SAFETY DATA SHEET
DOXYCYCLINE FOR INJECTION, USP

Strength: 100 mg/vial & 200 mg/vial **Revision No.:** 00

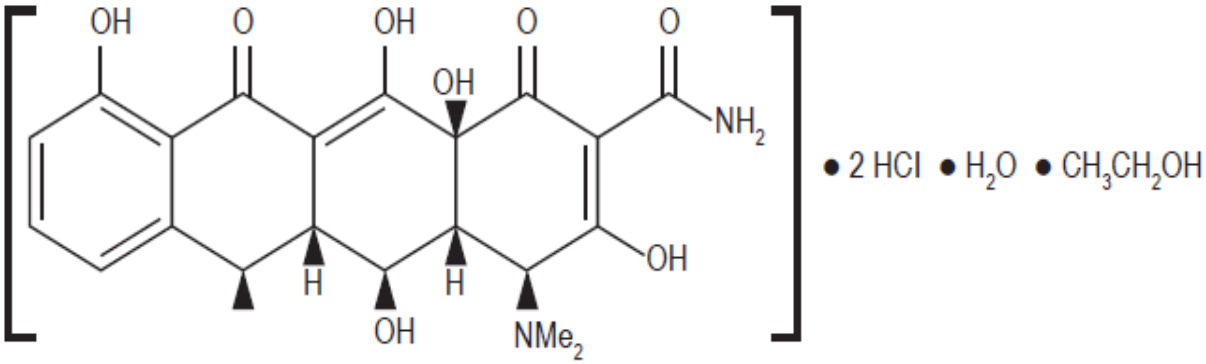
Pack Style: For 100 mg – 1x10 vial
For 200 mg – 1's vial

EMERGENCY OVERVIEW

Each Doxycycline for injection, USP intended for intravenous use after reconstitution contains Doxycycline hyclate and excipients generally considered to be non- toxic and non-hazardous in small quantities and under conditions of normal occupational exposure.

Section 1. IDENTIFICATION OF THE PRODUCT

Product Name: Doxycycline for injection, USP
Active Pharmaceutical Ingredient: Doxycycline hyclate
Formula: CH_3CH_2OH $(C_{22}H_{24}N_2O_8 \bullet HCl)_2 \bullet C_2H_6O \bullet H_2O$
Chemical Name: 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a - pentahydroxy – 6 – methyl - 1,11 – dioxo - 2-naphthacenecarboxamide, monohydrochloride, compound with ethyl alcohol (2:1), monohydrate



Mechanism of Action:

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

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.

Resistance

Cross resistance with other tetracyclines is common.

Antimicrobial Activity

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 for Doxycycline for injection.

Gram-Negative Bacteria

Acinetobacter species
Bartonella bacilliformis
Brucella species

Klebsiella species
Klebsiella granulomatis
Campylobacter fetus
Enterobacter aerogenes
Escherichia coli
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
Neisseria gonorrhoeae
Shigella species
Vibrio cholerae
Yersinia pestis

Gram-Positive Bacteria

Bacillus anthracis
Listeria monocytogenes
Streptococcus pneumonia

Anaerobic Bacteria

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 cumulative reports of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas 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 method1,2,4 (broth or agar).

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 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 microorganisms to doxycycline.

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to doxycycline can be determined by a standardized test method.

Manufacturer / supplier identification

Company:	Cadila Healthcare Ltd. Ahmedabad, India
Address:	Sarkhej – Bavla. N.H. 8A, Moraiya. Tal. Sanand. Dist. Ahmedabad – 382210. State: Gujarat. India
Contact for information:	Tel.: +91 79 6868100 Fax: +91 79 3750319
Emergency Telephone No.	Tel.: +91 79 6868100

Recommended use / Therapeutic Category

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

Labor and Delivery

The effect of tetracyclines on labor and delivery is unknown.

Nursing Mothers

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 serious 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.

Pediatric Use

Because of the effects of drugs of the tetracycline-class on tooth development and growth, use doxycycline in pediatric patients 8 years of age or less only when the potential benefits

are expected to outweigh the risks in severe or life-threatening conditions (e.g., anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies.

Restriction on Use / Contraindications: This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

SECTION 2. HAZARD(S) IDENTIFICATION

Dosage and Administration

Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE FOR INJECTION I.V. (100 to 200 MG/DAY) DIFFERS FROM THAT OF THE OTHER TETRACYCLINES (1 to 2 G/DAY). EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Studies to date have indicated that doxycycline at the usual recommended doses does not lead to excessive accumulation of doxycycline in patients with renal impairment.

