

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

MONODOKS 100 mg Capsules

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

**Active substance:**

115.414 mg doxycycline hyclate equivalent to 100 mg doxycycline.

**Excipients:**

Laktose monohydrate (from cow's milk)..... 78.586 mg

Tartrazine..... 0.1 mg

For a full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Capsule.

Yellow, almost odorless, granular powder with homogenous appearance inside opaque hard gelatin capsules with opaque red brown cap and opaque dark yellow body.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

MONODOKS is indicated for the treatment of infections caused by susceptible strains of the following Gram-negative and Gram-positive bacteria and other microorganisms:

- Respiratory system: Indicated for the treatment of respiratory tract infections due to susceptible strains of *Yersinia pestis*, *Actinobacillus actinomycelemcomilam*, *Haemophilus influenzae*, *Diplococcus pneumoniae*, *Staphylococcus aureus*, *Klebsiella* species and *Streptococcus* species (if the organism has been demonstrated to be sensitive). It is used to reduce incidence and progression after exposure to inhaled anthrax (aerosolized *Bacillus anthracis*).
- Urogenital system: Urogenital infections due to *Haemophilus ducrei* (soft canker), *Brucella* species (co-administered with streptomycin), *Actinobacillus actinomycelemcomilam*, *Enterobacter aerogenes*, *Escherichia coli* and *Klebsiella* species.
- Skin and soft tissue: Skin and soft tissue infections due to *Yersinia pestis*, *Francisella tularensis*, *Bartonella bacilliformis*, *Staphylococcus aureus* and *Bacillus anthracis* microorganisms.
- Gastrointestinal system: Infections due to *Vibrio cholerae* and *Shigella* species.
- Various other infections: Infections due to *Campylobacter fetus*, *Mima* species and *Herellea* species.

When penicillin is contraindicated, MONODOKS is an alternative drug in the treatment of infections caused by the following bacteria: *Treponema pallidum*, *Treponema perferne*, *Listeria monocytogenes*, *Clostridium* species, *Fusobacterium fusiforme* (Vincent infection), *Actinomyces* species.

MONODOKS is also indicated in the treatment of the following infections caused by susceptible

microorganisms:-

- Urogenital tract (urogenital infections due to susceptible *Klebsiella* species, *Enterobacter* species, *Escherichia coli*, *Streptococcus faecalis* and certain other microorganisms)
- Sexually-transmitted diseases (including uncomplicated urethral, endocervical or rectal infections [except for anorectal infections in men] due to susceptible *Chlamydia trachomatis*, non-gonococcal urethritis due to *Ureaplasma urealyticum* [T-mycoplasma], chancroid, granuloma inguinale and lymphogranuloma venereum infections.  
MONODOKS can also be used as an alternative drug in the treatment of gonorrhoea and syphilis; it can also be used for the treatment of gonococcal arthritis-dermatitis syndrome due to *Neisseria gonorrhoeae* and acute epididymo-orchitis).
- Respiratory tract (Pneumonia and lower respiratory tract infections due to susceptible *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae* and other microorganisms. *Mycoplasma pneumoniae* pneumonia. Treatment of chronic bronchitis and sinusitis)
- Skin and soft tissue (as an adjunctive therapy in cases of *Acne vulgaris* which requires antibiotic treatment)
- Gastrointestinal (Cholera, acute intestinal amebiasis [as an adjunct to other amoebicides], traveler's diarrhea)
- Ophthalmic (Infections due to susceptible strains of gonococci, staphylococci and *Haemophilus influenzae*, trachoma, inclusion conjunctivitis [can be used alone with MONODOKS or in combination with other topical agents])
- Various other infections (*Rickettsiae* (rocky mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers), psittacosis (ornithosis) -(*Chlamydia psittaci*), *Borrelia recurrentis*, brucellosis (in conjunction with streptomycin), plague, tularemia, chloroquine-resistant *falciparum malaria* (for prophylaxis of malaria and must be implemented according to current guidelines due to potential for resistance development); in addition to these, MONODOKS is also an alternative drug in the treatment of leptospirosis, gas gangrene and tetanus.

