			Bottle of 75 mL	27437-206-02	
			Bottle of 100 mL	27437-206-01	

## 17 PATIENT COUNSELING INFORMATION

### 17.1 Information for Patients

Patients should be counseled that antibacterial drugs, including cefixime, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When cefixime is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cefixime for oral suspension or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Manufactured for:

- 1) Suprax<sup>®</sup> (cefixime) Tablets USP, 400 mg; Suprax<sup>®</sup> (cefixime) Capsules, 400 mg and Suprax<sup>®</sup> (cefixime) for Oral Suspension USP, 200 mg/5 mL:

#### **Lupin Pharma**

Baltimore, Maryland 21202

United States.

- 2) Suprax<sup>®</sup> (cefixime) for Oral Suspension USP, 100 mg/5 mL:

#### **Lupin Pharmaceuticals Inc.**

Baltimore, Maryland 21202

United States.

Manufactured by:

#### **Lupin Limited**

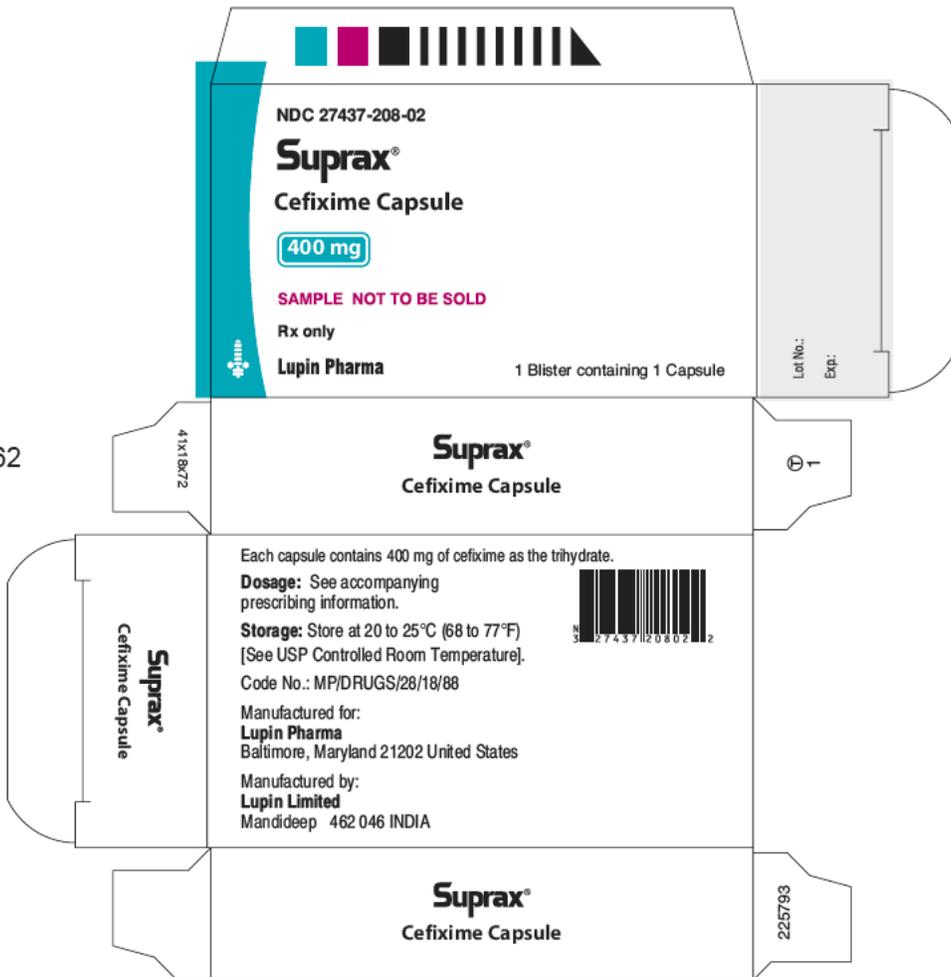
Mandideep 462 046

India.

May 2012

03.05.2012  
225793 Suprax 400 mg Option-1

D: 3139062



(b) (4)

## Artwork for USFDA Submission 2012

**NDC 27437-208-08**

**Suprax<sup>®</sup>**

**Cefixime Capsules**

**400 mg**

**Rx only**

**50 Capsules**

**Lupin Pharma**

Each capsule contains 400 mg of cefixime as the trihydrate.

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

This package not for household dispensing. Dispense in tight, light-resistant containers as defined in the USP.

