SUMMARY OF PRODUCT CHARACTERISTICS

1) NAME OF THE MEDICINAL PRODUCT
MIRACLIN 100 mg tablets

2) QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 115.4 mg of doxycycline hyclate (equivalent to 100 mg basic anhydride doxycycline).
For the full list of excipients, see section 6.1

3) PHARMACEUTICAL FORM
Tablets

4) CLINICAL PARTICULARS
4.1) Therapeutic indications
Infections from Gram-positive and Gram-negative germs sensitive to tetracycline.

4.2) Posology and method of administration
Posology
Two tablets in a single dose on the first day of treatment, then one tablet daily for the following days.
In case of severe infections strictly follow the instructions of the doctor.
In all Group A beta haemolytic streptococcal infections, treatment should be continued for at least ten days.

Method of administration
Each dose must be taken during meals with a full glass of water.
Patients should take the medicinal product in an upright position at least an hour before lying down.
In order to obtain maximum therapeutic safety it will anyway be appropriate to perform an antibiogram to ascertain that the strain of germs responsible for the disease to be treated is sensitive to the action of tetracycline.

4.3) Contraindications
Hypersensitivity to the active substance, to tetracycline or to any of the excipients listed in section 6.1.
Esophageal obstructive disorders, such as tightening or achalasia.
The medicinal product is not indicated for pregnant women or children under the age of twelve years (see sections 4.4 and 4.6).

4.4) Special warnings and precautions for use

Paediatric population
As with other tetracyclines, doxycycline may form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature infants who were given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the treatment was discontinued.

The use of tetracyclines during tooth development (last half of pregnancy, infancy and childhood up to the age of twelve years) may cause permanent discoloration of the teeth (yellow-brown). This adverse reaction is more common during long-term use of these antibiotics but it has also been observed following repeated short-term courses. Enamel hypoplasia has also been reported, therefore doxycycline should not be administered to this age group unless other drugs are not likely to be effective or are contraindicated.

General
Bulging fontanelles in infants and benign intracranial hypertension have been reported in individuals receiving tetracyclines at high-dose therapy. These conditions disappeared rapidly upon withdrawal of the treatment.

Clostridium Difficile Associated Diarrhoea (CDAD)
Cases of *Clostridium Difficile* Associated Diarrhoea have been reported with nearly all antibiotics, including doxycycline, and may range in severity from mild diarrhoea to leading to overgrowth of *C. Difficile*.
C. Difficile produces A and B toxins, which contribute to the development of diarrhoea. Hypertoxin-producing strains of *C. Difficile* increase morbidity and mortality as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD should be considered in all patients who develop diarrhoea following antibiotic treatment. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibiotics.

Superinfections
As with other antibiotics, treatment with tetracycline may give rise to superinfections caused by non-susceptible organisms, including fungi. The possibility of tetracycline-resistant staphylococcal enterocolitis should be considered. Constant monitoring of the patient is required. If a resistant organism is detected, the antibiotic treatment should be discontinued and appropriate therapy should be instituted.

Oesophagitis
Cases of oesophagitis and oesophageal ulcer, some of which severe, have been reported. Patients should be reminded to take the medicine with a full glass of water, also during meals, to remain in an upright position at least one hour after administration, and to not lie down immediately after administration.
If the patient experiences dysphagia or retrosternal pain, the treatment should be discontinued immediately and appropriate examinations should be performed.

Patients suffering from ascertained oesophageal reflux should also consider alternative therapies.

Photosensitivity
Photosensitivity manifested by an exaggerated sunburn reaction to sunlight or ultraviolet light exposure has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs; they should avoid exposure to direct sunlight or ultraviolet light, and the treatment should be discontinued at the first evidence of skin erythema.

Liver impairment
The administration of doxycycline in large doses and for long-term therapies (more than two weeks) may cause liver disorders and must therefore be monitored and the treatment should be discontinued in case of abnormal reactions.

Renal impairment
The excretion of doxycycline is not modified in subjects with impaired renal function. In these patients it is nonetheless advisable to proceed with caution and, if necessary, proceed to a downward adjustment of the dose.
Administration of tetracycline at the usual recommended dose may result in excessive accumulation in patients with renal impairment. In these cases dosage adjustment is recommended and blood tests (levels should never exceed 15 mg/ml) and liver function tests should be carried out. It should also be remembered that tetracycline performs an antianabolic action that may worsen impaired renal function.

Venereal diseases
Treatment of venereal diseases may obscure the symptoms of a coexisting syphilis. In these cases, blood tests should be performed for at least 4 months
In long-term therapy, periodic laboratory evaluation of organ systems, including haematopoietic, renal and hepatic studies should be performed.

