MONODOX- doxycycline monohydrate capsule
DIERCT RX

DOXYCYCLINE MONOHYDRATE

Doxycycline is a broad-spectrum antibacterial synthetically derived from oxytetracycline. Doxycycline capsules USP, 50 mg, 75 mg, and 100 mg contain doxycycline monohydrate equivalent to 50 mg, 75mg, and 100 mg of doxycycline for oral administration. The chemical designation of the light yellow to pale yellow powder is 2-Naphthacenecarboxamide,4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-,[4S-4ą,4aą,5ą,5aą,6ą,12aą)]-, monohydrate.

Structural formula:
structure

C22H24N2O8 • H2O M.W. = 462.45

Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

Inert ingredients: colloidal silicon dioxide; magnesium stearate; microcrystalline cellulose; sodium starch glycolate; and a hard gelatin capsule which contains titanium dioxide, FD&C Red # 3, D&C Yellow # 10, gelatin, sodium lauryl sulfate, for the 50 mg strength; iron oxide black, iron oxide red, iron oxide yellow, titanium dioxide, gelatin, sodium lauryl sulfate for the 75 mg strength and iron oxide black, Iron Oxide Red, Iron Oxide Yellow, Titanium Dioxide, FD & C Red # 3, D&C Yellow # 10, gelatin, sodium lauryl sulfate for the 100 mg strength. The capsules are printed with edible ink containing shellac, titanium dioxide, black iron oxide, brown iron oxide and potassium hydroxide for 50 mg, 75 mg and 100 mg strengths.

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degrees. They areconcentrated by the liver in the bile and excreted in the urine and feces at high concentrations in abiologically active form. Doxycycline is virtually completely absorbed after oral administration.

Following a 200 mg dose of doxycycline monohydrate, 24 normal adult volunteers averaged thefollowing serum concentration values:

values
Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal function(creatinine clearance about 75 mL/min). This percentage excretion may fall as low as 1-5%/72 hoursin individuals with severe renal insufficiency (creatinine clearance below 10 mL/min). Studies haveshown no significant difference in serum half-life of doxycycline (range 18 to 22 hours) in individualswith normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria. Cross resistance with other tetracyclines is common.

Doxycycline has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section of the package insert.

Gram-Negative Bacteria
Acinetobacter species
Bartonella bacilliformis
Brucella species
Enterobacter aerogenes
Escherichia coli

Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
Klebsiella granulomatis
Klebsiella species
Neisseria gonorrhoeae
Shigella species
Vibrio cholerae
Vibrio fetus
Yersinia pestis

Gram-Positive Bacteria
Bacillus anthracis
Streptococcus pneumoniae

Anaerobes
Clostridium species
Fusobacterium fusiforme
Propionibacterium acnes

Other Bacteria
Nocardiae and other aerobic Actinomyces species
Borrelia recurrentis
Chlamydophila psittaci
Chlamydia trachomatis
Mycoplasma pneumoniae
Rickettsiae
Treponema pallidum
Treponema pallidum subspecies pertenue
Ureaplasma urealyticum

Parasites
Balantidium coli
Entamoeba species
Plasmodium falciparum*

*Doxycycline has been found to be active against the asexual erythrocytic forms of Plasmodium falciparum, but not against the gametocytes of P. falciparum. The precise mechanism of action of the drug is not known.

Susceptibility Testing 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 the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs).These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method (broth and/or agar).1,2,4,6,7 The MIC values should be interpreted according to criteria provided 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 a standardized test method.1,3,4 This procedure uses paper disks impregnated with 30 mcg doxycycline to test the susceptibility of bacteria to doxycycline.The disk diffusion interpretive criteria are provided in Table 1.

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to doxycycline can be determined by a standardized test method.5 The MIC values obtained should be interpreted according to the criteria provided in Table1.

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A report of Susceptible (S) indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of Intermediate (I) indicates that the result should be considered equivocal, and, if the bacteria 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 product 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 (R) indicates that the pathogen 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 the supplies and reagents used in the assay, and the techniques of the individuals performing the test.1,2,3,4,5,6,7 Standard doxycycline and tetracycline powders should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 30 mcg doxycycline disk the criteria noted in Table 2 should be achieved.

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To reduce the development of drug-resistant bacteria and maintain effectiveness of doxycycline capsules, USP and other antibacterial drugs, doxycycline 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.

Doxycycline is indicated for the treatment of the following infections:
Rocky mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers caused by Rickettsiae.
Respiratory tract infections caused by Mycoplasma pneumoniae.
Lymphogranuloma venereum caused by Chlamydia trachomatis.
Psittacosis (ornithosis) caused by Chlamydophila psittaci.
Trachoma caused by Chlamydia trachomatis, although the infectious agent is not always eliminated as judged by immunofluorescence.
Inclusion conjunctivitis caused by Chlamydia trachomatis.
Uncomplicated urethral, endocervical or rectal infections in adults caused by Chlamydia trachomatis.
Nongonococcal urethritis caused by Ureaplasma urealyticum.
Relapsing fever due to Borrelia recurrentis.