#### **4.2 Posology and method of administration**

##### **Posology/frequency and duration of administration:**

The usual dose is 200 mg on the first day of treatment (administered as a single dose or 100 mg every 12 hours), 100 mg once daily on the following days. The maintenance dose may be administered as a single dose daily or as 50 mg every 12 hours. Particularly chronic infections of the urinary tract, 200 mg daily (100 mg every 12 hours) is recommended.

##### Dose recommendations for specific infections:

For uncomplicated gonococci infections in adults (except anorectal infections in men), 100 mg is administered twice a day for 7 days. As an alternate single visit dose, 300 mg starting dose followed in one hour by a second 300 mg dose is administered.

In cases of acute epididymo-orchitis caused by *Neisseria gonorrhoeae*, MONODOKS 100 mg is



administered twice a day for at least 10 days.

In primary and secondary syphilis, 300 mg MONODOKS should be administered daily at equally-divided doses for at least 10 days.

When MONODOKS is used in streptococcal infections, therapy should be continued for at least 10 days.

In cases of uncomplicated urethral, endocervical and rectal infections caused by *Chlamydia trachomatis* and in cases of nongonococcal urethritis caused by *Chlamydia trachomatis* and *Ureaplasma urealyticum*, 100 mg MONODOKS should be given twice a day for at least 7 days.

In cases of acute epididymo-orchitis caused by *Chlamydia trachomatis*, 100 mg MONODOKS twice a day is given for at least 10 days.

100 mg MONODOKS is administered twice a day in community-acquired pneumonia.

*Inhalational anthrax (post-exposure)*: In adults, 100 mg twice a day is recommended for 60 days.

In Lyme disease caused by *Borrelia*, 100 mg MONODOKS is administered twice daily for 14-21 days.

*Acne vulgaris*: 50 mg daily is recommended to be continued for 6-12 weeks.

*Louse and tick-borne relapsing fevers*: A single dose of 100 to 200 mg is recommended according to severity.

*Chloroquine-resistant falciparum malaria*: 200 mg daily for at least 7 days. Due to the severity of the infection, a rapid-acting schizonticide such as quinine should always be given in conjunction with MONODOKS; quinine dosage recommendations vary in different areas.

*Prophylaxis of malaria*: 100 mg daily is recommended in adults. Prophylaxis can begin 1-2 days before travel to malarious areas. It should be continued during travel in the malarious areas and for 4 weeks after the traveler leaves the malarious area. Geographical resistance patterns and appropriate chemoprophylaxis guidelines or suggestions of Malaria Reference Laboratory should be considered due to the potential of resistance development.

*For the scrub typhus*: 200 mg as a single dose.

*For the prevention of travelers' diarrhea in adults*: 200 mg on the first day of travel (administered as a single dose or as 100 mg every 12 hours) followed by 100 mg daily throughout the stay in the area. Data on the use of the drug prophylactically are not available beyond 21 days.

*For the prevention of leptospirosis*: 200 mg once each week throughout the stay in the area and 200 mg at the completion of the trip. Data on the use of the drug are not available beyond 21 days.

**Method of administration:**

Administration of adequate amounts of fluid along with oral forms of drugs in the tetracycline class in the remaining upright position for at least thirty minutes is recommended to reduce the risk of esophageal irritation or ulceration. If gastric irritation occurs, it is recommended that MONODOKS



be given with food or milk. The absorption of MONODOKS is not notably influenced by simultaneous ingestion of food or milk.

### **Additional information on special populations**

#### **Renal/Hepatic impairment:**

##### **Renal impairment:**

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that the use of MONODOKS administered at usual doses in patients with impaired renal function does not cause accumulation.

##### **Hepatic impairment:**

It should not be administered in severe hepatic impairment.