Adults:

The usual dosage of doxycycline for injection I.V. is 200 mg on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg depending upon the severity of infection, with 200 mg administered in one or two infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg daily for at least 10 days.

In the treatment of inhalational anthrax (post-exposure) the recommended dose is 100 mg of doxycycline, twice a day. Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.

For children above eight years of age:

The recommended dosage schedule for children weighing 100 pounds or less is 2 mg/lb of body weight on the first day of treatment, administered in one or two infusions. Subsequent daily dosage is 1 to 2 mg/lb of body weight given as one or two infusions, depending on the severity of the infection. For children over 100 pounds the usual adult dose should be used

In the treatment of inhalational anthrax (post-exposure) the recommended dose is 1 mg/lb (2.2 mg/kg) of body weight, twice a day in children weighing less than 100 lb (45 kg). Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.

For prophylaxis of malaria:

For adults, the recommended dose is 100 mg daily. For children over 8 years of age, the recommended dose is 2 mg/kg given once daily up to the adult dose. Prophylaxis should begin 1 to 2 days before travel to the malarious area. Prophylaxis should be continued daily during travel in the malarious area and for 4 weeks after the traveler leaves the malarious area.

General:

The duration of infusion may vary with the dose (100 to 200 mg per day), but is usually one to four hours. A recommended minimum infusion time for 100 mg of a 0.5 mg/mL solution is one hour. Therapy should be continued for at least 24 to 48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

Intravenous solutions should not be injected intramuscularly or subcutaneously. Caution should be taken to avoid the inadvertent introduction of the intravenous solution into the adjacent soft tissue.

To prepare a solution containing 10 mg/mL, the contents of the vial should be reconstituted with 10 mL (for the 100 mg/vial container) or 20 mL (for the 200 mg/vial container) of Sterile Water for Injection or any of the ten intravenous infusion solutions listed below. Each 100 mg of doxycycline for injection (i.e., withdraw entire solution from the 100 mg vial) is further diluted with 100 mL to 1000 mL of the intravenous solutions listed below. Each 200 mg of doxycycline for injection (i.e., withdraw entire solution from the 200 mg vial) is further diluted with 200 mL to 2000 mL of the following intravenous solutions:

1. Sodium Chloride Injection, USP
2. 5% Dextrose Injection, USP
3. Ringer's Injection, USP
4. Invert Sugar, 10% in Water
5. Lactated Ringer's Injection, USP
6. Dextrose 5% in Lactated Ringer's
7. Normosol-M® in D5-W (Abbott)
8. Normosol-R® in D5-W (Abbott)

9. Plasma-Lyte® 56 in 5% Dextrose (Travenol)
10. Plasma-Lyte® 148 in 5% Dextrose (Travenol)

This will result in desired concentrations of 0.1 to 1 mg/mL. Concentrations lower than 0.1 mg/mL or higher than 1 mg/mL are not recommended.

Adverse Effects

Gastrointestinal:
anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, and pancreatitis. Hepatotoxicity has been reported rarely. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Superficial discoloration of the adult permanent dentition, reversible upon drug discontinuation and professional dental cleaning has been reported. Permanent tooth discoloration and enamel hypoplasia may occur with drugs of the tetracycline class when used during tooth development.

Skin:
toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above.

Renal toxicity:
Rise in BUN has been reported and is apparently dose related.

Immune:
Hypersensitivity reactions including urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, exacerbation of systemic lupus erythematosus, and drug reaction with eosinophilia and systemic symptoms

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

Other:
Bulging fontanels in infants and intracranial hypertension in adults.

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

Over Dose Effect

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

Pregnancy Comments

Teratogenic Effects.

There are no adequate and well-controlled studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycline during human pregnancy is 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. 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 fifty-six (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

Warnings

The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown).This adverse reaction is more common during long-term use of the drugs, but it has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Use doxycycline in pediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g., anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including doxycycline, 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 strains 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 the use of antibacterial drugs. 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 use of antibacterial drugs not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Severe skin reactions, such as exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms have been reported in patients receiving doxycycline. If severe skin reactions occur, doxycycline should be discontinued immediately and appropriate therapy should be 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. treatment, prompt ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize.

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not

occur with the use of doxycycline in patients with impaired renal function.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

Precautions

General

As with other antibacterial drugs, use of doxycycline may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, doxycycline should be discontinued and appropriate therapy instituted.

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

Doxycycline offers substantial but not complete suppression of the asexual blood stages of *Plasmodium strains*.

