

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Ronaxan 250 mg tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substance:

Doxycycline base 250 mg (as doxycycline hyclate 270.53 mg)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Round, biconvex light yellow/yellow to beige scored tablet that could appear mottled.

The tablets can be divided into two equal parts.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

For the treatment of respiratory tract infections including rhinitis, tonsillitis and bronchopneumonia caused by *Bordetella bronchiseptica* and *Pasteurella* spp. susceptible to doxycycline.

For the treatment of canine ehrlichiosis caused by *Ehrlichia canis*.

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

Do not use in animals with renal or hepatic insufficiency.

Do not use in animals with diseases associated with vomiting or dysphagia (see also section 4.6).

Do not use in animals with known photosensitivity (see also section 4.6).

Do not use in puppies before completion of teeth enamel formation.

4.4 Special warnings for each target species

Ehrlichia canis infection: treatment should be initiated at the onset of clinical signs. Complete eradication of the pathogen is not always achieved, but treatment for 28 days generally leads to a resolution of the clinical signs and a reduction of the bacterial load. A longer duration of treatment, based on a benefit/risk assessment by the responsible veterinarian, may be required particularly in severe or chronic ehrlichiosis. All treated patients should be regularly monitored, even after clinical cure.

4.5 Special precautions for use

Special precautions for use in animals

Tablets should be administered with food in order to avoid vomiting and to reduce the likelihood of oesophageal irritation.

The product should be administered with caution to young animals, since tetracyclines as a class may cause permanent discolouration of the teeth, when administered during tooth development. However, human literature indicates that doxycycline is less likely than other tetracyclines to cause these abnormalities, due to its reduced ability to chelate calcium.

Use of the veterinary medicinal product should be based on identification and susceptibility testing of the target pathogens. If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at local/regional level.

Use of the veterinary medicinal product deviating from the instructions given in the summary of product characteristics (SPC) may increase the prevalence of bacteria resistant to doxycycline and may decrease the effectiveness of treatment with other tetracyclines, due to the potential for cross-resistance.

Use of the veterinary medicinal product should be in accordance with official, national and regional antimicrobial policies.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

People with known hypersensitivity to doxycycline or other tetracyclines should avoid contact with the veterinary medicinal product and personal protective equipment consisting of gloves should be worn when handling the veterinary medicinal product.

In case of skin irritation, seek medical advice immediately and show the package leaflet or the label to the physician.

Accidental ingestion, especially by children, may cause adverse reactions such as emesis. To avoid accidental ingestion, blisters should be inserted back into the outer packaging and kept in a safe place. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

4.6 Adverse reactions (frequency and seriousness)

Gastrointestinal adverse reactions including vomiting, nausea, salivation, oesophagitis and diarrhoea have been reported very rarely in spontaneous reports.

Photosensitivity and photodermatitis can occur following tetracycline therapy, after exposure to intense sunlight or ultraviolet light. (See also section 4.3).

Use of tetracycline during the period of tooth development may lead to tooth discolouration.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Laboratory studies in rats and rabbits have not produced any evidence of teratogenic or embryotoxic effects of doxycycline. However, as there is no information available in the target species, use is not recommended during pregnancy.

Use only according to the benefit-risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Doxycycline should not be used concurrently with other antibiotics, especially bactericidal drugs such as the β -lactams. Cross-resistance to tetracyclines may occur.

The half-life of doxycycline is reduced by concurrent administration of barbiturates, phenytoin and carbamazepine.

Dosage adjustments may be necessary in subjects under anticoagulant therapy, as tetracyclines depress the plasma activity of prothrombin.

Simultaneous administration of oral absorbents, antacids and preparations including multivalent cations should be avoided as they reduce doxycycline availability.

4.9 Amounts to be administered and administration route

For oral use.

The dosage is 10 mg doxycycline per kg bodyweight per day corresponding to one tablet per 25 kg bodyweight. To ensure a correct dosage, bodyweight of the animals should be determined as accurately as possible to avoid overdosing or underdosing. In order to adjust the dosage, the tablets can be divided into two equal parts. The dosage can be divided into two daily administrations. The duration of treatment might be adapted depending on the clinical response, after benefit/risk assessment by the veterinarian.

Disease	Dosage regimen	Duration of treatment
Respiratory tract infection	10 mg/kg per day	5-10 days
Canine ehrlichiosis	10 mg/kg per day	28 days

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Vomiting may occur in dogs with 5 times the recommended dose. Increased levels of ALT, GGT, ALP and total bilirubin were reported in dogs at 5-fold overdose.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use; Tetracyclines.

ATCvet code: QJ01AA02.

5.1 Pharmacodynamic properties

Doxycycline is a broad-spectrum tetracycline-class antibiotic active against a large number of gram positive and gram negative bacteria including both aerobic and anaerobic species.

