Brand Name : AGODOX CAPSULES **Generic Name :** Doxycycline Capsules BP 100 mg	2021
Module 1 Administrative Information and Product Information **1.5** Product Information	**Confidential**

1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of products characteristics)

SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

AGODOX CAPSULES (Doxycycline Capsules BP 100 mg)

2. Qualitative and Quantitative Composition:

Each hard gelatin capsule contains: Doxycycline Hyclate BP ≡ to (Anhydrous) Doxycycline 100 mg

3. Pharmaceutical form:

Green coloured hard gelatin capsule of size '2' having printed "DOXY 100" "AGOG" on cap & body alternatively containing yellow coloured powder.

4. Clinical particulars:

4.1 Therapeutic Indications:

Pneumonia

Depending on the identification of susceptible microorganisms, doxycycline has been found to be clinically effective in the treatment of single and multiple lobe pneumonia and bronchopneumonia due to pneumococci and other Streptococcus spp., Staphylococcus spp., Haemophilus influenzae, Klebsiella pneumoniae and Mycoplasma pneumoniae.

Other respiratory tract infections

Doxycycline has been used to treat pharyngitis, tonsillitis, otitis media, bronchitis and sinusitis caused by susceptible strains of β-hemolytic streptococci, Staphylococcus spp., pneumococci and Haemophilus influenzae. In streptococcal infections, treatment

should be continued for 10 days to prevent complications such as the development of rheumatic fever or glomerulonephritis.

Genitourinary tract infections

Doxycycline has been used to treat pyelonephritis, cystitis and urethritis caused by susceptible strains of the Klebsiella-Enterobacter group, Escherichia coli, Staphylococcus spp., Neisseria gonorrhoeae, and Chlamydia trachomatis.

Acute uncomplicated gonococcal infections have been treated with 100 mg doxycycline twice daily for a recommended duration of 10 days. Chlamydial infections have responded to 100 mg doxycycline twice daily for a least a week.

Soft tissue infections

Doxycycline has been used to treat a number of soft tissue infections including impetigo, furunculosis, cellulites, abscess, infected traumatic and postoperative wounds and paronychia caused by susceptible strains of Staphylococcus aureus, Staph. albus, Streptococcus spp., Escherichia coli and the Klebsilla-Enterobacter group. Tetracycline treatment should go hand in hand with relevant surgical procedures.

Ophthalmic infections

Doxycycline has been effective in the treatment of ophthalmic infections caused by susceptible strains of gonococci, staphylococci and Haemophilus influenzae. It has also been used to treat trachoma, but subsequent immunofluorescence has shown that the causative agent is not always eliminated. Inclusion conjunctivitis has sometimes been treated with doxycycline alone, sometimes in combination with topical agents.

Gastrointestinal infections

Susceptible strains of Entamoeba histolytica, enteropathogenic Escherichia coli, Shigella and Salmonella species have been treated successfully with doxycycline. In acute intestinal amebiasis, the tetracycline may be used as an adjunct to specific amebicidal therapy. It can be used in the prophylaxis of traveler's diarrhea in adults, the dose being 200 mg on the first day and 100 mg daily for the rest of the stay. Data are not available on its prophylactic use beyond 21 days.

Acne

Doxycycline, in common with other tetracyclines, has been used in the systemic treatment of severe acne vulgaris. The recommended dose is 50 mg daily, Treatment continues for a relatively long period, with the expectation of maximum improvement after about 3 or 4 months. It may be necessary, however, to continue for at least 2 years, but such prolonged treatment is not without hazards. Pseudomembranous colitis is a risk that must be borne in mind. Photosensitivity may prove a problem in summer months.

Regd. Office & Factory : Plot No. 33, Sector II, The Vasai Taluka Industrial Co-op. Estate Ltd. Gauraipada, Vasai (E), Dist. Thane - 401 208. INDIA.
Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

Miscellaneous group of infections

Doxycycline has been used in the following infections: psittacosis, prostatitis and trigonitis due to Proteus species; Mycoplasma; Rickettsiae; Bacteroides; Yersinia; Brucella; Listeria; Bordetella pertussis; Bacillus anthracis; Clostridium welchii; Neisseria meningitis; spirochetes (Treponema spp.); Calymmato-bacterium granulomatis; louse-borne typhus; leptospirosis; scrub typhus.