Doxycycline does not suppress *P. falciparum*'s sexual blood stage gametocytes. Subjects completing this prophylactic regimen may still transmit the infection to mosquitoes outside endemic areas.

Prescribing doxycycline 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.

Information For Patients

Patients taking doxycycline for malaria prophylaxis should be advised:

— that no present-day antimalarial agent, including doxycycline, guarantees protection against malaria.
— to avoid being bitten by mosquitoes by using personal protective measures that help avoid contact with mosquitoes, especially from dusk to dawn (e.g., staying in well-screened areas, using mosquito nets, covering the body with clothing, and using an effective insect repellent).
— that doxycycline prophylaxis:
— should begin 1–2 days before travel to the malarious area,
— should be continued daily while in the malarious area and after leaving the malarious area,
— should be continued for 4 further weeks to avoid development of malaria after returning from an endemic area,
— should not exceed 4 months.

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 eruption, etc.) occurs. Sunscreen or sunblock should be considered.
— to drink fluids liberally along with doxycycline to reduce the risk of esophageal irritation and ulceration.
— 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.
— that the absorption of tetracyclines is reduced when taking bismuth subsalicylate.
— that the use of doxycycline might increase the incidence of vaginal candidiasis.

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

Diarrhea is a common problem caused by antibacterial drugs,which usually ends when the antibacterials are discontinued. Sometimes after starting treatment with antibacterial drugs, 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 antibacterial drug. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions:

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.

Absorption of tetracyclines is impaired by bismuth subsalicylate.

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

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

Concurrent use of tetracycline may render oral contraceptives less effective.

Drug/Laboratory Test Interactions
False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Section 3. COMPOSITION / INFORMATION ON INGREDIENTS

Component	Exposure limit	CAS no.
Principle component		
Doxycycline hyclate	Not found	24390-14-5
Inactive ingredients		
Ascorbic acid	Not found	89924-69-6
Mannitol	Not found	69-65-8
Water for injection	Not found	7789-20-0
Nitrogen gas	Not found	93037-13-9

Section 4. FIRST - AID MEASURES

In case of inhalation: remove to fresh air. If not breathing give artificial respiration or give oxygen by trained personnel. Get immediate medical attention.

In case of skin contact: immediately wash skin with soap and plenty of water for at least 15 minutes. Remove contaminated clothing. Get medical attention if symptoms occur. Wash clothing before reuse.

In case of eye contact: hold eyelids apart and flush eyelids with plenty of water for at least 15 minutes. Have eyes examined and tested by medical personnel.

In case of ingestion: wash out mouth with water, provided the person is conscious. Never give naything by mouth to an unconscious person. Get medical attention. Do not induce vomiting unless directed to do so by medical professional.

Section 5. FIRE FIGHTING MEASURES

Suitable extinguishing media: use alcohol resistant foam, carbon dioxide, water or dry chemical spray. Use water spray to cool fire exposed containers.

Unsuitable extinguishing media: a solid water stream may be inefficient

Flammable properties and hazards: no data available.

Flash point : no data

Explosive limits: no data

Auto ignition point: no data

Fire fighting instructions: as in any fire wear self contained breathing apparatus pressure-demand and full protective gear to prevent contact with skin and eyes.

Section 6. ACCIDENTAL RELEASE MEASURES

Protective precautions, protective equipment & emergency procedures:
Avoid raisning and breathing dust and provide adequate ventilation.
As conditions warrant wear a NIOSH approved self contained breathing apparatus, or respirator and appropriate personal protection.

Environmental procedures
Take steps to avoid release into the environment.
Methods and material for containment and cleaning up
Contain spill and collect as appropriate.
Transfer to chemical waste container for disposal in accordance with local regulations.

Section 7. HANDLING AND STORAGE

Storage Store at 20° to 25°C (68° to 77°F)
PROTECT FROM LIGHT.
Retain in carton until time of use.

Conditions for safe storage Storage Conditions: Store as directed by product packaging.
Specific end use(s): Pharmaceutical drug product

Precautions for safe handling	keep locked up. Keep away from heat. Keep away from sources of ignition. Empty containers pose a fire risk; evaporate the residue under a fume hood. Ground all equipment containing material. Do not ingest. Do not breathe dust. Wear suitable protective clothing. If ingested, seek medical advice immediately and show the container or the label. Avoid contact with skin and eyes

Section 8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Spill:	Lightly wet doxycycline hyclate with water and absorb in absorbent materials. Dispose of according to local, state and federal guidelines.
Release to air:	if dust is generated, reduce exposure by ventilating area; clean up spills immediately to prevent dusting.
Release to water:	refer to local water authority. Drain disposal is not recommended refer to local state and federal disposal guidelines.

