# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

DOXY 200, 200 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is doxycycline.
Each tablet contains doxycycline monohydrate equivalent to 200 mg of doxycycline base.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Round tablet, olive-yellow coloured, scored. DOXY 200 tablet can split be in egal doses.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Doxycycline is indicated in adult and children over 8 years old for the treatment of infections caused by sensitive pathogenic germs. The high prevalence of resistance of certain pathogenic germs should be taken into consideration: see section 5.1.

- Rickettsiosis: crimson fever group (Rocky Mountain fever and other rickettsia fever diseases), Typhus and brush typhus group
- Q fever
- Respiratory tract infections: *Mycoplasma pneumoniae* pneumonia
- Genito- urinary tract infections:
    - Infections due to *Chlamydia trachomatis* including uncomplicated urethral, endocervical infections and epididymo-orchitis
    - Alternative drug in treatment of syphilis (in case of known allergy to penicillin)
    - Lymphogranuloma venereum
    - Acute pelvis affection
- Gastro-intestinal tract infections: cholera adjuvant treatment
- Stage I Lyme disease (including dermal form or erythema migrans)
- Leptospirosis
- Acne vulgaris and acne conglobata
- Malaria treatment and prophylaxis

Contrary to other antibiotics, information regarding local resistance prevention and official recommendations for prescribing antibiotics should be consulted before prescribing doxycycline.

### 4.2 Posology and method of administration

Posology

**Adults and children over 12 years old**

- Respiratory tract infections: single loading dose of 200 mg or 100 mg twice daily with 12 hours interval on the first day of treatment followed by a maintenance dosage of 100 mg once daily at the same time each day thereafter during 5 to 10 days.
- uncomplicated urethral and endocervical infections caused by *Chlamydia trachomatis* :100 mg twice daily during 7 days.

- Epididymo-orchitis caused by *Chlamydia trachomatis*: 100 mg twice daily during 10 days.
- Primary and secondary syphilis: 100 mg twice daily during 14 days.
- Lymphogranuloma venereum: 100 mg twice daily during 21 days.
- Acute pelvis affection: 100 mg twice daily during 10 days always in association with an active antibiotic against *N. gonorrhoeae,* anaerobic bacteria, facultative gram negative bacteria and streptococci.
- Stage I Lyme disease (including dermal form): 100 to 200 mg daily during 10 to 20 days.
- Leptospirosis: 2 x 100 mg daily during 7 days.
- Acne vulgaris: 50 mg daily during up to 12 weeks.
- Malaria treatment: *P. falciparum* induced malaria in region where it is chloroquine-resistant *P.falciparum* malaria: 200 mg daily (as a single dose) or 100 mg twice daily with 12 hours interval) during at least 7 days. A fast acting schizonticide should always be associated.
- Malaria prevention: only in regions where exists chloroquine-resistant *P.falciparum* malaria, in case of intolerance or contraindication to mefloquine or atovaquone/proguanil association): 100 mg daily. The prophylaxis (prevention) should start 1 to 2 days before departure, and should continue throughout the stay (less than 4 months) and for 4 weeks after the return from impacted regions.
- Rickettsiosis: crimson fever group (Rocky Mountain fever and other rickettsia fever diseases), Typhus and brush typhus group: 100 mg every 12 hours. Patients must be treated at least during 3 days after fever ends and until clinical improvements. Minimal treatment period is 5 to 7 days.
- Fever Q: acute state: 100 mg every 12 hours until 14 days.

*Paediatric population*

**Children aged between 8 and 12 years (see section 4.4)**

The use of doxycycline for the treatment of acute infection in children aged between 8 and 12 years should be carefully justified in situations where other medicines are not available, are not likely to be efficient or are contraindicated.