##### **Pediatric population:**

For pediatric patients above 8 years of age:

In pediatric patients weighing 45 kg and less, 4.4 mg/kg is administered as divided into two doses on the first 24 hours of treatment, which is followed by 2.2 mg/kg divided into dose intervals applied to adults and in a way not to exceed 200 mg. For more severe infections, up to 4.4 mg/kg daily may be used. For pediatric patients over 45 kg the usual adult dose should be used.

Inhalational anthrax (post-exposure):

In children weighing less than 45 kg, 2.2 mg/kg is administered twice a day for 60 days and children weighing 45 kg or more should receive the adult dose.

The use of drugs of the tetracycline class during tooth development (infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-grey-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Drugs of the tetracycline class should be therefore used in these groups of patients except for anthrax only when other drugs are ineffective or contraindicated (see section 4.4).

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

Bulging fontanelles has been reported in infants. This symptom disappears when drug is discontinued.

##### **Geriatric population:**

Clinical data requiring a dose adjustment is not available.

### **4.3 Contraindications**

MONODOKS is contraindicated in:

- Hypersensitivity to any active substance or excipients of the ingredients (doxycycline hyclate or titanium dioxide etc.)
- Children under the age of 8 years except for anthrax (including inhaled anthrax for post-exposure prophylaxis)
- Patients with severe hepatic insufficiency

- Pregnant women
- Breast-feeding women

#### **4.4 Special warnings and precautions for use**

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients likely 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.

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

All infections due to a group A  $\beta$ -hemolytic streptococci should be treated for at least 10 days.

When treating venereal disease, where co-existent syphilis is suspected, Dark-field examination should be utilized before starting treatment and monthly serological tests in the blood should be performed for at least 4 months once a month. In long-term therapy, periodic laboratory assessments of organ systems including hematopoietic renal and hepatic examinations should be made.

The use of drugs of the tetracycline class during tooth development (second half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-grey-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracycline drugs, therefore, should not be used in this age group, except for anthrax including inhalational anthrax (post-exposure), unless other drugs are not likely to be effective or are contraindicated (see section 4.2 and 4.3).

*Clostridium difficile*-associated diarrhea (CDAD) have been reported with use of nearly all antibacterial agents, including MONODOKS capsules, and may range in severity from mild diarrhea to fatal colitis. Treatments with antibacterial agents alter the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to 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.

Bulging fontanelles in infants and benign intracranial hypertension in adults have been reported in individuals receiving tetracycline. These conditions disappeared when the drug was discontinued (see section 4.2).



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

Doxycycline induces substantial but entire suppression of the asexual blood stages of Plasmodium strains. Doxycycline is unable to suppress the sexual blood stage gametocytes of *P. falciparum*. Patients completing this prophylactic treatment regimen may still acquire the infection from mosquitoes outside endemic areas.

Cases of esophagitis and esophageal ulcerations have been reported in patients receiving doxycycline (see section 4.2).

For warnings of hepatic and renal impairment, see section 4.2.

There have been rare reports of porphyria in patients receiving doxycycline.

Tetracyclines can cause exacerbation of systemic lupus erythematosus (SLE).

Due to the potential for weak neuromuscular blockade, care should be taken in administering tetracyclines to patients with myasthenia gravis.

MONODOKS contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption problem should not take this medicine.

MONODOKS contains tartrazine. It may cause allergic reactions.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

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

The absorption of doxycycline is impaired by concurrently administered antacids containing aluminum, calcium, or magnesium. They should not be given concomitantly with oral doxycycline therapy.

Doxycycline levels are reduced when concurrently administered with iron, bismuth subsalicylate, barbiturate, sucralfate, didanosine and quinapril.

Because tetracyclines have been shown to depress plasma prothrombin activity when given with anticoagulants such as warfarin, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

An increase in digoxin toxicity may be observed when it is co-administered with digoxin.

