DICLOXACILLIN SODIUM - dicloxacillin sodium capsule
H.J. Harkins Company, Inc.

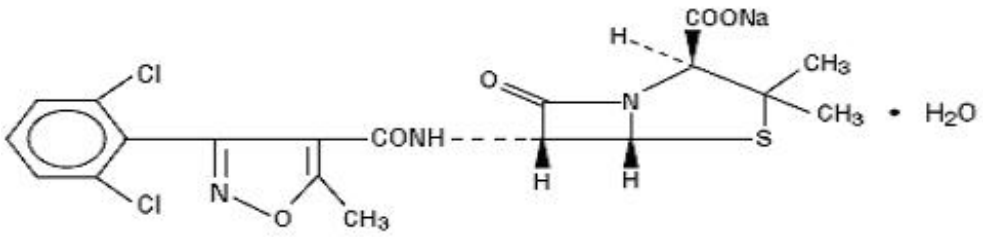
DICLOXACILLIN SODIUM CAPSULES USP
3123
3125
Rx only

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

DESCRIPTION

Dicloxacillin sodium is a semisynthetic antibiotic substance which resists destruction by the enzyme penicillinase(beta - lactamase). It is monosodium (2*S*,5*R*,6*R*)-6-[3-(2,6-dichlorophenyl)- 5-methyl-4-isoxazolecarboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0]heptane-2-carboxylate monohydrate.

Dicloxacillin is administered orally via capsule form or powder for reconstitution. Structurally, dicloxacillin sodium may be represented as follows:



$C_{19}H_{16}Cl_2N_3NaO_5$ S·H_2O MW 510.32

Inactive Ingredients

Capsules

Magnesium Stearate.

Capsule Shell and Print Constituents

D&C Yellow #10 Aluminum Lake, FD&C Blue #1 Aluminum Lake, FD&C Blue #2 Aluminum Lake, FD&C Red #40 Aluminum Lake, Gelatin, Pharmaceutical Glaze, Silicon Dioxide, Sodium Lauryl Sulfate, Synthetic Black Iron Oxide, Titanium Dioxide and may contain Carboxymethylcellulose Sodium and/or Propylene Glycol.

CLINICAL PHARMACOLOGY

Microbiology

Dicloxacillin exerts a bactericidal action against penicillin-susceptible microorganisms during the state of active multiplication. All penicillins inhibit the biosynthesis of the bacterial cell wall.

The drugs in this class are highly resistant to inactivation by staphylococcal penicillinase and are active

against penicillinase-producing and nonpenicillinase-producing strains of *Staphylococcus aureus*. The penicillinase- resistant penicillins are active *in vitro* against a variety of other bacteria.

Susceptibility Plate Testing

Quantitative methods of susceptibility testing that require measurements of zone diameters or minimal inhibitory concentrations (MICs) give the most precise estimates of antibiotic susceptibility. One such procedure has been recommended for use with discs to test susceptibility to this class of drugs. Interpretations correlate diameters on the disc test with MIC values.

A penicillinase-resistant class disc may be used to determine microbial susceptibility to dicloxacillin.

TABLE I shows the interpretation of test results for penicillinase-resistant penicillins using the FDA Standard Disc Test Method (formerly Bauer-Kirby-Sherris-Turck method) of disc bacteriological susceptibility testing for staphylococci with a disc containing 5 micrograms of methicillin sodium.

With this procedure, a report from a laboratory of “susceptible” indicates that the infecting organism is likely to respond to therapy. A report of “resistant” indicates that the infecting organism is not likely to respond to therapy. A report of “intermediate” susceptibility suggests that the organism might be susceptible if high doses of the antibiotic are used, or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained.

In general, all staphylococci should be tested against the penicillin G disc and against the methicillin disc. Routine methods of antibiotic susceptibility testing may fail to detect strains of organisms resistant to the penicillinase-resistant penicillins. For this reason, the use of large inocula and 48 hour incubation periods may be necessary to obtain accurate susceptibility studies with these antibiotics. Bacterial strains which are resistant to one of the penicillinase-resistant penicillins should be considered resistant to all of the drugs in the class.