For children of 45 kg or less – Initial dose:

- Treatment of acute infections: 4.4 mg/kg (either in a single dose or divided in two doses) with a maintenance dose of 2.2 mg/kg (either in a single dose or divided in two doses). In the of more serious infections, a maximum dose of 4.4 mg/kg should be administered in all the treatment course.
- Rickettsiosis: crimson fever group (Rocky Mountain fever and other rickettsia fever diseases), Typhus and brush typhus group: 2.2 mg/kg twice daily. Patients must be under surveillance during at least 3 days after fever ends. Minimal period treatment is 5 to 7 days.
- Malaria treatment: 4 mg/kg (as a single dose or divided into 2 equal doses with 12 hours interval) on the first day, followed by 2 mg/kg (as a single dose or divided into 2 equal doses) during at least 6 days. A fast acting schizonticide should always be associated.
- Malaria prevention: 2 mg/kg daily as a single dose. The prophylaxis (prevention) should start 1 to 2 days before departure, and should continue throughout the stay (less than 4 months) and for 4 weeks after the return from impacted regions.

For children of 45 kg and more – The adult dose should be used for the treatment of acute infections, for the treatment and prophylaxis of malaria and for Rickettsiosis treatment.

**Children under 8 years old**
Doxycycline should not be used in children under 8 years old because of the risk of teeth discolouration (see sections 4.4 and 4.8).

*Posology in case of renal failure:*
No dose reduction is required in patient with impaired renal function.
Studies up to now show that the administration of doxycycline at usual recommended doses do not result in excessive accumulation of this antibiotic in patients with impaired renal function.

*Use in dialysis patients:*
Haemodialysis and peritoneal dialysis do not impact the serum half-life of doxycycline.

*Posology in case of liver failure:*
Doxycycline should be administered carefully in patients with liver failure (see section 4.4).

Method of administration
In order to limit oesophagus' irritation or ulceration, tetracycline group tablets administration should be taken with adequate amounts of fluid (100 ml or half glass of water). This should be done in the sitting or standing position and the patient should be advised to remain upright for at least thirty minutes after taking a dose. After administration, it is recommended to wait 30 minutes before bedtime. Tablets can be prepared in suspension with 50ml of water.

In case of gastric irritation, it is recommended to take the tablet during a meal or with milk without any absorption alteration. Studies indicate that the absorption of doxycycline is less significantly influenced by simultaneous ingestion of food or milk
Milk and dairy products seem to less alter the absorption of doxycycline than the absorption of tetracycline.

## 4.3 Contraindications

- Hypersensitivity to the active substance, to whatever tetracycline or to any of the excipients listed in section 6.1.
- Known obstructive oesophageal disorders.
- DOXY 200 should not be administered to children under the age of 8 years, except in severe pathology or life threatening situation when benefits overrule the risks, especially when no other treatment is available (see section 4.4).
- DOXY 200 is contraindicated during the 2nd and 3rd pregnancy trimesters and breastfeeding, unless life threatening pathology (e.g. rickettsiosis such as Rocky Mountain spotted fever) when there is a positive benefit/risk balance – and no other treatment is available (see sections 4.4 and 4.6).

In any cases, the use of doxycycline is not recommended during pregnancy and should only be prescribed when no other alternative treatment is available.
Treatment duration should be as short as possible.

## 4.4 Special warnings and precautions for use

**Cases of oesophageal undesirable effects (oesophagitis and ulceration), sometimes**

**serious, have been reported with doxycycline. Patients should be instructed to take this medicine with an enough liquid volume and wait at least 30 minutes after the intake before going to bed (see section 4.2). Discontinuation of doxycycline and investigation of oesophageal disorder should be considered if symptoms such as dyspepsia or retrosternal pain occur. Caution is required in the treatment of patients with known oesophageal reflux disorders.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including doxycycline, and some cases has ranged in severity from mild to life-threatening situations. The potential symptoms are the following: massive aqueous diarrhoea (sometimes bloody), severe abdominal pains and cramps, nausea, dehydration, fever. Without treatment, these symptoms can provoke peritonitis, shock, toxic megacolon.