Myasthenia gravis
Doxycycline should be administered with caution to patients suffering from myasthenia gravis (see section 4.8).
Jarisch-Herxheimer reaction:
Jarish-Herxheimer reaction can occur in some patients with spirochete infections shortly after the beginning of the treatment with doxycycline. Patients should be reassured that it is a usually self-limiting effect of the antibiotic treatment with doxycycline of the infections caused by spirochete.

4.5) Interaction with other medicinal products and other forms of interaction
Absorption of oral tetracycline is reduced by:

- antacids containing aluminium, calcium or magnesium,
- food and beverage containing milk or dairy products,
- products containing iron salts, oral preparations containing zinc or bismuth.

Concomitant administration should therefore be avoided or, at least, it should be separated by at least two hours.

Rare cases of increased blood concentration levels of lithium, methotrexate, digoxin, and ergot derivatives have been reported in literature following concomitant administration of tetracycline.

Oral anticoagulants

A prolonged prothrombin time has been reported in patients receiving warfarin and doxycycline. Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Penicillin

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines, including doxycycline, concomitantly with penicillin.

Anticonvulsants

Barbiturates (phenobarbital, primidone), carbamazepine and phenytoin decrease the half-life of doxycycline.

Alcoholic beverage

The half-life of doxycycline may be decreased by the concomitant use of alcoholic beverage.

Oral contraceptives

Tetracycline may reduce the effectiveness of oral contraceptives. Some cases of pregnancy or breakthrough bleeding have been attributed to the concurrent use of tetracycline with oral contraceptives.

Ciclosporin:

Doxycycline may increase blood concentration levels of ciclosporin. Co-administration should therefore be monitored.

Interactions with other medicinal products

Not recommended concomitant use:

Systemic retinoids:

Concomitant use with tetracyclines increases the risk of developing benign intracranial hypertension (a reversible increase of pressure in the skull).

Methoxyflurane:
There have been reports of nephrotoxicity and death in some cases when tetracycline therapy has been combined with methoxyflurane.

Interactions with laboratory test results
False increase of urinary catecholamine for the fluorescent treponemal antibody absorption (FTA-ABS) test may occur.

4.6) Fertility, pregnancy and breastfeeding

Pregnancy
There are no controlled data in human pregnancy. Use of doxycycline during pregnancy is contraindicated (see sections 4.3 e 4.4).

Results of animal studies indicate that tetracyclines cross the placenta, are found in foetal tissues, and can have toxic effects on the developing foetus (often related to retardation of skeletal development). Evidence of embryotoxicity also has been noted in animals treated early in pregnancy.

Breastfeeding
As with any tetracycline, doxycyline should not be taken whilst breastfeeding as it passes into the milk of breast-feeding mothers (see section 4.3).

Fertility
The effects of MIRACLIN on fertility are not known.

4.7) Effects on ability to drive and use machines
There is no evidence to suggest that effects of doxycycline will affect the ability to drive vehicles and operate machines.

4.8) Undesirable effects

Systems and organs	***Very common ≥1/10***	***Common ≥1/100 a <1/10***	***Uncommon ≥1/1.000 a <1/100***	***Rare ≥1/10.000 a <1.000***	***Not known***
Blood and lymphatic system disorders				Thrombocytopenia Haemolytic anaemia Neutropenia Eosinophilia	

Systems and organs	***Very common ≥1/10***	***Common ≥1/100 a <1/10***	***Uncommon ≥1/1.000 a <1/100***	***Rare ≥1/10.000 a <1.000***	***Not known***
Immune system disorders		Anaphylactic reactions (including hypersensitivity, Henoch–Schönlein purpura, hypotension, Pericarditis, Angioedema, Exacerbation of systemic lupus erythematosus, Dyspnoea, Serum sickness, Peripheral oedema, Tachycardia and Urticaria)		Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome)	Jarisch-Herxheimer reaction (see paragraph 4.4)
Endocrine disorders				Black pigmentation of the thyroid	
Metabolism and nutrition disorders				Anorexia, porphyria	
Nervous system disorders		Headache		Bulging fontanelles, Benign intracranial hypertension*	
Ear and labyrinth disorders				Tinnitus	
Vascular disorders				Flushing	

Systems and organs	***Very common ≥1/10***	***Common ≥1/100 a <1/10***	***Uncommon ≥1/1.000 a <1/100***	***Rare ≥1/10.000 a <1.000***	***Not known***
Gastrointestinal disorders		Nausea/vomiting	Dyspepsia (pyrosis/gastritis)	Pseudomembranous colitis, *Clostridium Difficile* Associated Diarrhoea, Oesophageal ulcers, Oesophagitis, Enterocolitis, Inflammatory lesions (with candidiasis) in the anogenital area, Abdominal pain, Diarrhoea, Dysphagia, Glossitis	
Hepatobiliary disorders				Hepatotoxicity, Hepatitis, Impaired liver function, Jaundice, Pancreatitis	
Skin and subcutaneous tissue disorders	Photosensitivity skin reactions	Erythematous or maculopapular rash		Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Exfoliative dermatitis, Photo-onycholysis	
Musculoskeletal and connective tissue disorders				Arthralgia, Myalgia, Exacerbation of the symptoms of myasthenia gravis (see section 4.4)	