Plasmodium falciparum malaria

Doxycycline is used in the treatment of chloroquine resistant falciparum malaria at a dose of 200 mg daily for at least 7 days and should be used in combination with a rapid-acting schizonticide such as quinine. It has also been studied in the treatment of falciparum malaria in combination with mefloquine or artesunate, chloroquine or following on after treatment with artemisinin.

Doxycycline is effective in malaria prophylaxis and is used for malaria due to chloroquine and/or pyrimethamine-sulfadoxine resistant Plasmodium falciparum. The adult dose used is 100 mg daily, which should be started 1 to 2 days before travel and continued for 4 weeks after travel. Trials show that it can be effective by itself or in combination with other drugs.

4.2 Posology and Method of Administration:

The usual dosage and frequency of administration of Doxycycline differs from that of the other Doxycyclines. 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 paediatric patients above eight years of age

The recommended dosage schedule for paediatric patients weighing 100 pounds or less is 2 mg/lb of body weigh 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 paediatric patients over 100 lbs 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, administered 300 mg 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.

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.

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

Administration of adequate amounts of fluid along with capsule forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration. 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 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%.

Method of administration : Oral

4.3 Contraindications:

Hypersensitivity

Doxycycline is contraindicated in anyone who has shown hypersensitivity to any of the tetracyclines.

Children under 12 years of age

If any tetracycline is taken during tooth development, it is likely that a yellow-gray-brown discoloration will develop, and that this will be permanent. This effect has been noted after both long-term and repeated short-term use. Enamel hypoplasia may also develop.

Patients with systemic lupus erythematosus

Tetracyclines are thought to exacerbate (or possibly induce) SLE, although evidence for this effect is rather scanty.

4.4 Special Warnings and Precautions for Use :

Doxycycline has a lower affinity for binding with calcium than other tetracyclines. In consequence its absorption appears to be less likely to be tooth discoloration.

Oesophageal ulceration may be a particular problem if capsules are taken with insufficient fluid or in a recumbent posture: Doxycycline should be taken with at least half a glass of water, in an upright position, and one hour or more before retiring to bed.

Unlike other tetracyclines Doxycyline does not appear to accumulate in patients with renal failure, and aggravation of renal impairment may be less likely. However, its kinetics may be affected by agents that inhibit or induce hepatic metabolism, such as alcohol, antiepileptic agents, or rifampicin.

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

Potentially hazardous interactions

It is possible that on rare occasions interference with the absorption of a tetracycline, described under other interactions, might be hazardous in a seriously ill patient.

Anticoagulants

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

Other significant interactions

Drugs or other substances which interact with tetracyclines generally give rise to interactions which are only of nuisance value and they can usually be avoided by simple expedients. Most interactions are based on a physicochemical reaction in the gastrointestinal tract which reduces the bioavailability of the tetracycline in question. The most common interacting substances are the divalent or trivalent cations present in antacids, milk, and other foods, and calcium, magnesium, and iron preparations.

In the case of iron preparations for example, each drugs impairs the absorption of the other. To ensure the desired response from each drug, the administration of one should not be followed by the other in less than 2-3 h. However, unlike most tetracyclines, doxycycline does not interact with food or milk in this way.

Barbiturates, carbamazepine and phenytoin

These drugs all decrease the half-life of doxycycline and result in reduced plasma concentration of the antibiotic.

Oral contraceptives

There is a possibility of reduced contraceptive effect when a broad-spectrum antibiotic is given concurrently with oral contraceptives.

Potentially useful interactions

No interactions of this type have been described.

4.6 Pregnancy and Lactation:

Pregnancy

Because of the risk of damage to the teeth of the fetus, the drug should not be given to pregnant women.

Lactation

Tetracyclines enter breast milk, and mother taking these drugs should not breast-feed.

4.7 Effects on ability to drive and use machines:

Patients experiencing visual disturbances, dizziness, vertigo, somnolence, or other central nervous system disturbances while taking Doxycycline Capsules should refrain from driving or using machines.