A colitis associated to the antibiotherapy might occur during the treatment with doxycycline in the 2 following months. The use of intestinal peristaltism inhibitors is contraindicated. A careful anamnesis should be carried out to establish the relation between the antibiotherapy and the occurrence of diarrhoea.

The use of antibiotics may occasionally result in over-growth of non-susceptible organisms, including *Candida*. The potential symptoms consist in frequent episodes of vaginitis, vaginal discharges or vaginal itching. If a resistant organism appears, the antibiotic should be discontinued and appropriate therapy instituted.

The anti-anabolic effects of tetracycline may induce an increase in blood ureic nitrogen levels. the clinical experience up to now shows that this phenomenon is not observed in patients on doxycycline that have an impaired renal function.

DOXY 200 should be administered with caution in patient with hepatic failure. Rare cases of liver dysfunction were reported; due to the oral and parenteral administration of tetracycline, including doxycycline.

In case of prolonged treatment (long term therapy), periodic laboratory evaluation of organ systems, including haemopoietic, renal and hepatic studies, should be performed.

Severe skin reactions such as exfoliative dermatitis, erythema multiforme, Stevens- Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients receiving doxycycline (see section 4.8). If severe skin reaction occur, treatment should be discontinued immediately and replaced with appropriate therapy.

Photosensitivity manifested by an exaggerated sunburn reaction when exposed has been observed in some patients taking tetracyclines, including doxycycline. The risk of phototoxicity is more significant in patients on a prolonged doxycycline treatment (malaria prophylaxis, treatment of acne), especially if the light intensity is higher, as in tropical countries. The use of sunscreen or sun block should be considered. Patients likely to be exposed to sunlight or direct ultraviolet light should be advised that this reaction can occur with tetracycline drugs. The treatment should be discontinued at the first evidence of skin erythema.

The treatment of venereal diseases required appropriate diagnostic procedures. Patients on doxycycline for the treatment of a sexually transmitted disease still have a risk of developing

other sexually transmitted infections. An appropriate management and a follow up of the patients are recommended.

Although doxycycline is not degraded into toxic epianhydro derivatives, as it was reported for others tetracycline, the use of expired tablets should be avoided.

DOXY 200 should be administered with caution in patient undergoing anaesthesia with methoxyflurane (see section 4.5).

Tetracycline may exacerbate a disseminated lupus erythematosus (DLE) (see section 4.8).

Because of a risk of a weak neuromuscular blockade, it is recommended to be careful in case of administration of tetracyclines to patients with myasthenia gravis.

Some patients with spirochete infections might experience Jarisch-Herxheimer reaction shortly after the initiation of a doxycycline treatment. It is advised to reassure the patients by informing that it is a consequence of an antimicrobial treatment of spirochete infection that usually spontaneously resolves.

Benign intracranial hypertension (cerebral pseudotumor) has been associated with the use of tetracyclines, including doxycycline (see section 4.8). Following symptoms can be associated: headache, blurred vision, doubled vision, sight loss, nausea, vomiting, tinnitus, retrobulbar pain, photopsia. Papillary oedema can be confirmed by fundus examination. Benign intracranial hypertension (cerebral pseudotumor) is generally transitory after treatment discontinuation; however, cases of blindness after having intracranial hypertension (cerebral pseudotumor) have been reported with tetracyclines, including doxycycline. In case of visual impairment during treatment, ophthalmic evaluation should be performed quickly. As intracranial pressure can remain high during several weeks after treatment discontinuation, patients must be under monitoring until stabilisation. Concomitant use isotretinoin with doxycycline should be avoided, because isotretinoin is also known to provoke benign intracranial hypertension (cerebral pseudotumor).

*Paediatric population*
As other tetracycline, doxycycline forms a stable calcium complex in any generating bone tissue. A slower development of the fibula has been observed in premature children administered with 25 mg/kg every 6 hours oral tetracycline. This reaction was reversible at treatment stop.