Systems and organs	***Very common ≥1/10***	***Common ≥1/100 a <1/10***	***Uncommon ≥1/1.000 a <1/100***	***Rare ≥1/10.000 a <1.000***	***Not known***
Renal and urinary disorders				Rise in blood urea nitrogen (BUN)	

Frequency convention according to CIOMS III: Very common ≥ 1/10 (≥ 10%), Common ≥ 1/100 to < 1/10 (≥ 1% and < 10%), Uncommon ≥ 1/1.000 to < 1/100 (≥ 0.1% and < 1%), Rare ≥ 1/10.000 to < 1/1.000 (≥ 0.01% and < 0.1%) Very rare < 1/10 000 (< 0.01%), Not known: (frequency cannot be estimated from the available data).

* During the treatment with tetracyclines, and amongst them doxycycline, cases of benign intracranial hypertension with possible symptoms of headache, vomiting, visual disturbance such as blurred vision, scotoma, double vision or permanent sight loss were reported. The onset of clinical symptoms, including headache and visual disturbance, should suggest a possible diagnosis of intracranial hypertension. In case of suspected increase of the intracranial pressure during the treatment with tetracycline, the administration must be interrupted.

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 website: https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9) Overdose
In case of overdose proceed to gastric irrigation. Haemodialysis is not indicated in case of overdose as it does not alter the medicine serum half-life.

5) PHARMACOLOGICAL PROPERTIES

5.1) Pharmacodynamic properties
Pharmacotherapeutic category: Systemic antibacterial agent.
ATC Code: J01AA02
Doxycycline is a broad-spectrum antibiotic, whose action is performed, even at low concentration, on Gram-positive and some Gram-negative organisms, as well as on rickettsiae, mycoplasma, Chlamydia, some typical mycobacteria and amoebas. Doxycycline differs from other tetracyclines because it is highly absorbed by the gastrointestinal tract and because of the remarkable duration of its therapeutic action.

5.2) Pharmacokinetic properties
Absorption

Doxycycline is virtually completely absorbed in the upper part of the gastrointestinal tract; administration during meals does not affect the level of absorption. Therapeutically relevant serum levels are achieved one hour following administration, with a concentration peak between the second and fourth hours following administration. Following oral administration of a single 200 mg dose to adults, the following data were observed: peak serum levels higher than 3 mcg/ml; residual concentration after 24 hours higher than 1 mcg/ml; 16-22 hours serum half-life. Bonding capacity with proteins varies between 82% and 93% (weak bond).

Distribution

Doxycycline presents a good intra- and extra-cellular diffusion. At the usual recommended dose, therapeutically relevant levels are observed in: ovaries, uterus, placenta, testis, prostate, bladder, kidneys, pulmonary tissue, skin, muscles, lymphatic nodes, liver, bile, stomach, bowels, saliva. In the spinal fluid, concentration is equal to 3-36% of serum concentration 4 hours following administration of a 200 mg dose.

Elimination

Approximately 60% of the administered dose is excreted along with faecal matter; the remaining percentage is excreted in the urine. In case of renal failure, excretion by the kidney is lower, and a higher percentage is excreted with faeces. Nonetheless, instances of accumulation in patients with renal failure have been reported. Haemodialysis does not alter the serum half-life.

5.3) Preclinical safety data

Acute toxicity: DL_{50} higher than 1500 mg/kg in mice (per os).
Sub-acute toxicity: increase in body weight, blood counts and autoptic examination of the principal organs of animals treated with doxycycline during 8 weeks at a daily dosage of 100 mg/kg have not highlighted significant differences compared with the control group.

6) PHARMACEUTICAL PARTICULARS

6.1) List of excipients

Microcrystalline cellulose, dibasic calcium phosphate, crospovidone, corn starch, magnesium stearate, sodium carboxymethylamide, talc, sodium lauryl sulfate, colloidal silex.

6.2) Incompatibilities

None known.

6.3) Shelf life

3 years

6.4) Special precautions for storage

Do not store above 25°C

6.5) Nature and contents of container
10 tablets packed in aluminium/PVC/PVDC blister.

6.6) Special precautions for disposal and other handling
No special requirements.

7) MARKETING AUTHORISATION HOLDER
LABORATORIO FARMACOLOGICO MILANESE S.r.l.- Via Monterosso 273, 21042 Caronno Pertusella (VA)

8) MARKETING AUTHORISATION NUMBER
07796/07501/VAR/2021
05021/07071/REN/2019

9) DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of latest renewal: Feb 25, 2020

10) DATE OF REVISION OF THE TEXT
24th October 2019.