Doxycycline inhibits bacterial protein synthesis by binding to the 30-S ribosomal subunits. This interferes with binding of aminoacyl-tRNA to the acceptor site on the mRNA ribosome complex and prevents coupling of amino acids to the elongating peptide chains; doxycycline has a predominantly bacteriostatic activity.

The penetration of doxycycline into the bacterial cell takes place by both active transport and passive diffusion.

The main mechanisms of acquired resistance to tetracycline class antibiotics include active efflux and ribosomal protection. A third mechanism is enzymatic degradation. The genes mediating resistance may be carried on plasmids or transposons, as for example, *tet(M)*, *tet(O)*, and *tet(B)* that can be found in both gram-positive and gram-negative organisms including clinical isolates.

Cross-resistance to other tetracyclines is common but depends on the mechanism conferring resistance. Due to the greater liposolubility and greater ability to pass through cell membranes (in comparison to tetracycline), doxycycline retains a certain degree of efficacy against microorganisms with acquired resistance to tetracyclines via efflux pumps. However, resistance mediated by ribosomal protection proteins confer cross-resistance to doxycycline.

The following MIC values for the targeted bacteria were collected between 2017 and 2018 as a part of ongoing European surveillance studies:

Bacterial pathogen	Origin (<i>number of strains tested</i>)	MIC ₅₀ (µg/ml)	MIC ₉₀ (µg/ml)
<i>Bordetella bronchiseptica</i>	Dog – respiratory tract (38)	0.12	0.5
<i>Pasteurella</i> spp.	Dog – respiratory tract (27)	0.12	0.25

Antibiotic susceptibility data for *Ehrlichia canis* are limited.

5.2 Pharmacokinetic particulars

Absorption

After oral administration, the bioavailability of doxycycline is 45% in dogs. Peak concentrations of 4.5 µg/ml are reached within 3 hours after oral administration, supporting that doxycycline is rapidly absorbed from the gastro-intestinal tract.

Distribution

Doxycycline is broadly distributed throughout the organism due to its physicochemical characteristics, as it is highly liposoluble. The distribution volume is 1.72 l/kg in dogs, supporting that doxycycline diffuses from blood into tissues. Protein binding is reported as 91.75 % ± 0.63 and 91.4% in the literature. The tissue concentrations, with the exception of the skin, are generally higher than the plasma levels, including the excretion organs (liver, kidney and intestines) and for the lungs.

Elimination

After a single administration, the half-life elimination ($T_{1/2}$) is 7.84 hours. Excretion occurs in an unchanged active form (90%) via the faeces (approximately 75%), via the urine (approximately 25%) and less than 5% via the bile ducts.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Magnesium stearate

6.2 Major incompatibilities

None known.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the blister in the outer carton.

6.5 Nature and composition of immediate packaging

Blisters (polyvinyl chloride acetyl chloride complex and aluminium foil) of 10 tablets packed in a cardboard box.

Cardboard box containing 1 blister of 10 tablets
Cardboard box containing 2 blisters of 10 tablets
Cardboard box containing 10 blisters of 10 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally.

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally.

10. DATE OF REVISION OF THE TEXT

To be completed nationally.

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE**Cardboard for 1 x 10 tablets, 2 x 10 tablets and 10 x 10 tablets****1. NAME OF THE VETERINARY MEDICINAL PRODUCT**

Ronaxan 250 mg tablets for dogs
doxycycline hyclate

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains:
Doxycycline base 250 mg(as doxycycline hyclate 270.53 mg)

3. PHARMACEUTICAL FORM

Tablets

4. PACKAGE SIZE

1 x 10 tablets
2 x 10 tablets
10 x 10 tablets

5. TARGET SPECIES

Dogs

6. INDICATION(S)**7. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)**9. SPECIAL WARNING(S), IF NECESSARY**

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the blister in the outer carton.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”
--

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally.

16. MARKETING AUTHORISATION NUMBER(S)
--

To be completed nationally.

17. MANUFACTURER’S BATCH NUMBER
--

Lot {number}

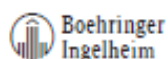
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister of 10 tablets

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Ronaxan 250 mg
doxycycline hyclate

2. NAME OF THE MARKETING AUTHORISATION HOLDER



3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Lot {number}

5. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Ronaxan 250 mg tablets for dogs

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
To be completed nationally.

Manufacturer responsible for batch release:
Boehringer Ingelheim Animal Health France SCS
4 Chemin du Calquet
31000 Toulouse
France

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Ronaxan 250 mg tablets for dogs
doxycycline hyclate

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENTS

Each tablet contains:

Active substance:
Doxycycline base 250 mg (as doxycycline hyclate 270.53 mg)

Round, biconvex light yellow/yellow to beige scored tablet that could appear mottled.
The tablets can be divided into two equal parts.