The administration of a medicine of the tetracycline group during the period of teeth generation (from the second half of pregnancy, neonatal period and childhood up to 8 years old) might induce an irreversible change in teeth colour (yellowish, greyish, brownish). This undesirable effect is more frequent with the long term administration, but has been observed following repeated short term treatments. Enamel hypoplasia has also been reported.
Use doxycycline in children under 8 years old only if the potential benefits are greater than the risk in serious or deadly conditions (for instance Rocky Mountain spotted fever), only in the absence of appropriate therapeutic alternatives (see section 4.3).
Although the risk of permanent teeth colouration is rare in children aged from 8 to 12 years, the use of doxycycline should be carefully justified in situations where other medicines are not available, are not efficient or are contra-indicated.

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

There have been reports of prolonged prothrombin time in patients taking warfarin and doxycycline. Because the tetracyclines have been shown to depress plasma prothrombin

activity, patients who are on coumarin anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin (beta-lactamine), it is advisable to avoid giving doxycycline in conjunction with beta-lactams.

Antacids containing aluminium, calcium or magnesium, or other cations or others (as strontium ranelate), or bismuth salts, impair doxycycline absorption and therefore is contraindicated to patients taking concurrently doxycycline.

Likewise, in case of concomitant treatment with iron preparations, a sufficient time interval should be respected between the intake of these preparations and DOXY 200.

Concomitant use of phenobarbital, carbamazepine, primidone, phenytoin or alcohol may increase the metabolism of doxycycline (reduced half-life). The efficacy is however maintained if doxycycline is administered twice daily.

The efficacy of oestrogen-progestin oral contraceptive treatment may be reduced when concomitant administered with antibiotics.

The concomitant use of tetracyclines and methoxyflurane has been reported to increase the renal toxicity.

Isotretinoin should not be administered concomitantly with tetracyclines.

Concomitant administration of doxycycline with rifampicin may reduce the plasma levels of doxycycline, thereby decreasing its activity.

Concomitant administration with methotrexate may increase the risk of toxicity of methotrexate.

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy
Studies in animals are insufficient to conclude on reproductive toxicity (see section 5.3). However, given the available clinical data available (tetracyclines penetrate bone and teeth during growth, which may result in reversible slowing of bone growth, irreversible staining of teeth and possibly an increased risk of cavities). Doxycycline is contraindicated during 2$^{nd}$ and 3$^{rd}$ trimesters of pregnancy except for life threatening situations (e.g. rickettsiosis such as Rocky Mountain spotted fever) when the benefits of the treatment outweigh the risks and no other alternative treatment is available (see sections 4.3 and 4.4). In any cases, the use of doxycycline is not recommended during pregnancy and should not be prescribed, only in the case where no other alternative treatment is available. In addition, duration treatment should be as short as possible.
Women in childbearing age should use effective contraception throughout treatment.

Breast-feeding
Tetracyclines are excreted in the milk of lactating women in quantities that effects in new-born/infants are probable. The concentration in breast milk corresponds to 30 to 40% of mother's plasmatic concentration. Doxycycline is contraindicated during breast-feeding except in life threatening situations (e.g. rickettsiosis such as Rocky Mountain spotted fever) when the benefits of the treatment outweigh the risks and no other alternative treatment is available (see sections 4.3 and 4.4).

Fertility
No effect on fertility has been observed in female rats that received doxycycline; the effect on male fertility was not studied (see section 5.3). No clinical data exists on destructive effect on male and female fertility.

## 4.7 Effects on ability to drive and use machines

The effect of doxycycline on the ability to drive and operate heavy machinery has not been studied. There is no evidence to suggest that DOXY 200 may effect these abilities.