4.8 Undesirable effects:

Potentially life-threatening effects

None involving this drug has been reported, but anaphylaxis has occurred on very rare occasions with other tetracyclines and fatal liver damage has occurred in pregnant women given a tetracycline. Staphylococcal enterocolitis due to resistant organisms or pseudomembranous colitis due to infection with Clostridium difficile may also occur.

Severe or irreversible adverse effects

As previously mentioned, tetracyclines cause permanent staining of developing teeth and hypoplasia of enamel. Some of the reactions mentioned below may cause severe illness on occasions.

Regd. Office & Factory : Plot No. 33, Sector II, The Vasai Taluka Industrial Co-op. Estate Ltd. Gauraipada, Vasai (E), Dist. Thane - 401 208. INDIA.
Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

Symptomatic adverse effects

Nausea is the most frequently reported adverse effect, but it occurs in less than 4% of patients. Skin reactions-a maculopapular or erythematous rash-occur in less than 3% of patients.

Overgrowth of resistant organisms may occur, causing glossitis, stomatitis and vaginitis, as well as staphylococcal enterocolitis (mentioned above).

In general, tetracyclines have been associated with the following adverse effects, their incidence being at the 1-2% level or lower.

Gastrointestinal

Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis and anogenital inflammatory lesions. Esophagitis and/or esophageal ulceration have occurred in patients taking capsules or tablets immediately before retiring to bed.

Dermatological

As noted above, maculopapular and erythematous rashes occur in less than 3% of patients; more rarely, exfoliative dermatitis. Photosensitivity can occur, particularly in fair-skinned patients but with less frequency than with other tetracyclines.

Hypersensitivity

Urticaria, angioneurotic edema, anaphylactic purpura, pericarditis and exacerbation of systemic lupus erythematosus may occur.

Hematological

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

Miscellaneous

Bulging fontanelles may occur in infants and benign intracranial hypertension in adults, both reversible on stopping the drug. A microscopic brown-black discoloration of thyroid tissue has been noted, but has proved to be of no clinical significance.

Other effects

The antianabolic effect of tetracyclines may cause an increase in blood urea. Renal impairment decreases the clearance of some tetracyclines, leading to changes in blood urea levels, but this does not happen with doxycycline.

4.9 Overdose:

Acute overdosage with tetracyclines is extremely rare, and if it occurs no specific treatment is required. Any gastrointestinal upset should be treated symptomatically. As tetracyclines form insoluble complexes with cations, antacids may be administered in appropriate circumstances.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Doxycycline is primarily a bacteriostatic antibiotic. It has a similar spectrum of activity to other tetracycline but in particular is more active against Staphylococcus aureus and Nocardia. The drug is often active against penicillin-resistant strains of Staph, aureus and against strains of those organisms that are resistant to other tetracyclines.

Certain Gram-negative strains of Escherichia coli, Proteus mirabilis and Klebsiella, which are often resistant to tetracycline, may be sensitive to doxycycline. In addition, 70-90% of the various anaerobes are sensitive to doxycycline and Bacteroides fragilis is more likely to be sensitive to doxycycline than to other tetracyclines.

Doxycycline is active against most strains of Haemophilus influenzae and is particularly useful for infections with H. ducreyi, Actinomyces, Brucella and Vibrio cholerae. It is also active against Nocardia, Chlamydia, Mycoplasma and a wide range of Rickettsiae. Doxycvcline is active against spirochetes such as Borellia recurrentis, Treponema pallidum and T. pertenue. It is also active against Plasmodium falciparum. Like all tetracyclines, it will alter the enteric flora.

Studies which established human tolerance and dose-response relationships were performed in the 1960s.
Resistance to tetracyclines

Resistance to tetracyclines develops slowly and organisms that show resistance to one tetracycline frequently show resistance to others in the group (with some exceptions for minocycline and doxycycline). Most resistance is mediated by a plasmid and is an inducible trait, appearing only after exposure of the bacteria to the drug. Resistance seems to occur because the plasmid implants genetic material in the cell for a number of proteins and this affects the penetration of the cell wall by tetracycline.