Doxycycline is also indicated for the treatment of infections caused by the following gram-negative microorganisms:
Chancroid caused by Haemophilus ducreyi.
Plague due to Yersinia pestis.
Tularemia due to Francisella tularensis.
Cholera caused by Vibrio cholerae.

Campylobacter fetus infections caused by Campylobacter fetus.
Brucellosis due to Brucella species (in conjunction with streptomycin).
Bartonellosis due to Bartonella bacilliformis.
Granuloma inguinale caused by Calymmatobacterium granulomatis.

Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriologic testing indicates appropriate susceptibility to the drug:
Escherichia coli
Enterobacter aerogenes
Shigella species
Acinetobacter species
Respiratory tract infections caused by Haemophilus influenzae.
Respiratory tract and urinary tract infections caused by Klebsiella species.

Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:
Upper respiratory infections caused by Streptococcus pneumoniae.
Anthrax due to Bacillus anthracis, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized Bacillus anthracis.

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections:
Uncomplicated gonorrhea caused by Neisseria gonorrhoeae.
Syphilis caused by Treponema pallidum.
Yaws caused by Treponema pertenue.
Listeriosis due to Listeria monocytogenes.
Vincent's infection caused by Fusobacterium fusiforme.
Actinomycosis caused by Actinomyces israelii.
Infections caused by Clostridium species.

In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides.

In severe acne, doxycycline may be useful adjunctive therapy.

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

As with other antibacterial preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracyclines including doxycycline. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Concomitant use of isotretinoin and doxycycline should be avoided because isotretinoin is also known to cause pseudotumor cerebri.

Although IH typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize.

Incision and drainage or other surgical procedures should be performed in conjunction with antibacterial therapy when indicated.

Prescribing doxycycline capsules in the absence of 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.

All patients taking doxycycline should be advised:

–to avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if phototoxicity (e.g., skin eruptions, etc.) occurs. Sunscreen or sunblock should be considered. (See WARNINGS.)

–to drink fluids liberally along with doxycycline to reduce the risk of esophageal irritation and ulceration. (See ADVERSE REACTIONS.)

–that the absorption of tetracyclines is reduced when taken with foods, especially those which contain calcium. However, the absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk. (See Drug Interactions.)

–that the absorption of tetracyclines is reduced when taking bismuth subsalicylate. (See Drug Interactions.)

–not to use outdated or poorly stored doxycycline.

–that the use of doxycycline might increase the incidence of vaginal candidiasis.

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.

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

In venereal disease when coexistent syphilis is suspected, a dark-field examination should be done before treatment is started and the blood serology repeated monthly for at least four months.

In long-term therapy, periodic laboratory evaluations of organ systems, including hematopoietic, renal, and hepatic studies should be performed.

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines in conjunction with penicillin.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, and iron-containing preparations.

Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Concurrent use of tetracycline may render oral contraceptives less effective.

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Long-term studies in animals to evaluate the carcinogenic potential of doxycycline have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with related antibacterial, oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors). Likewise,

although mutagenicity studies of doxycycline have not been conducted, positive results in in vitro mammalian cell assays have been reported for related antibacterial (tetracycline, oxytetracycline). Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

Teratogenic Effects.

Pregnancy Category D:

There are no adequate and well-controlled studies on the use of doxycycline in pregnant short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for treatment of anthrax exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS - the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair), but the data are insufficient to state that there is no risk.8

A case-control study (18,515 mothers of infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. (Sixty-three [0.19%] of the controls and 56 [0.30%] of the cases were treated with doxycycline.) This association was not seen when the analysis was confined to maternal treatment during the period of organogenesis (i.e., in the second and third months of gestation) with the exception of a marginal relationship with neural tube defect based on only two exposed cases.9

A small prospective study of 81 pregnancies describes 43 pregnant women treated for 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age.10

The effect of tetracyclines on labor and delivery is unknown.

Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated; however, the effects of prolonged exposure to doxycycline in breast milk are unknown.11 Because of the potential for adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See WARNINGS.)

Due to oral doxycycline’s virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines.

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. Hepatotoxicity has been reported. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline class. Most of these patients took medications immediately before going to bed. (See DOSAGE AND ADMINISTRATION.)

Skin: Maculopapular and erythematous rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See WARNINGS.)

Renal Toxicity: Rise in BUN has been reported and is apparently dose related. (See WARNINGS.)

Hypersensitivity Reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported with tetracyclines.

Other: Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracyclines. (See PRECAUTIONS-General.)

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid gland. No abnormalities of thyroid function are known to occur.

To report SUSPECTED ADVERSE REACTIONS, contact G&W Laboratories, Inc. at 1-800-922-1038 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life, and it would not be of benefit in treating cases of overdosage.