## 4.8 Undesirable effects

The undesirable effects most frequently reported (incidence ≥1/100 to < 1/10) are: nausea, vomiting, overgrowth of *Candida* with vaginitis, photosensitivity reaction with skin rash. Severe hypersensitivity reactions as anaphylactic shock and DRESS have been rarely reported and may have fatal consequences.
The following frequencies of adverse events have been observed in patients treated with tetracyclines and specifically with doxycycline. They are ranked according to the following: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to <1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10 000),
not known (cannot be estimated from the available data).

| **System Organ Class** | Very common (≥ 1/10) | Common (≥ 1/100 to < 1/10) | Uncommon (≥ 1/1000 to <1/100) | Rare (≥ 1/10000 to < 1/1000) | Very rare (< 1/10000 | Not known (cannot be estimated from the available data) |
|---|---|---|---|---|---|---|
| Blood and lymphatic system disorders | | | | Thrombocytopenia, Haemolytic anaemia, neutropenia and eosinophilia | | |
| Immune system disorders | | | | Hypersensitivity (including Anaphylactic shock,anaphylactic reaction, Schönlein-Henoch purpura, angioedema, exacerbation of | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | disseminated lupus erythematosus, dyspnoea, serum sickness, peripheral oedema, urticarial) Medicine reactions with eosinophilia and systemic symptoms (DRESS) Jarisch-Herxheimer reaction (see section 4.4)[a,d] | | |
| Endocrine disorders | | | | Brown-black microscopic discolouration of thyroid tissue | | |
| Metabolism and nutrition disorders | | | | Reduced appetite | Hypoglycaemia | |
| Nervous system disorders | | Headache | | Fontanelle protrusion[f] benign intracranial hypertension in adults | | |
| Ear and labyrinth disorders | | | | Tinnitus | | |
| Ocular disorders | | | | Visuals disturbances[g] | | |
| Cardiac disorders | | | | Pericarditis, tachycardia | | |
| Vascular disorders | | | | Flushing, hypotension | | |
| Gastrointestinal disorders | | Nausea, vomiting | Dyspepsia (pyrosis/ gastritis) | Pancreatitis[a], pseudomembranous colitis, colitis due to *C. difficile*, oesophageal ulceration, oesophagitis, enterocolitis, inflammatory lesions (with | | Teeth disolouration[b] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | superinfection due to *Candida*) in the anogenital tract, abdominal pains, diarrhoea, dysphagia, glossitis | | |
| Hepatobiliary disorders | | | | Hepatotoxicity, liver dysfunction, hepatitis | | |
| Skin and subcutaneous tissue disorders | | Photosensitivity reactions Rash (including maculopapular rash and erythematous rash) | | toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Exfoliative dermatitis, photo-onycholysis, Skin hyperpigmentation[a,e] | | |
| Musculoskeletal and connective tissue disorders | | | | arthralgia Myalgia, | | |
| Renal and urinary tract disorders | | | | Increased blood level urea | | |
| Reproductive system and breast disorders | | Overgrowth of *Candida* that may cause vaginal candidiasis, vaginal discharge, vaginitis | | | | |

[a] This undesirable effect has been spontaneously reported during post-marketing surveillance and has not been observed during the clinical trials. The frequency was calculated using the following rule: the upper limit of the 95 % confidence interval of the frequency is lower of equal to 3/X, X being equal to 3833, the number of patients exposed during the clinical and epidemiological trials.

[b] A permanent reversible and superficial teeth discolouration has been reported with the use of doxycycline, but the frequency cannot be estimated based on the available data.

[c] the phototoxicity risk depends on the dose and is potentially higher in patient with long therapy (see section 4.4).

[d] In the scope of spirochetes infections treated with doxycycline.

[e] With a chronic use of doxycycline.

[f] In association with tetracyclines, including doxycycline, benign intracranial hypertension has been reported, accompanied with possible symptoms of headache or visual disturbances, should suggest a diagnostic of intracranial hypertension (see section 4.4).

[g] Associated to a benign intracranial hypertension (cerebral pseudotumor), see section 4.4.

As with other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature children given oral tetracyclines in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued (see sections 4.4 and 4.6).