Table I STANDARDIZED DISC TEST METHOD OF BACTERIOLOGICAL SUSCEPTIBILITY TESTING USING A CLASS DISC CONTAINING 5 MICROGRAMS OF METHICILLIN SODIUM

Diameter of Zone	Diameter of Zone	Diameter of Zone
Indicating “Susceptible”	Indicating	Indicating “Resistant”
at least	“Intermediate”	Less than
14 mm	10 – 13 mm	10 mm

Pharmacokinetics

Methicillin sodium is readily destroyed by gastric acidity and must be administered by intramuscular or intravenous injection. The isoxazolyl penicillins (cloxacillin, dicloxacillin and oxacillin) and nafcillin are more acid-resistant and may be administered orally.

Absorption of the isoxazolyl penicillins after oral administration is rapid but incomplete; peak blood levels are achieved in 1-1.5 hours. In one study, after ingestion of a single 500 mg oral dose, peak serum concentrations range from 5-7 micrograms/milliliter for oxacillin, from 7.5-14.4 mcg/mL for cloxacillin and from 10-17 mcg/mL for dicloxacillin.

Oral absorption of cloxacillin, dicloxacillin, oxacillin and nafcillin is delayed when the drugs are administered after meals.

Once absorbed, the penicillinase-resistant penicillins bind to serum protein, mainly albumin. The degree of protein binding reported varies with the method of study and the investigator (see **TABLE II**).

TABLE II
PENICILLINASE-RESISTANT PENICILLINS PERCENT PROTEIN BINDING ± SD

Methicillin	37.3 ± 7.9
Nafcillin	89.9 ± 1.5
Oxacillin	94.2 ± 2.1
Cloxacillin	95.2 ± 0.5
Dicloxacillin	97.9 ± 0.6

The penicillinase-resistant penicillins vary in the extent to which they are distributed in the body fluids. With normal doses, insignificant concentrations are found in the cerebrospinal fluid and aqueous humor. All the drugs in this class are found in therapeutic concentrations in the pleural, bile and amniotic fluids.

The penicillinase-resistant penicillins are rapidly excreted, primarily as unchanged drug in the urine by glomerular filtration and active tubular secretion. The elimination half-life for dicloxacillin is about 0.7 hour. Nonrenal elimination includes hepatic inactivation and excretion in bile.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of dicloxacillin sodium capsules USP and other antibacterial drugs, dicloxacillin sodium capsules USP should be used only to treat or prevent 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 antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Dicloxacillin is indicated in the treatment of infections caused by penicillinase-producing staphylococci which have demonstrated susceptibility to the drug. Cultures and susceptibility tests should be performed initially to determine the causative organisms and their sensitivity to the drug. (see **CLINICAL PHARMACOLOGY – Susceptibility Plate Testing).**

Dicloxacillin may be used to initiate therapy in suspected cases of resistant staphylococcal infections prior to the availability of laboratory test results. The penicillinase-resistant penicillins should not be used in infections caused by organisms susceptible to penicillin G. If the susceptibility tests indicate that the infection is due to an organism other than a resistant staphylococcus, therapy should not be continued with a penicillinase-resistant penicillin.

CONTRAINDICATIONS

A history of a hypersensitivity (anaphylactic) reaction to any penicillin is a contraindication.

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactic shock with collapse) reactions have occurred in patients receiving penicillin. The incidence of anaphylactic shock in all penicillin-treated patients is between 0.015% and 0.04%. Anaphylactic shock resulting in death has occurred in approximately 0.002% of the patients treated. Although anaphylaxis is more frequent following a parenteral administration, it has occurred in patients receiving oral penicillins.

When penicillin therapy is indicated, it should be initiated only after a comprehensive patient drug and allergy history has been obtained. If an allergic reaction occurs, the drug should be discontinued and the patient should receive supportive treatment, e.g., artificial maintenance of ventilation, pressor amines, antihistamines and corticosteroids. Individuals with a history of penicillin hypersensitivity may also experience allergic reactions when treated with a cephalosporin.

PRECAUTIONS

General

Prescribing dicloxacillin sodium capsules USP in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Dicloxacillin should generally not be administered to patients with a history of sensitivity to any penicillin.

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma. Whenever allergic reactions occur, penicillin should be withdrawn unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to penicillin therapy.

The oral route of administration should not be relied upon in patients with severe illness, or with nausea, vomiting, gastric dilatation, cardiospasm or intestinal hypermotility. Occasionally, patients will not absorb therapeutic amounts of orally administered penicillin.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. If new infections due to bacteria or fungi occur, the drug should be discontinued and appropriate measures taken.

Information for the Patient

Patients should be counselled that antibacterial drugs including dicloxacillin sodium capsules USP should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When dicloxacillin sodium capsules USP are 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 dicloxacillin sodium capsules USP or other antibacterial drugs in the future.