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours or 50 mg every 6 hours) followed by a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For pediatric patients above eight years of age: The recommended dosage schedule for pediatric patients weighing 100 pounds or less is 2 mg/lb of body weight divided into two doses on the first day of treatment, followed by 1 mg/lb of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 2 mg/lb of body weight may be used. For pediatric patients over 100 pounds the usual adult dose should be used.

Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice a day for 7 days. As an alternate single visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose.

Acute epididymo-orchitis caused by N. gonorrhoeae: 100 mg, by mouth, twice a day for at least 10 days.

Primary and secondary syphilis: 300 mg a day in divided doses for at least 10 days.

Uncomplicated urethral, endocervical, or rectal infection in adults caused by Chlamydia trachomatis: 100 mg, by mouth, twice a day for at least 7 days.

Nongonococcal urethritis caused by C. trachomatis and U. urealyticum: 100 mg, by mouth, twice a day for at least 7 days.

Acute epididymo-orchitis caused by C. trachomatis: 100 mg, by mouth, twice a day for at least 10 days.

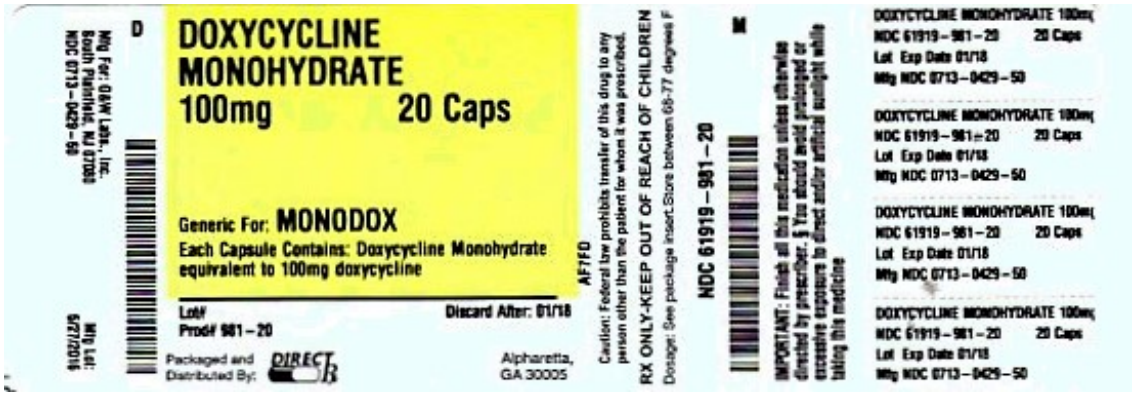
Inhalational anthrax (post-exposure): ADULTS: 100 mg of doxycycline, by mouth, twice a day for 60 days. CHILDREN: weighing less than 100 pounds (45 kg); 1 mg/lb (2.2 mg/kg) of body weight, by mouth, twice a day for 60 days. Children weighing 100 pounds or more should receive the adult dose.

When used in streptococcal infections, therapy should be continued for 10 days.

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration. (See ADVERSE REACTIONS.) If gastric irritation occurs, doxycycline may be given with food. Ingestion of a high fat meal has been shown to delay the time to peak plasma concentrations by an average of one hour and 20 minutes. However, in the same study, food enhanced the average peak concentration by 7.5% and the area under the curve by 5.7%.

Doxycycline Capsules, USP 50 mg have a yellow opaque cap and a white opaque body. The capsules are imprinted “NL 790” with white ink on the cap and “50 mg” with brown ink on the body, filled with yellow to beige powder. Each capsule contains doxycycline monohydrate equivalent to 50 mg

doxycycline.



MONODOX

doxycycline monohydrate capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61919-981(NDC:0713-0429)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DOXYCYCLINE (UNII: N12000U13O) (DOXYCYCLINE ANHYDROUS - UNII:334895S862)	DOXYCYCLINE ANHYDROUS	100 mg

Inactive Ingredients	
Ingredient Name	**Strength**
GELATIN (UNII: 2G86QN327L)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
POTASSIUM HYDROXIDE (UNII: WZH3C48M4T)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
FD&C RED NO. 3 (UNII: PN2ZH5LOQY)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SHELLAC (UNII: 46N107B71O)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics			
Color	yellow (YELLOW (Opaque Body) , BROWN (Opaque Cap)) , brown (YELLOW (Opaque Body) , BROWN (Opaque Cap))	**Score**	score with uneven pieces
Shape	CAPSULE	**Size**	19mm
		Imprint	

Flavor		**Imprint Code**	NL792;100mg
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61919-981-20	20 in 1 BOTTLE; Type 0: Not a Combination Product	05/27/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204446	05/27/2016	

Labeler - DIERCT RX (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	repack(61919-981)

Revised: 5/2016 DIERCT RX