The use of drugs of tetracycline class during tooth development ($2^{nd}$ and $3^{rd}$ trimesters of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discolouration of the teeth (yellow-grey-brown). The adverse reaction is more common in case long-term use of the drugs but has also been observed following repeated short-term courses. Enamel hypoplasia has also been reported (see sections 4.4 and 4.6).

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation 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

Treatment
In the event of over dosage, discontinue the medication and symptomatic treatment plus appropriate supportive treatment is indicated. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of over dosage.

# 5. PHARMACOLOGICAL PROPERTIES

Doxycycline monohydrate is a (broad spectrum) antibiotic synthetically derived from oxytetracycline. the chemical name of this light yellow crystalline powder is 6-deoxy-5-oxytetracycline.
Doxycycline has a high degree of lipid solubility and a low affinity for calcium. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Tetracyclines, ATC code: J01AA02

Mechanism of action
Doxycycline inhibits the bacterial protein synthesis, binding the bacterial 30S ribosomal subunit. It also affects the pseudo-bacterial protein synthesis of the infracellular plastids of some protozoans. Doxycycline is bacteriostatic. It is active against a broad panel of Gram positive and Gram negative bacteria, including atypical and obligate intracellular bacteria (spirochetes, rickettsia, chlamydia mollicutes) and some protozoans.

Resistance
Resistance to tetracyclines is generally due to ribosomal protection (by linkage to ribosome of proteins that are normally soluble) and efflux mechanisms. Inactivation of tetracyclines may happen in some organisms as *Bacteroides* spp.

Threshold of sensitivity trials

The thresholds of the *European Committee on Antimicrobial Susceptibility Testing* (EUCAST – version 5.0, 2015) for the sensitivity trials are presented below.

| **Organisms** | **Thresholds (CMI (mg/l)** | |
|---|---|---|
| | **Sensitive (≤ S)** | **Resistant (R >)** |
| *Staphylococcus* spp. | 1 | 2 |
| *Streptococcus pneumoniae* | 1 | 2 |
| *Streptococcus* of A, B, C, G groups | 1 | 2 |
| *Haemophilius influenzae* | 1 | 2 |
| *Moraxella catarrhalis* | 1 | 2 |
| *Campylobacter jejuni* and *coli* | --[1] | --[1] |

[1]Tetracycline (S ≤ 2 mg/1 ; R > 2 mg/l) may be used to determine the sensitivity to doxycycline.

| **Organisms** | **Thresholds of zone diameters (mm)** | |
|---|---|---|
| | **Sensitive (≤ S)** | **Resistant (R >)** |
| *Staphylococcus* spp. | 23 | 20 |
| *Streptococcus pneumoniae* | --[A] | --[A] |
| *Streptococcus* of A, B, C, G groups | 23 | 20 |
| *Haemophilius influenzae* | --[A] | --[A] |
| *Moraxella catarrhalis* | --[A] | --[A] |
| *Campylobacter jejuni* and *coli* | --[1] | --[1] |

[A]Tetracycline sensitive isolates (S ≤ 25 mm ; R > 22 mm) are equally sensitive to doxycycline, but some tetracycline resistant isolates might be sensitive to doxycycline. Tetracycline resistant isolates should be tested for sensitivity to doxycycline using the CMI determination method.

[1] Tetracycline (S ≥ 30 mm; R < 30 mm) may be used to determine the sensitivity to doxycycline.

Relation pharmacokinetics/pharmacodynamics

The relation between the area under the concentration-time (AUC) of the medicine in the circulation curve and the minimal inhibitory concentration (MIC) of the medicine for the pathogen organism (AUC/MIC) is the parameter that gives the best correlation with the efficacy of doxycycline.

Clinical efficacy again specific pathogens

The efficacy has been demonstrated during clinical trials against the pathogens enumerated under each sensitive to doxycycline *in vitro* indication.