Patients receiving penicillins should be given the following information and instructions by the physician:

1. Patients should be told that penicillin is an antibacterial agent which will work with the body's natural defenses to control certain types of infections. They should be told that the drug should not be taken if they have had an allergic reaction to any form of penicillin previously, and to inform the physician of any allergies or previous allergic reactions to any drugs they may have had (see **WARNINGS**).
2. Patients who have previously experienced an anaphylactic reaction to penicillin should be instructed to wear a medical identification tag or bracelet.
3. Because most antibacterial drugs taken by mouth are best absorbed on an empty stomach, patients should be directed, unless circumstances warrant otherwise, to take penicillin one hour before meals or two hours after eating (see **CLINICAL PHARMACOLOGY - Pharmacokinetics**).
4. Patients should be told to take the entire course of therapy prescribed, even if fever and other symptoms have stopped (see **PRECAUTIONS - General**).
5. If any of the following reactions occur, stop taking your prescription and notify the physician: shortness of breath, wheezing, skin rash, mouth irritation, black tongue, sore throat, nausea, vomiting, diarrhea, fever, swollen joints or any unusual bleeding or bruising (see **ADVERSE**

REACTIONS).

6. Do not take any additional medications without physician approval, including nonprescription drugs such as antacids, laxatives or vitamins.
7. Discard any liquid forms of penicillin after seven days if stored at room temperature or after 14 days if refrigerated.

Laboratory Tests

Bacteriologic studies to determine the causative organisms and their susceptibility to the penicillinase-resistant penicillins should be performed (see **CLINICAL PHARMACOLOGY - Microbiology**). In the treatment of suspected staphylococcal infections, therapy should be changed to another active agent if culture tests fail to demonstrate the presence of staphylococci.

Periodic assessment of organ system function, including renal, hepatic and hematopoietic, should be made during prolonged therapy with the penicillinase-resistant penicillins.

Blood cultures, white blood cell and differential cell counts should be obtained prior to initiation of therapy and at least weekly during therapy with penicillinase-resistant penicillins.

Periodic urinalysis, blood urea nitrogen and creatinine determinations should be performed during therapy with the penicillinase-resistant penicillins and dosage alterations should be considered if these values become elevated. If any impairment of renal function is suspected or known to exist, a reduction in the total dosage should be considered and blood levels monitored to avoid possible neurotoxic reactions (see **DOSAGE AND ADMINISTRATION**).

SGOT and SGPT values should be obtained periodically during therapy to monitor for possible liver function abnormalities.

Drug Interactions

Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin and concurrent use of these drugs should be avoided.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been conducted with these drugs.

Studies on reproduction (nafcillin) in rats and rabbits reveal no fetal or maternal abnormalities before conception and continuously through weaning (one generation).

Pregnancy Category B

Reproduction studies performed in the mouse, rat and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to the penicillinase-resistant penicillins. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate or well-controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Penicillins are excreted in breast milk. Caution should be exercised when penicillins are administered to a nursing woman.

Pediatric Use

Because of incompletely developed renal function in newborns, penicillinase-resistant penicillins (especially methicillin) may not be completely excreted, with abnormally high blood levels resulting. Frequent monitoring of blood levels is advisable in this group, with dosage adjustments when

necessary. All newborns treated with penicillins should be monitored closely for clinical and laboratory evidence of toxic or adverse effects (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Body as a Whole

The reported incidence of allergic reactions to penicillin ranges from 0.7% to 10% (see **WARNINGS**). Sensitization is usually the result of treatment, but some individuals have had immediate reactions to penicillin when first treated. In such cases, it is thought that the patients may have had prior exposure to the drug via trace amounts present in milk and vaccines.

Two types of allergic reactions to penicillin are noted clinically, immediate and delayed.

Immediate reactions usually occur within 20 minutes of administration and range in severity from urticaria and pruritus to angioneurotic edema, laryngospasm, bronchospasm, hypotension, vascular collapse and death. Such immediate anaphylactic reactions are very rare (see **WARNINGS**) and usually occur after parenteral therapy, but have occurred in patients receiving oral therapy. Another type of immediate reaction, an accelerated reaction, may occur between 20 minutes and 48 hours after administration and may include urticaria, pruritus and fever. Although laryngeal edema, laryngospasm and hypotension occasionally occur, fatality is uncommon.