5.2 Pharmacokinetic Properties:

The preferred analytical method is by high pressure liquid chromatography after a single-step extraction from biological samples. This provides a limit of detection of 50 µg. 1^{-1}.
Doxycycline is almost completely absorbed by adults in the fasting state, the mean bioavailability being of the order of 93%. A dose of 100 mg every 24 h, following an initial loading dose of 200 mg gave serum concentrations in 12 normal volunteers of

3.1-3.5 $mg.1^{-1}$ 3 h after each dose and 1.4-1.9 $mg.1^{-1}$ 24 h after each dose. Presystemic (first-pass) metabolism does not occur. The drug is cleared intact by renal and biliary mechanisms. Total body clearance is in the range 2.5-4.4 $1.h^{-1}$. Tissue distribution is good, with a tissue/serum concentration ratio always greater than 1 except in the gut and lymphoid tissue. There is strong affinity for renal and lung tissue. Plasma protein binding is in the range 82-93% and transfer into the milk of lactating women occurs. The volume of distribution ranges from 0.9 to 1.8 $1.kg^{-1}$ and the plasma half-life ranges from 18 to 22 h.

Oral absorption	~93%
Presystemic metabolism	nil
Plasma half-life	
range	18-22 h
Volume of distribution	0.9-1.8 $I.kg^{-1}$
Plasma protein binding	82-93%

Concentration-effect relationship

The therapeutic range will depend upon the minimum inhibitory concentration (MIC) of the antibiotic for the organism in question. Full susceptibility occurs when the MIC is less than 4.0 $mg.1^{-1}$, and intermediate susceptibility occurs when the MIC is between 4.0 and 12.5 $mg.1^{-1}$. Concentrations greater than 25 $mg.1^{-1}$ are usually required to inhibit most strains of group B and group D streptococci and strains of Staphylococcus aureus. The MIC for Streptococcus pyogenes is usually about 1.0 $mg.1^{-1}$, while many strains of Neisseria have a similar MIC.

Metabolism

Doxycycline is eliminated in the urine and in the bile. 20-26% of the active drug is excreted in the urine within 48 h (40% in 2 h) and 20-40% in the feces over the same time period. No significant metabolism occurs.

5.3 Pre-clinical safety data:

Animal studies have revealed no specific organ damage or general toxicity at doses close to those used in humans. In teratogenicity tests (chicks and rats), tetracyclines were found in general to cross the placenta, causing fetal damage often characterized by retardation of skeletal development. In mutagenicity tests (monkeys), no important gross or microscopic abnormalities were found. Mild yellow ultraviolet fluorescence was noted in the liver, kidneys and bones and small amounts of intracytoplasmic granular material were present in thyroid tissue.

Regd. Office & Factory : Plot No. 33, Sector II, The Vasai Taluka Industrial Co-op. Estate Ltd. Gauraipada, Vasai (E), Dist. Thane - 401 208. INDIA.
Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

6. Pharmaceutical particulars:

6.1 List of Excipients:

Maize starch	BP
Talcum	BP
Magnesium stearate	BP
Empty hard gelatin capsule size ‘2’ (Green/green – printed doxy 100/ AGOG /Alternatively	In house

6.2 Incompatibilities:

None Reported

6.3 Shelf-Life:

36 months from the date of manufacture.

6.4 Special Precautions for Storage:

Do not store above 30ºC. Store in a cool, dry and dark place. Protect from light.

6.5 Nature and Contents of Container:

10 capsules packed in one blister. Such 10 blisters packed in unit printed duplex board carton along with its package insert. Such cartons are packed in export worthy shippers. These Shippers are sealed with BOPP tape.

1000 capsules packed in a poly bag. Such 1 bag packed in a HDPE Jar along with its package insert. Such Jars are packed in export worthy shippers. These Shippers are sealed with BOPP tape.

6.6 Special precautions for disposal:

None reported.

Regd. Office & Factory : Plot No. 33, Sector II, The Vasai Taluka Industrial Co-op. Estate Ltd. Gauraipada, Vasai (E), Dist. Thane - 401 208. INDIA.
Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

7. Registrant:

AGOG PHARMA LTD.
Plot No. 33, Sector II,
The Vasai Taluka Industrial
Co-Op. Estate Ltd., Gauraipada,
Vasai (E), Dist. Thane, India.

8. Manufacturer:

AGOG PHARMA LTD.
Plot No. 33, Sector II,
The Vasai Taluka Industrial
Co-Op. Estate Ltd., Gauraipada,
Vasai (E), Dist. Thane, India.

9. Date of revision of the text :