*Respiratory tract infections*

Atypical microorganisms

- *Mycoplsma pneumoniae*

Gram positive microorganisms

- *Streptococcus pneumoniae*

Gram negative microorganisms

- *Haemophilius influenzae*
- *Klebsiella pneumoniae*

*Genito-urinary infections*

Atypical microorganisms

- *Chlamydia trachomatis*
- *Ureaplasma urealytium*

Gram negative microorganisms
- *Nesseria gonorrhoeae*
- *Treponema pallidum*
- *Haemophilius ducreyi*
- *Klebsiella granulomatis*

Gram negative and Gram positive anaerobia microorganisms

*Dermatological microorganisms*
Gram positive microorganisms
- *Propionibacterium acnes*

*Gastrointestinal infections*
Gram negative microorganisms
- *Vibrio cholera*

*Vectorial transmission and zoonotic infections*
Gram negative microorganisms
- *Borrelia burgdorferi*
- *Leptospira* spp.

*Rickettsia*
*Coxiella burnetii*
*Orientia tsutsugamuchi*
Protozonans
- *Plasmodium falciparum*

Antimicrobial activity against other pertinent pathogens
Clinical efficacy was not established against the following pathogens though *in vitro* studies suggest they would be sensitive to doxycycline in absence of acquired resistance mechanisms.

Gram positive microorganisms
*Staphylococcus* spp.
*Clostridium* spp.

Gram negative microorganisms
*Brucella* spp.

Other microorganisms
*Chlamydia* spp.
Other rickettsia

## 5.2 Pharmacokinetic properties

Absorption
Doxycycline is completely absorbed after oral administration. Studies reported to date indicate that the absorption of doxycycline, unlike certain other tetracyclines, is not notably influenced by the ingestion of food. Its absorption is not significantly affected by the presence of milk or dairy products than the absorption of tetracycline.
Tetracyclines form biologically inactive chelates when in presence with metals. Consequently, concomitant administration with antacids and irons salts preparations should be avoided.
Following a 200 mg dose the first day, followed by a 100 mg dose daily, the peak serum concentration varies between 1.5 to 3 micrograms/ml of doxycycline. Two hours following the administration, the peak serum levels vary between 2.6 to 3.0 micrograms/ml.

The mean serum level 24 hours after dosing was 1.5 micrograms/ml.
The table below indicates the mean serum levels (µg/ml) after administration of respectively:

(1) 100 mg doxycycline every 12 hours the first day and then 50 mg, every 12 hours the following days
(2) 100 mg doxycycline every 12 hours the first day and then 100 mg, every 24 hours the following days
(3) 100 mg doxycycline every 12 hours

| **Dosage** | **Serum concentration (µg/ml) after** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 h | 2 h | 8 h | 12 h* | 24 h* | 48 h* | 72 h* | 96 h* | 144 h* |
| (1) | 1,346 | 1,440 | 1,061 | 0,876 | 1,250 | 1,124 | N.D. | 1,294 | 1,279 |
| (2) | 1,374 | 1,302 | 1,027 | 0,887 | 1,515 | 1,042 | N.D. | 0,711 | 0,714 |
| (3) | 1,413 | 1,107 | 0,936 | 1,005 | 1,831 | N.D. | 2,651 | N.D. | 2,519 |

* Before the dosage
N.D.: Not Determined

Distribution
At pH= 7.4, the protein binding varies between 89.1 ± 3 % (n = 47, dialysis method) and 91.1 ± 4.6 % (n = 16, ultracentrifugation method). After the administration of repeated doses, the half-life of doxycycline varies from 18 to 22 hours.

The volume of distribution represents 158 % of the body weight, 1.58 l/kg of body weight.

As other tetracyclines, doxycycline does not cross the haemato-encephalic barrier in significant quantity. After absorption, doxycycline is well distributed in tissues.

Biotransformation
Generally, no significant metabolism occurs. In case of concomitant administration of doxycycline with hepatic enzyme inducers, a decrease of the half-life of doxycycline has been observed.