Delayed allergic reactions to penicillin therapy usually occur after 48 hours and sometimes as late as two to four weeks after initiation of therapy. Manifestations of this type of reaction include serum sickness-like symptoms (i.e., fever, malaise, urticaria, myalgia, arthralgia, abdominal pain) and various skin rashes. Nausea, vomiting, diarrhea, stomatitis, black or hairy tongue and other symptoms of gastrointestinal irritation may occur, especially during oral penicillin therapy.

Nervous System Reactions

Neurotoxic reactions similar to those observed with penicillin G may occur with large intravenous doses of the penicillinase-resistant penicillins, especially with patients with renal insufficiency.

Urogenital Reactions

Renal tubular damage and interstitial nephritis have been associated with the administration of methicillin sodium and, infrequently, with the administration of nafcillin and oxacillin. Manifestations of this reaction may include rash, fever, eosinophilia, hematuria, proteinuria and renal insufficiency. Methicillin-induced nephropathy does not appear to be dose-related and is generally reversible upon prompt discontinuation of therapy.

Metabolic Reactions

Agranulocytosis, neutropenia and bone marrow depression have been associated with the use of methicillin sodium and nafcillin. Hepatotoxicity, characterized by fever, nausea and vomiting associated with abnormal liver function tests, mainly elevated SGOT levels, has been associated with the use of oxacillin.

RECOMMENDED DOSAGES FOR DICLOXACILLIN IN MILD TO MODERATE AND SEVERE INFECTIONS

DRUG	ADULTS		CHILDREN	
	Mild to Moderate	Severe	Mild to Moderate	Severe
Dicloxacillin	125 mg	250 mg	12.5	25

Dicloxacillin	every	mg every	mg/kg/day*	mg/kg/day*
	6 hours	6 hours	in equally	in equally
			divided doses	divided doses
			every 6 hours	every 6 hours
* Patients weighing less than 40 kg (88 lbs)				

DOSAGE AND ADMINISTRATION

Bacteriologic studies to determine the causative organisms and their sensitivity to the penicillinase-resistant penicillins should always be performed. Duration of therapy varies with the type and severity of infection as well as the overall condition of the patient, therefore it should be determined by the clinical and bacteriological response of the patient. In severe staphylococcal infections, therapy with penicillinase-resistant penicillins should be continued for at least 14 days. Therapy should be continued for at least 48 hours after the patient has become afebrile, asymptomatic and cultures are negative. The treatment of endocarditis and osteomyelitis may require a longer term of therapy.

Concurrent administration of the penicillinase-resistant penicillins and probenecid increases and prolongs serum penicillin levels.

Probenecid decreases the apparent volume of distribution and slows the rate of excretion by competitively inhibiting renal tubular secretion of penicillin. Penicillin-probenecid therapy is generally limited to those infections where very high serum levels of penicillin are necessary.

Oral preparations of the penicillinase-resistant penicillins should not be used as initial therapy in serious, life-threatening infections (see **PRECAUTIONS - General**). Oral therapy with the penicillinase-resistant penicillins may be used to follow up the previous use of a parenteral agent as soon as the clinical condition warrants. For intramuscular gluteal injections, care should be taken to avoid sciatic nerve injury. With intravenous administration, particularly in elderly patients, care should be taken because of the possibility of thrombophlebitis.

NB: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

HOW SUPPLIED

Dicloxacillin sodium capsules USP are available as follows:

250 mg: Each capsule contains dicloxacillin sodium monohydrate equivalent to 250 mg dicloxacillin, with green colored cap and light green colored body, imprinted "TEVA" on the cap and “3123” on the body, available in bottles of 100.

500 mg: Each capsule contains dicloxacillin sodium monohydrate equivalent to 500 mg dicloxacillin, with green colored cap and light green colored body, imprinted "TEVA" on the cap and “3125” on the body, available in bottles of 100.

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

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

References Available Upon Request.

Manufactured In Canada By:

TEVA CANADA LIMITED

Toronto, Canada M1B 2K9

Manufactured For:

