Minocycline Hydrochloride Capsules U.S.P.

Cynomycin®

1. NAME OF THE MEDICINAL PRODUCT

Cynomycin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains: Minocycline hydrochloride U.S.P. equivalent to 100 mg minocycline.

Each hard gelatin capsule contains: Minocycline hydrochloride U.S.P. equivalent to 50 mg minocycline.

For a full list of excipients, see section 6.1.

All strengths/presentations mentioned in this document might not be available in the market.

3. PHARMACEUTICAL FORM

Hard Gelatin Capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Minocycline hydrochloride capsules are indicated in the treatment of the following infections due to susceptible strains of the designated microorganisms:

- Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsial pox and tick fevers caused by *Rickettsiae.*
- Respiratory tract infections caused by *Mycoplasma pneumoniae*.
- Lymphogranuloma venereum caused by *Chlamydia trachomatis*.
- Psittacosis (Ornithosis) due to *Chlamydia psittaci*.
- Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated, as judged by immunofluorescence.
- Inclusion conjunctivitis caused by *Chlamydia trachomatis.*

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- Non-gonococcal urethritis, endocervical or rectal infections in adults caused by *Ureaplasma urealyticum* or *Chlamydia trachomatis*.
- Relapsing fever due to *Borrelia recurrentis*.
- 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 *Campylabacter 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 tetracyclines, culture and susceptibility testing are recommended.

Minocycline hydrochloride is indicated for the 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.

Minocycline hydrochloride is indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

- Upper respiratory tract infections caused by *Streptococcus pneumoniae*.
- Skin and skin structure infections caused by *Staphylococcus aureus*. (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection.)

When penicillin is contraindicated, minocycline hydrochloride is an alternative drug in the treatment of the following infections:

- Uncomplicated urethritis in men due to *Neisserie gonorrhoeae* and for the treatment of other gonococcal infections.
- Infections in women caused by *Neisseria gonorrhoeae*.
- Meningitis due to *Neisseria meningitidis*.
- Syphilis caused by *Treponema pallidum* subspecies *pallidum*.
- Yaws caused by *Treponema pallidum* subspecies *pertenue*.
- Listeriosis due to *Listeria monocytogenes*.
- Anthrax due to *Bacillus anthracis*.
- Vincent's infection caused by *Fusobacterium fusiforme*.
- Actinomycosis caused by *Actinomyces israelii*.
- Infections caused by *Clostridium* species.

In acute intestinal amebiasis, minocycline hydrochloride may be a useful adjunct to amebicides. In severe acne, minocycline may be useful adjunctive therapy.

Oral minocycline hydrochloride is indicated in the treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. In order to preserve the usefulness of minocycline hydrochloride in the treatment of asymptomatic meningococcal carriers, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline hydrochloride be reserved for situations in which the risk of meningococcal meningitis is high.

Oral minocycline hydrochloride is not indicated for the treatment of meningococcal infection.

Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochloride has been used successfully in the treatment of infections caused by *Mycobacterium marinum*.

4.2 Posology and Method of Administration

Method of Administration: For oral use.

The duration of therapy is guided by the severity of the infection and the patient's clinical and bacteriological progress.

Adults: The usual dosage of minocycline hydrochloride capsules is 200 mg initially followed by 100 mg every 12 hours. The total daily dose should not exceed 400 mg in 24 hours.

In the treatment of acne, the recommended dosage is 100 mg daily given twice a day.

In the treatment of uncomplicated gonococcal infections other than urethritis and anorectal infections in men, the initial oral dose is 200 mg, followed by 100 mg every 12 hours for a minimum of four days.

In the treatment of uncomplicated gonococcal urethritis in men, the recommended dose is 100 mg every 12 hours for five days.

For the treatment of syphilis, the usual dosage of minocycline hydrochloride should be administered over a period of 10 to 15 days.

In the treatment of meningococcal carrier state, the recommended dosage is 100 mg every 12 hours for five days.

Mycobacterium marinum infections: Although optimal doses have not been established, 100 mg every 12 hours for 6 to 8 weeks has been used successfully in a limited number of cases.

In the treatment of uncomplicated urethral, endocervical or rectal infection in adults caused by *Chlamydia trachomatis* or *Ureaplasma urealyticum*, the recommended dose is 100 mg every 12 hours for at least seven days.