Elimination
Doxycycline is partially excreted (about 40 % of the resorbed dose) by the kidneys, unchanged form. Non-excreted doxycycline is presumed being excreted by direct diffusion from lumen intestinal mucous where is inactivated by complex formation with faecal matter. Though only a few percentage of the administered dose is eliminated in the bile, biliary concentration are usually 5 to 10 times higher than serum concentrations. Excretion of doxycycline by the kidney is about 40 % in 72 hours in individuals with normal function (creatinine clearance above 75 ml/min).

Linearity/Non-linearity
Doxycycline seems to exhibit a linear pharmacokinetics.

Kidney damage
Studies have shown no significative difference between serum half-life of doxycycline in normal individuals and in patients with severe renal failure. This percentage excretion may fall as low as 1 to 5 % in 72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 ml/min); in this case, the fraction of drug is not eliminated with urine but mainly excreted in the faeces.
Haemodialysis does not alter serum half-life.

Liver damage

No pharmacokinetics study has been carried out in patients with liver failure.

*Paediatric population*
Children and adolescent between 2 and 18 years old)
In the population, the few pharmacokinetics data of doxycycline (concentration per time) after IV administration doses and oral doses as standard treatment in 44 paediatrics patients (from the age of 2 to 18) revealed that at the allometric scale, doxycycline clearance (CL) of patients aged ≥ 2 to ≤ 8 (median [interval] 3,58 [2,27–10,82] l/h/70 kg, N = 11) does not differ significantly from the one of patients aged > 8 to 18 (3,27 [1,11–8,12] l/h/70 kg, N = 33). In paediatric patients ≤ 45 kg, the CL of doxycycline is normalised with the weight in patients ≥ 2 à ≤ 8 ans (median [interval] 0,071 [0,041–0,202] l/kg/h, N = 10) that does not differ significantly from the one of patients aged > 8 to 18 (0,081 [0,035–0,126] l/kg/h, N = 8). In patients >45 kg no significant clinical difference of the doxycycline normalised CL was observed between the two groups : ≥ 2 to ≤ 8 (0,050 l/kg/h, N = 1) and > 8 to 18 (0,044 [0,014–0,121] l/kg/h, N = 25).
No clinical significative difference of the CL between the oral and IV administration was observed in the cohort sub-groups oral dose (N =19) or IV (N= 21) alone.

Elderly
No data available on pharmacokinetics parameters in elderly people.

## 5.3 Preclinical safety data

No evidence of fertility effect was highlighted during study displaying female rats receiving doxycycline before matting, during gestation and breast-feeding; doses 8 times greater human based on the mg/m$^2$ relation. Effect on male fertility was not evaluated.

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 antibiotics, oxytetracycline (adrenal and pituitary tumours) and minocycline (thyroid tumours).
Likewise, although mutagenicity studies of doxycycline have not been conducted, positive results in *in-vitro* mammalian cell assays have been reported using related antibiotics (tetracycline, oxytetracycline).

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Maize starch, microcrystalline cellulose, sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), sodium lauryl sulphate, colloidal anhydrous silica, magnesium stearate, talc.

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

3 years

## 6.4 Special precautions for storage

Keep out of the reach and sight of children.
Store in the original package, protect from heat, light and moisture.
Store below 30°C.

## 6.5 Nature and contents of container

Box of 8 scored tablets in blister pack (PVC-Aluminium).

## 6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

# 7. MARKETING AUTHORISATION HOLDER

Exphar sa
Zoning Industriel de Nivelles Sud - Zone II
Avenue Thomas Edison 105
1402 Thines,
Belgium
Phone +32 (0)67 68 84 05
Fax +32 (0)67 68 84 19

# 8. CATEGORY OF DISTRIBUTION

☐ Over-the counter medicine ☒ Prescription only medicines

List I

# 9. MANUFACTURER

Gracure Pharmaceuticals Ltd.,
E-1105, RIICO Industrial Area, Phase-III,
Bhiwadi, District Alwar (Raj.)
INDIA

# 10. DATE OF REVISION OF THE TEXT

03/2022