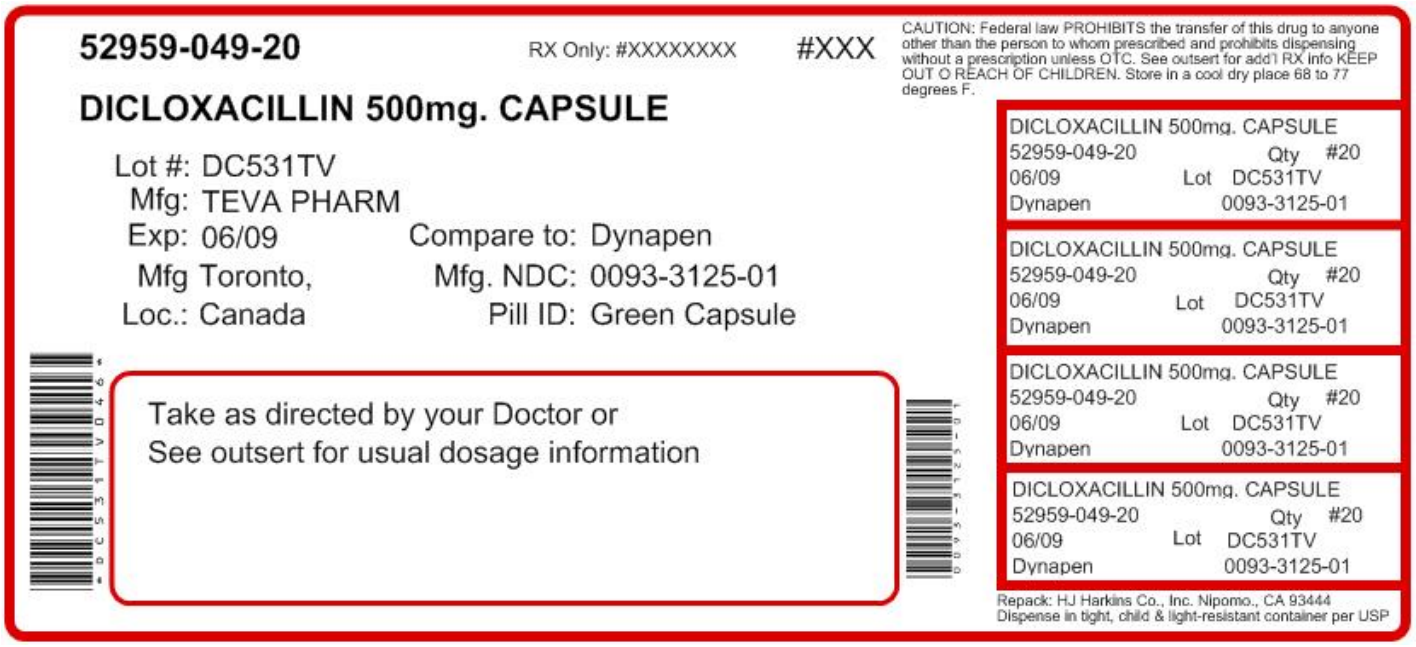
TEVA PHARMACEUTICALS USA

Sellersville, PA 18960

Rev. E 10/2010

Repacked by:
H.J. Harkins Company, Inc.
513 Sandydale Drive
Nipomo, CA 93444

PRINCIPAL DISPLAY PANEL



Dicloxacillin Sodium Capsules 500 mg 100s Label Text

NDC 0093-**3125**-01

New Product Appearance

DICLOXACILLIN

SODIUM

Capsules USP

500 mg*

Rx only

100 Capsules

TEVA

DICLOXACILLIN SODIUM

dicloxacillin sodium capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:52959-049(NDC:0093-3125)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DICLOXACILLIN SODIUM (UNII: 4HZT2V9KX0) (DICLOXACILLIN - UNII:COF19H7WBK)	DICLOXACILLIN	500 mg

Inactive Ingredients

Ingredient Name	Strength
MAGNESIUM STEARATE (UNII: 70097M6I30)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
ALUMINUM OXIDE (UNII: LMI26O6933)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
GELATIN (UNII: 2G86QN327L)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
CARBOXYMETHYLCELLULOSE SODIUM (UNII: K679OBS311)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	

Product Characteristics

Color	GREEN (light green) , GREEN	**Score**	no score
Shape	CAPSULE	**Size**	22mm
Flavor		**Imprint Code**	TEVA;3125
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52959-049-20	20 in 1 BOTTLE		
2	NDC:52959-049-21	21 in 1 BOTTLE		
3	NDC:52959-049-28	28 in 1 BOTTLE		
4	NDC:52959-049-30	30 in 1 BOTTLE		
5	NDC:52959-049-40	40 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA062286	01/20/2011	

Labeler - H.J. Harkins Company, Inc. (147681894)

Establishment

Name	Address	ID/FEI	Business Operations
TEVA Pharmaceuticals USA Inc		118234421	MANUFACTURE

Revised: 12/2011 H.J. Harkins Company, Inc.