Section 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance

Physical state	Injection
Description	A yellow lyophilized powder or cake filled in an amber coloured glass vial. Doxycycline for Injection, USP (equivalent to **100 mg Doxycycline** with 480 mg ascorbic acid and 300 mg mannitol), lyophilized in a flip-top vial, in packages of 10. **NDC Number :** 68382-910-10 Doxycycline for Injection, USP (equivalent to **200 mg Doxycycline** with 960 mg ascorbic acid and 600 mg mannitol), lyophilized in a flip-top vial, packaged individually. **NDC Number :** 68382-911-01
Pure/Mixture	Mixture

Section 10. STABILITY AND REACTIVITY

Doxycycline for injection is stable for 48 hours in solution when diluted with Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, to concentrations between 1 mg/mL and 0.1 mg/mL and stored at 25°C. Doxycycline for injection in these solutions is stable under fluorescent light for 48 hours, but must be protected from direct sunlight during storage and infusion. Reconstituted solutions (1 to 0.1 mg/mL) may be stored up to 72 hours prior to start of infusion if refrigerated and protected from sunlight and artificial light. Infusion must then be completed within 12 hours. Solutions must be used within these time periods or discarded.

Doxycycline for injection, when diluted with Ringer's Injection, USP, or Invert Sugar, 10% in Water, or Normosol-M® in D5-W (Abbott), or Normosol-R® in D5-W (Abbott), or Plasma-Lyte® 56 in 5% Dextrose (Travenol), or Plasma-Lyte® 148 in 5% Dextrose (Travenol) to a concentration between 1 mg/mL and 0.1 mg/mL, must be completely infused within 12 hours after reconstitution to ensure adequate stability. During infusion, the solution must be protected from direct sunlight. Reconstituted solutions (1 to 0.1 mg/mL) may be stored up to 72 hours prior to start of infusion if refrigerated and protected from sunlight and artificial light. Infusion must then be completed within 12 hours. Solutions must be used within these time periods or discarded.

When diluted with Lactated Ringer's Injection, USP, or Dextrose 5% in Lactated Ringer's, infusion of the solution (ca. 1 mg/mL) or lower concentrations (not less than 0.1 mg/mL) must be completed within six hours after reconstitution to ensure adequate stability. During infusion, the solution must be protected from direct sunlight. Solutions must be used within this time period or discarded.

Solutions of doxycycline hyclate for injection, at a concentration of 10 mg/mL in Sterile Water for Injection, when frozen immediately after reconstitution are stable for eight weeks when stored at –20°C. If the product is warmed, care should be taken to avoid heating it after the thawing is complete. Once thawed the solution should not be refrozen.

Section 11. TOXICOLOGICAL INFORMATION

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term studies in animals to evaluate carcinogenic potential of doxycycline have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with the related antibacterial drugs, 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 drugs (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.

ECOLOGICAL INFORMATION

Toxicity: Avoid release into the environment. Runoff from fire control or dilution water may cause pollution.

Section 13. DISPOSAL CONSIDERATION

Disposal Recommendations Dispose of waste in accordance with all applicable laws and regulations. Member State specific and Community specific provisions must be considered. Considering the relevant known environmental and human health hazards of the material, review and implement appropriate technical and procedural waste water and waste disposal measures to prevent occupational exposure and environmental release. It is recommended that waste minimization be practiced. The best available technology

should be utilized to prevent environmental releases. This may include destructive techniques for waste and wastewater.

Section 14. TRANSPORT INFORMATION

The product is not hazardous when shipping via air (IATA), ground (DOT), or sea (IMDG).

Section 15. REGULATORY INFORMATION

Generic Medicine, ANDA Number - 207757

Section 16. OTHER INFORMATION

NFPA (National Fire Protection Association (U.S.A).) Rating:
These ratings are based on NFPA code 704 and are intended for use by emergency personnel to determine the immediate hazards of a material

Health:	2
Flammability:	1
Instability:	0

Chemwatch hazard ratings:

Flammability:	1
Toxicity:	2
Body contact:	2
Reactivity:	1
Chronic:	3

Date of issue: January 20, 2018 **Supersedes edition:** New Edition

The information presented in the safety data sheet is, to the best our knowledge, accurate and reliable. It characterizes the product with regard to the appropriate safety precautions. It does not represent a guarantee of the properties of the product.