**Dosage:**  
See accompanying prescribing information.

Manufactured for:  
**Lupin Pharma**  
Baltimore, Maryland 21202 United States

Manufactured by:  
**Lupin Limited**  
Mandideep 462 046 INDIA  
Code No. MP/DRUGS/28/18/88

225784

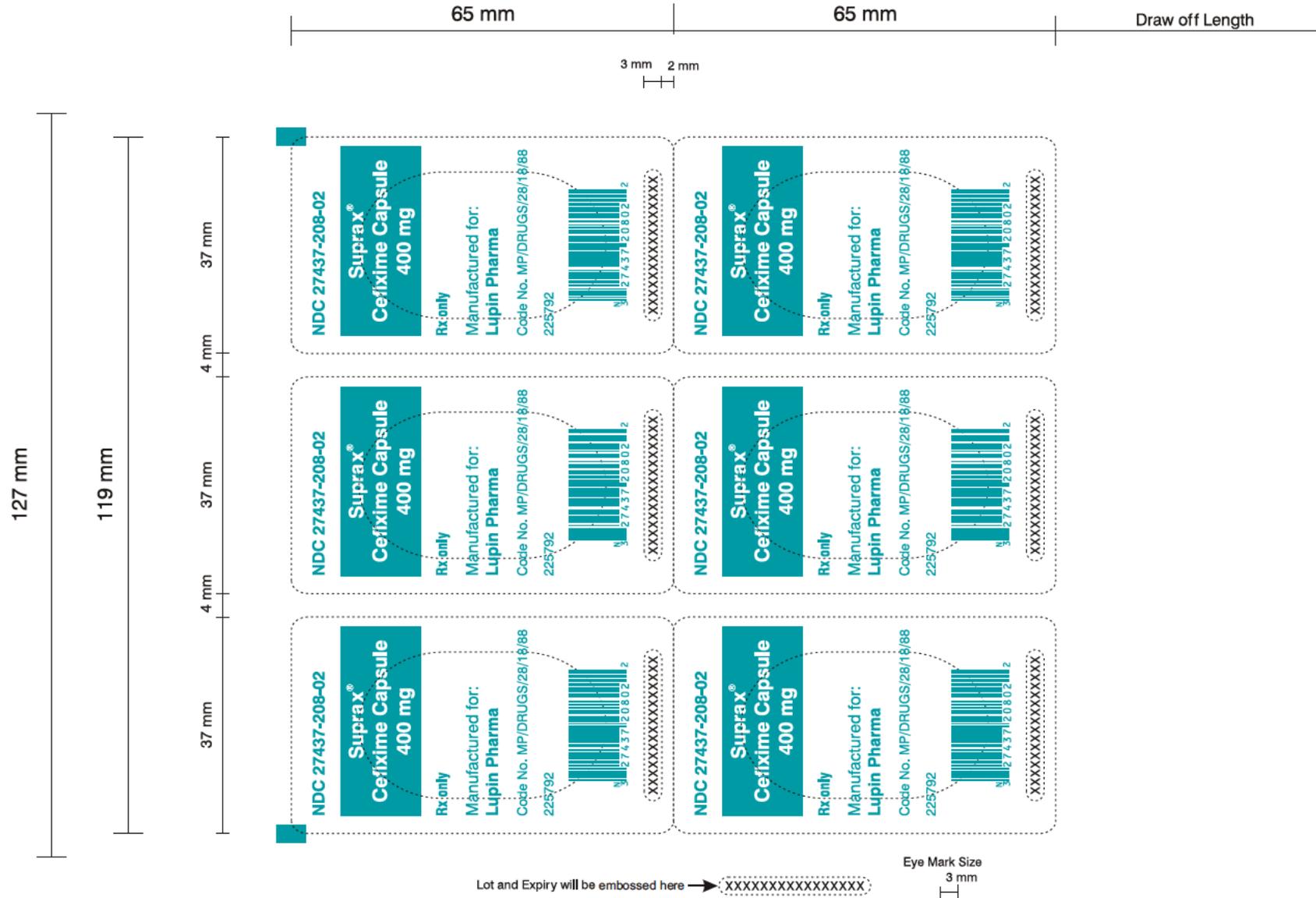
27437208084

LOT NO.  
EXP.

18 x 36 mm

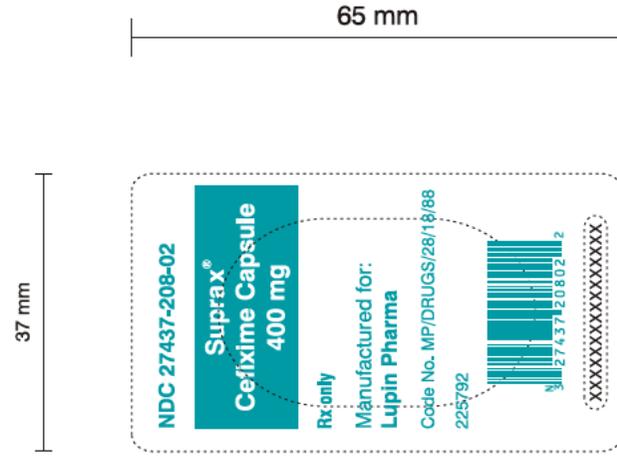
(b) (4)

# Artwork for USFDA Submission 2012



(b) (4)

# Artwork for USFDA Submission 2012



-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

KATHERINE A LAESSIG  
06/01/2012