To reduce the risk of esophageal irritation and ulceration, capsules should be taken with adequate amounts of fluid (at least approximately one glass of water).

Absorption of minocycline hydrochloride may be impaired by aluminium, calcium, magnesium, iron containing preparations, food, milk and other dairy products.

Use in Children (above 8 years of age)

The initial dosage of minocycline hydrochloride is 4 mg/kg followed by 2 mg/kg every 12 hours.

Use in the Elderly

Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range (see section 4.4).

Use in Patients with Renal Impairment

In patients with renal impairment, the total daily dose should not exceed 200 mg in 24 hours (see section 4.4).

4.3 Contraindications

Minocycline hydrochloride is contraindicated in patients with hypersensitivity to any of the tetracyclines or components of the product formulation.

4.4 Special Warnings and Special Precautions for Use

Warnings

Polyarteritis nodosa, a multisystem vascular disorder, has been reported with minocycline (see section 4.8) especially in patients on long term maintenance therapy (e.g. > 6 months) for skin conditions. Patients should be closely monitored for signs and symptoms potentially indicative of polyarteritis nodosa, such as pyrexia, malaise, weight decreased, arthralgia, myalgia, livedo reticularis or numbness.

Lupus-like syndrome consisting of positive antinuclear antibody, arthralgia, arthritis, joint stiffness, or joint swelling has been reported with minocycline (see section 4.8) especially in patients on long-term maintenance therapy (e.g., > 6 months) for skin conditions. Patients should be closely monitored for signs and symptoms potentially indicative of lupus-like syndrome such as: pyrexia, myalgia, hepatitis, rash, vasculitis.

Minocycline hydrochloride capsules, like other tetracycline-class antibiotics, can cause fetal harm when administered to a pregnant woman. 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 drug but also has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracycline drugs, therefore, should not be used during tooth development unless the expected benefits of therapy outweigh the risks.

Precautions
Pseudotumor cerebri (benign intracranial hypertension) has been reported with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. Bulging fontanels have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve after discontinuation of the tetracycline, the possibility for permanent sequelae exists. Photosensitivity has been observed in some individuals taking tetracyclines. Patients should be advised that an exaggerated sunburn reaction can occur with tetracycline drugs and should avoid direct sunlight.

Use in patients with hepatic impairment
Hepatotoxicity has been associated with minocycline hydrochloride, therefore, minocycline hydrochloride should be used with caution in patients with hepatic dysfunction and in conjunction with other hepatotoxic drugs.

Use in patients with renal impairment
The antianabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). In patients with significantly impaired renal function, higher serum levels of tetracyclines may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, even usual oral and parenteral doses may lead to excessive systemic accumulation of the drug and possible liver toxicity.

Laboratory monitoring
Periodic laboratory evaluations of organ system function, including hematopoietic, renal and hepatic should be conducted.

Pediatric use
Minocycline hydrochloride is not recommended for use in children below 8 years of age unless the expected benefits of therapy outweigh the risks.

Elderly use
Clinical studies of minocycline hydrochloride did not include sufficient number of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Tetracyclines have been shown to depress plasma prothrombin activity, concomitant anticoagulant therapy may require downward adjustment of anticoagulant dosage.

Bacteriostatic drugs may interfere with the bactericidal action of penicillin. Avoid giving tetracycline class drugs in conjunction with penicillin.

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

Absorption of the standard oral formulations of minocycline is impaired by food, milk, and other dairy products. However, absorption of the pellet-filled capsules formulation is not significantly impaired by food or milk (see section 5.2).

The concurrent use of tetracyclines with oral contraceptives may render oral contraceptives less effective.

Administration of isotretinoin should be avoided shortly before, during and shortly after minocycline therapy. Each drug alone has been associated with pseudotumor cerebri.

Increased risk of ergotism when ergot alkaloids or their derivatives are given with tetracyclines

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

4.6 Pregnancy and Lactation

Pregnancy
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 been noted in animals treated early in pregnancy.

Minocycline hydrochloride like other tetracycline class antibiotics crosses the placenta and may cause fetal harm when administered to a pregnant woman. If minocycline hydrochloride 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 use of tetracyclines during tooth development (last half of pregnancy) may cause permanent discoloration of the teeth. Enamel hypoplasia has also been reported.

