1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

1.1 (Invented) name of the medicinal product

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INN (GENERIC NAME)

DOXYCYCLINE CAPSULES BP 100 MG

1.2 Strength :- 100 MG

1.3 Pharmaceutical form :- Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DOXYCYCLINE CAPSULES BP 100 MG

Each Capsule Contains:
Doxycycline Hyclate BP
Eq. to Doxycycline 100mg
Excipients q.s.
Approved colour used in E.H.G. Capsule shell

Batch Size: 100,000 Capsules

Sr. No.	Ingredients	Specification	Label amount mg	% Overages	Qty. / Capsule Mg	Reason for Inclusion
ACTIVE						
1.	Doxycycline Hyclate Eq. to Doxycycline*	BP	100 mg	--	115.0	Active
EXCEPIENTS						
2.	Maize Starch**	BP	--	--	63.59	Binder
3.	Purified Talc	BP	--	--	56.00	Diluent
4.	Sodium Benzoate	BP	--	--	0.200	Diluent
5.	Sodium Metabisulphite	BP	--	--	0.200	Lubricant
6.	E.H.G. Capsule size “2” Green/Green	IH	--	--	1.00(No.)	Drug Encasement

*115 mg of Doxycycline Hyclate Eq. to 100 mg of Doxycycline
**8 % Maize starch should be taken extra to compensate loss on drying.
BP = British Pharmacopoeia
IHS = In-house Specification

3. PHARMACEUTICAL FORM. :

Hard gelatin capsules having Green coloured cap and Green coloured body, containing yellow coloured powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline capsules and other antibacterial drugs, doxycycline capsules 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 Capsules 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 Capsules 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 *Klebsiella 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 Capsules 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 Capsules 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 pallidum* subspecies *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.

4.2 Posology and method of administration:
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.
Pediatric Patients:

For all pediatric patients weighing less than 45 kg with severe or life-threatening infections (e.g. anthrax, Rocky Mountain spotted fever), the recommended dosage is 2.2 mg/kg of body weight administered every 12 hours. Children weighing 45 kg or more should receive the adult dose (see **WARNINGS** and **PRECAUTIONS**).
For pediatric patients with less severe disease (greater than 8 years of age and weighing less than 45 kg), the recommended dosage schedule is 4.4 mg/kg of body weight divided into two doses on the first day of treatment, followed by a maintenance dose of 2.2 mg/kg of body weight (given as a single daily dose or divided into twice daily doses). For pediatric patients weighing over 45 kg, the usual adult dose should be used.

The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

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, it is recommended that doxycycline be given with food or milk. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.

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

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 45 kg 1mg/lb 2.2 mg/kg of body weight, by mouth, twice a day for 60 days. Children weighing 45 kg or more should receive the adult dose.

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

4.4 Special warnings and precautions for use:
The use of drugs of the tetracycline class, including doxycycline, 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 has been observed following repeated short-term courses of older tetracycline drugs. Enamel hypoplasia has also been reported. Use of doxycycline in pediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in sever 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 capsules, 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 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.

Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracyclines including doxycycline capsules. 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 capsules 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.

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six 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 embryo toxicity has been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, 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.

4.5 Interaction with other medicinal products and other forms of interaction:

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.

4.6 Pregnancy and lactation:
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.9

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.10

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.11

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.1.2 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**.)

4.7 Effects on ability to drive and use machines:

Not known

4.8 Undesirable Effects:

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, and pancreatitis. 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.

4.9 OVERDOSE:

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.

5 Pharmacological Properties:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: tetracyclines,
ATC code: J01AA02
Doxycycline is primarily a bacteriostatic antibiotic.

Mechanism of action

The main mechanism of action of doxycycline is on protein synthesis. Doxycycline passes directly through the lipid bilayer of the bacterial cell wall and an energy dependent active transport system pumps the drug through the inner cytoplasmic membrane. Once inside the cell doxycycline inhibits protein synthesis by binding to 30S ribosomes and prevents the addition of amino acids to the growing peptide chain. Doxycycline will impair protein synthesis in mammalian cells at very high concentrations but these cells lack the active transport system found in bacteria.

5.2 Pharmacokinetic properties:

Absorption

Doxycycline is almost completely absorbed and is not subject to presystemic metabolism, the mean bioavailability being approximately 93%.

Distribution

Tissue distribution is good and Doxycycline has a strong affinity for renal and lung tissue. Plasma protein binding is in the range 82-93% and Doxycycline is transferred into breast milk. The volume of distribution for doxycycline ranges from 0.9-1.8 lkg^{-1} and the plasma half life ranges from 18-22 hours.

Biotransformation

No significant metabolism occurs.

Elimination

Doxycycline is cleared intact by renal and biliary mechanisms.

5.3 Preclinical safety data :
Not applicable.

6 Pharmaceutical Particulars
6.1 List of Excipients.

Sr. No.	Ingredients	Specifications
1.	Maize Starch	BP
2.	Purified Talc	BP
3.	Sodium Benzoate	BP
4.	Sodium Metabisulphite	BP
5.	E.H.G. Capsule size "2" Green/Green	IH

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 Years

6.4 Special precautions for storage
Store in cool & dry place

6.5 Nature and contents of container
Blister pack of 10 Capsules.