Doxycycline may increase the levels/effects of benzodiazepines, calcium channel blockers, mirtazapine, nateglinide, nefazodone, quinidine, sildenafil (and other pde-5 inhibitors), tacrolimus, venlafaxine, phenytoin, carbamazepine and other CYP3A4 substrates.

Concurrent use of tetracycline may render oral contraceptives less effective.



Alcohol may decrease the half-life of doxycycline.

Doxycycline may increase the plasma concentration of cyclosporine. Co-administration should only be undertaken with appropriate monitoring.

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

**Interactions with laboratory tests:**

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

**Additional information on special populations:**

There is no study conducted on interactions.

**Pediatric population:**

There is no study conducted on interactions.

**4.6 Fertility, pregnancy and lactation**

**General principles**

Pregnancy category is D.

**Women of child-bearing potential/Birth control (Contraception)**

There are no adequate scientific and clinical data although there are studies indicating that efficacy of oral contraceptive drugs are reduced with co-administration of tetracyclines. Women should use an appropriate contraception method while using MONODOKS.

**Pregnancy**

MONODOKS is contraindicated in the last half of pregnancy considering its possible negative effects on tooth development of the infant to be born.

Results of animal studies indicate that tetracyclines cross into 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 with tetracyclines 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.

There are no adequate and well-controlled studies on the use 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, but the data are insufficient to state that there is no risk.

**Breast-feeding**

MONODOKS is excreted in human milk; however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infants 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. Because of the potential for adverse reactions in nursing infants from



doxycycline, nursing should be suspended when the drug is required to be used in nursing women.

### **Fertility**

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.

### **4.7 Effects on ability to drive and use machines**

No information is available as to its effect on ability to drive and use machines.

### **4.8 Undesirable effects**

Undesirable effects observed during clinical trials are listed below according to their frequency:

Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

### **Infections and infestations**

*Not known:* Superinfections (As with other antibiotics, overgrowth of non-susceptible organisms may cause candidiasis, glossitis, staphylococcal enterocolitis, pseudomembranous colitis and inflammatory lesions in the anogenital region, vaginitis).

### **Blood and lymphatic system disorders**

*Not known:* Hemolytic anemia, thrombocytopenia, neutropenia, porphyria, and eosinophilia.

### **Immune system disorders**

*Not known:* Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, exacerbations of systemic lupus erythematosus.

### **Endocrine disorders**

*Not known:* When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid tissue. No abnormalities of thyroid function are known to occur.

### **Nervous system disorders**

*Not known:* Headache, bulging fontanelles in infants (this symptom disappears when drug is discontinued), benign intracranial hypertension.

### **Ear and labyrinth disorders**

*Not known:* Tinnitus.

### **Cardiac disorders**

*Not known:* Pericarditis.

### **Gastrointestinal disorders**

*Rare:* Esophagitis, esophageal ulceration (Esophagitis and esophageal ulceration rarely occur in capsule and tablet forms of tetracyclines group of drugs. Most of these patients have received their drugs immediately before going to bed), dysphagia.

*Not known:* Anorexia, nausea, vomiting, diarrhea, glossitis, enterocolitis, inflammatory lesions in anogenital region, abdominal pain, pancreatitis.

### **Hepatobiliary disorders**

*Rare:* Hepatotoxic effect (This effect may develop either with oral or parenteral use of tetracyclines). Transient increases in liver function tests, hepatitis, jaundice, hepatic failure may occur.

### **Skin and subcutaneous tissue disorders**

*Not known:* Maculopapular and erythematous rashes, photosensitivity reactions (see section 4.4), exfoliative dermatitis.

### **Musculoskeletal, connective tissue and bone disorders**

*Not known:* Arthralgia and myalgia.

### **Renal and urinary disorders**

*Not known:* BUN increase.

### **Other**

*Not known:* Tetracyclines may usually cause discoloration of tooth color related with prolonged use and enamel hypoplasia.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

## **4.9 Overdose**

Clinical symptoms related to overdose of doxycycline hyclate are nausea, anorexia and diarrhea.