Tetracyclines administered during the last trimester form a stable calcium complex throughout the human fetal skeleton. A decrease in fibula growth rate has been observed in premature human infants given oral tetracycline in the dose of 25 mg/kg every 6 hours. Changes in fibula growth rate were shown to be reversible when the drug was discontinued.

Congenital anomalies including limb reductions have been reported in post-marketing experience.

Lactation
Minocycline hydrochloride is excreted in human milk, therefore, a decision should be made whether to discontinue breast-feeding or to discontinue minocycline.

4.7 Effects on Ability to Drive and Use Machines

Patients should use caution when driving a vehicle or using hazardous machinery while on minocycline hydrochloride therapy. Central nervous system side effects, including light-headedness, dizziness or vertigo have been reported with minocycline hydrochloride therapy. These symptoms may disappear during therapy and usually disappear when the drug is discontinued.

4.8 Undesirable Effects

Adverse reactions are listed in the Table in CIOMS frequency categories under MedDRA system/organ classes:

Common: >1%
Uncommon: >0.1% and <1%
Rare: >0.01% and <0.1%
Very rare: <0.01%

System Organ Class	Adverse Reaction
Blood and Lymphatic System Disorders	
Rare:	Eosinophilia, leukopenia, neutropenia, thrombocytopenia
Very rare:	Hemolytic anemia, pancytopenia
Frequency undetermined:	Agranulocytosis,
Cardiac Disorders	
Very rare:	Myocarditis, pericarditis
Ear and Labyrinth Disorders	
Rare:	Impaired hearing, tinnitus
Endocrine Disorders	
Very rare:	Abnormal thyroid function, brown-black discoloration of thyroid
Gastrointestinal Disorders	
Rare:	Diarrhea, nausea, stomatitis, discoloration of teeth, vomiting
Very rare:	Dyspepsia, dysphagia, enamel hypoplasia, enterocolitis, esophagitis, esophageal ulceration, glossitis, pancreatitis, pseudomembranous colitis
Frequency undetermined:	Oral cavity discoloration (including tongue, lip and gum)
General Disorders	
Uncommon:	Fever
Very rare:	Discoloration of secretions
Hepatobiliary Disorders	
Rare:	Increased liver enzymes, hepatitis
Very rare:	Hepatic cholestasis, hepatic failure (including fatalities), hyperbilirubinemia, jaundice

Frequency undetermined:	Autoimmune hepatitis

Immune System Disorders

Rare:	Anaphylaxis/anaphylactoid reaction
Frequency undetermined:	Hypersensitivity

Infections and Infestations

Very rare:	Oral and anogenital candidiasis, vulvovaginitis

Metabolism and Nutrition Disorders

Rare:	Anorexia

Musculoskeletal, Connective Tissue, and Bone Disorders

Rare:	Arthralgia, lupus-like syndrome, myalgia
Very rare:	Arthritis, bone discoloration, exacerbation of systemic lupus erythematosus (SLE), joint stiffness, joint swelling

Nervous System Disorders

Common:	Dizziness (light headedness)
Rare:	Headache, hypesthesia, paresthesia, pseudotumor cerebri, vertigo
Very rare:	Bulging fontanel
Frequency undetermined:	Convulsions, sedation

Renal and Urinary Disorders

Rare:	Increased BUN
Very rare:	Acute renal failure, interstitial nephritis

Reproductive System and Breast Disorders

Very rare:	Balanitis

Respiratory, Thoracic, and Mediastinal Disorders

Rare:	Cough, dyspnea
Very rare:	Bronchospasm, exacerbation of asthma, pulmonary eosinophilia
Frequency undetermined:	Pneumonitis

Skin and Subcutaneous Tissue Disorders

Rare:	Alopecia, erythema multiforme, erythema nodosum, fixed drug eruption; hyperpigmentation of skin, photosensitivity, pruritus, rash, urticaria
Very rare:	Angioedema, exfoliative dermatitis, hyperpigmentation of nails, Stevens-Johnson Syndrome, toxic epidermal necrolysis
Frequency undetermined:	Acute febrile neutrophilic dermatosis

Vascular disorders

Frequency undetermined:	Polyarteritis Nodosa, Vasculitis

The following syndromes have been reported. In some cases, involving these syndromes, death has been reported. If any of these syndromes are recognized, the drug should be discontinued immediately:

- Drug reaction with eosinophilia and systemic symptoms consisting of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, pericarditis. Fever and lymphadenopathy may be present.