After gastrointestinal decontamination, monitoring is required and in case of hypotension, fluid supplement may be needed.

Dialysis is not recommended in case of overdose as it would not alter serum half-life.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Systemic antibacterial drugs, tetracyclines

ATC code: J01AA02

Doxycycline hyclate (hydrochloride monohydrate) is a broad-spectrum antibacterial of tetracyclines synthetically derived from oxytetracycline. It is in form of light yellow crystalline powder and highly lipophilic with a low affinity for calcium binding.

Doxycycline hyclate is considered to be primarily bacteriostatic and exerts its antimicrobial effect by inhibiting protein synthesis of microorganisms. It is clinically effective in the treatment of a variety of infections caused by a wide range of gram-negative and gram-positive bacteria (see section 4.1).

### **5.2 Pharmacokinetic properties**

#### **General properties**

##### Absorption:

Doxycycline hyclate is virtually completely absorbed after oral administration. Its administration with food or milk reduces its absorption by 20%. Following a 200 mg single dose, it reaches the



mean peak serum concentration within 2 hours and is available in serum at therapeutic concentrations for 24 hours.

Distribution:

It is widely distributed into body fluids such as synovial, pleural, prostatic, seminal and bronchial secretions and only small amounts are diffused into the cerebrospinal fluid and saliva. It crosses into placenta; and transferred into breast milk. It binds to plasma proteins by 90%.

Biotransformation:

It is not metabolized in liver; it is partly inactivated via chelation in digestive tract.

Elimination:

In individuals with normal renal function, it is excreted in urine by 40% within 72 hours. Its serum half-life is 18-22 hours. No alteration in serum half-life has been detected in hemodialysis or in cases with impaired renal function. It is concentrated in the bile by liver and excreted in urine and feces in its biological active forms.

Linearity/Non-linearity:

Doxycycline curve in plasma is linear at concentrations of 0.1-10 mg/ml.

**5.3 Preclinical safety data**

Hyperpigmentation of the thyroid has been produced by members of the tetracycline class in the following species: in rats with oxytetracycline, doxycycline, tetracycline PO<sub>4</sub> and metacycline; in minipigs with doxycycline, minocycline, tetracycline PO<sub>4</sub> and metacycline; in dogs with doxycycline and minocycline; in monkeys with minocycline.

Minocycline, tetracycline PO<sub>4</sub>, metacycline, doxycycline, tetracycline base, oxytetracycline HCl and tetracycline HCl were goitrogenic in rats fed a low iodine diet. This goitrogenic effect was accompanied by high radioactive iodine uptake. Administration of minocycline also generated a large goitre with high radioiodine intake in rats fed a relatively high iodine diet.

Treatment of various animal species with this class of drugs has also resulted in the induction of thyroid hyperplasia in the following: in rats and dogs (minocycline), in chickens (chlortetracycline); and in rats and mice (oxytetracycline). Adrenal gland hyperplasia has been observed in goats and rats treated with oxytetracycline.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Sodium lauryl sulphate  
Maize starch  
Lactose monohydrate (from cow's milk)  
Magnesium stearate

Gelatin capsule

Erythrosine  
Indigo carmine  
Tartrazine  
Titanium dioxide  
Gelatin (from bovine bone)



## **6.2 Incompatibilities**

It does not have any pharmaceutical incompatibility.

## **6.3 Shelf life**

60 months.

## **6.4 Special precautions for storage**

Store at room temperature below 25°C. Protect from light.

## **6.5 Nature and contents of container**

Transparent PVC/PVDC /Al blister packs of 14 capsules.

## **6.6 Special precautions for disposal and other handling**

Any unused product or waste material should be disposed of in accordance with local disposal regulations.

## **7. MARKETING AUTHORIZATION HOLDER**

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## **8. MARKETING AUTHORIZATION NUMBER**

113/28

## **9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**

Date of first authorization : 06.11.1972

Date of last renewal : 19.03.2013

## **10. DATE OF REVISION OF THE TEXT**