- Serum sickness-like syndrome consisting of fever; urticaria or rash; and arthralgia, arthritis, joint stiffness, or joint swelling. Eosinophilia may be present.

4.9 Overdose

The adverse events more commonly seen in overdose are dizziness, nausea, and vomiting.

No specific antidote for minocycline hydrochloride is known.

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Minocycline hydrochloride is not removed in significant quantities by hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Minocycline hydrochloride, a semisynthetic derivative of tetracycline, is 4-7,bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride.

Its structural formula is $C_{23}H_{27}N_3O_7$•HCl and its molecular weight is 493.94.

Minocycline hydrochloride is a yellow, crystalline powder; sparingly soluble or soluble in water, slightly soluble in alcohol; practically insoluble in chloroform and in ether; dissolves in solutions of alkali hydroxides and carbonates.

Microbiology
The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. The tetracyclines, including minocycline hydrochloride, have similar antimicrobial spectra of activity against a wide range of gram-positive and gram-negative organisms. Cross-resistance of gram-positive and gram-negative organisms to tetracyclines is common. Almost all *S. pyogenes* strains are resistant to minocycline hydrochloride. Therefore, minocycline hydrochloride should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.

5.2 Pharmacokinetic Properties

Absorption
Minocycline hydrochloride is quickly and almost completely absorbed from the gastrointestinal tract following oral administration.

Following a single dose of two 100 mg tablets of minocycline hydrochloride, maximum serum concentrations were attained in 2 to 4 hours and ranged from 2.6 to 4.17 pg/mL (average 3.52 μg/mL).

Following a single dose of two 100 mg capsules of minocycline hydrochloride, maximum serum concentrations averaged 3.64 μg/mL.

Distribution
Minocycline hydrochloride distributes largely to all tissues due to its high degree of lipophilicity.

Studies have shown that minocycline hydrochloride is found in high concentration in lung tissue and mucus in man.

Serum levels of 1.4-1.8 μg/mL were maintained at 12 and 24 hours with intravenous doses of 100 mg every 12 hours for 3 days. Following 200 mg intravenous doses given once daily for 3 days, the serum levels had fallen to approximately 1 μg/mL at 24 hours.

Metabolism
Minocycline hydrochloride is extensively metabolized in humans.

Minocycline hydrochloride is mainly excreted in the bile and a small amount is recovered in the urine as active form. The amount of active drug recovered in the feces after oral administration ranges from 20%-34%.

Elimination
The mean serum half-life is approximately 16 hours for oral and intravenous administration.

Effect of Food
Absorption of the standard oral formulations of minocycline is impaired by food, milk, and other dairy products.

Special Populations
In patients with hepatic dysfunction, the minocycline hydrochloride serum half-life ranged from 10.7 to 16.9 hours.

The majority of studies in patients with varying degrees of renal impairment showed no significant difference in pharmacokinetics parameters as compared to healthy subjects.

5.3 Preclinical Safety Data

Dietary administration of minocycline hydrochloride in long-term tumorgenicity studies in rats resulted in evidence of thyroid tumor production. In the rat, chronic treatment with minocycline hydrochloride has resulted in goiter accompanied by elevated radioactive iodine uptake and evidence of thyroid tumor production. Minocycline hydrochloride has been observed to cause a dark discoloration of the thyroid in animals (rats, mice, dogs, and monkeys). Minocycline hydrochloride has also been found to produce thyroid hyperplasia in rats and dogs.

In addition, there has been evidence of oncogenic activity in rats in studies with a related antibiotic, oxytetracycline (i.e., adrenal and pituitary tumors). Likewise, although mutagenicity studies of minocycline hydrochloride have not been conducted, positive results in *in vitro* mammalian cell assays (i.e., mouse lymphoma and Chinese hamster lung cells) have been reported for related antibiotics (tetracycline hydrochloride and oxytetracycline).

Segment I (fertility and general reproduction) studies have provided evidence that minocycline hydrochloride impairs fertility in male rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Dried Corn Starch IP, Magnesium Stearate IP

6.2 Incompatibilities

Not known

6.3 Shelf Life

24 Months

6.4 Special Precautions for Storage

Store at a temperature not exceeding 30°C. Protect from light.

6.5 Nature and Contents of Container

100 mg capsules - Strip of 4
50 mg capsules - Strip of 6

6.6 Instructions for Use and Handling

Keep out of reach of children.