4. INDICATION(S)

For the treatment of respiratory tract infections including rhinitis, tonsillitis and bronchopneumonia caused by *Bordetella bronchiseptica* and *Pasteurella* spp. susceptible to doxycycline.

For the treatment of canine ehrlichiosis (a disease transmitted by ticks) caused by *Ehrlichia canis*.

5. CONTRAINDICATIONS

Do not use in cases of hypersensitivity to the active substance or any of the excipients.
Do not use in animals with renal or hepatic insufficiency.
Do not use in animals with diseases associated with vomiting or dysphagia (difficulty to swallow) (see also section “Adverse reactions”).
Do not use in animals with known photosensitivity (see also section “Adverse reactions”).
Do not use in puppies before completion of teeth enamel formation.

6. ADVERSE REACTIONS

Gastrointestinal adverse reactions including vomiting, nausea (signs the animal may be sick), salivation (drooling), oesophagitis (irritation of the oesophagus) and diarrhoea have been reported very rarely in spontaneous reports.

Photosensitivity and photodermatitis (irritation of the skin) can occur following tetracycline therapy, after exposure to intense sunlight or ultraviolet light. (See also section “Contraindications”).

Use of tetracycline during the period of tooth development may lead to tooth discolouration.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

For oral use.

The dosage is 10 mg doxycycline per kg bodyweight per day corresponding to one tablet per 25 kg bodyweight. The dosage can be divided into two daily administrations. The duration of treatment might be adapted depending on the clinical response, after benefit/risk assessment by the veterinarian.

Disease	Dosage regimen	Duration of treatment
Respiratory tract infection	10 mg/kg per day	5-10 days
Canine ehrlichiosis	10 mg/kg per day	28 days

9. ADVICE ON CORRECT ADMINISTRATION

To ensure a correct dosage, bodyweight of the animals should be determined as accurately as possible to avoid overdosing or underdosing. In order to adjust the dosage, the tablets can be divided into two equal parts. Tablets should be administered with food in order to avoid vomiting.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Do not store above 25°C.

Keep the blister in the outer carton.

Do not use this veterinary medicinal product after the expiry date which is stated on the carton after EXP.

The expiry date refers to the last day of that month.

12. SPECIAL WARNING(S)

Special warnings for each target species

For the veterinarian

Ehrlichia canis infection: treatment should be initiated at the onset of clinical signs. Complete eradication of the pathogen is not always achieved, but treatment for 28 days generally leads to a resolution of the clinical signs and a reduction of the bacterial load. A longer duration of treatment, based on a benefit/risk assessment by the responsible veterinarian, may be required particularly in severe or chronic ehrlichiosis. All treated patients should be regularly monitored, even after clinical cure.

Special precautions for use in animals

Tablets should be administered with food in order to avoid vomiting and to reduce the likelihood of oesophageal irritation.

The product should be administered with caution to young animals, since tetracyclines as a class may cause permanent discolouration of the teeth, when administered during tooth development. However, human literature indicates that doxycycline is less likely than other tetracyclines to cause these abnormalities, due to its reduced ability to chelate calcium.

For the veterinarian

Use of the veterinary medicinal product should be based on identification and susceptibility testing of the target pathogens. If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at local/regional level.

Use of the veterinary medicinal product deviating from the instructions given in the leaflet may increase the prevalence of bacteria resistant to doxycycline and may decrease the effectiveness of treatment with other tetracyclines, due to the potential for cross resistance.

Use of the veterinary medicinal product should be in accordance with official, national and regional antimicrobial policies.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

People with known hypersensitivity to doxycycline or other tetracyclines should avoid contact with the veterinary medicinal product and personal protective equipment consisting of gloves should be worn when handling the veterinary medicinal product.

In case of skin irritation, seek medical advice immediately and show the package leaflet or the label to the physician.

Accidental ingestion, especially by children, may cause adverse reactions such as emesis. To avoid accidental ingestion, blisters should be inserted back into the outer packaging and kept in a safe place. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Pregnancy and lactation

Laboratory studies in rats and rabbits have not produced any evidence of teratogenic or embryotoxic effects (malformations or deformities of the embryo) of doxycycline. However, as there is no information available in the target species, use is not recommended during pregnancy.

Use only according to the benefit/risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction

Doxycycline should not be used concurrently with other antibiotics especially bactericidal drugs such as the β -lactams (for example penicillin, ampicillin). Cross-resistance to tetracyclines may occur.

The half-life of doxycycline is reduced by concurrent administration of barbiturates (some types of sedatives or tranquilisers), phenytoin and carbamazepine (two types of anti-epileptic medications).

Dosage adjustments may be necessary in subjects under anticoagulant therapy (blood thinners), as tetracyclines depress the plasma activity of prothrombin.

Simultaneous administration of oral absorbents, antacids (protectants for the stomach) and preparations including multivalent cations should be avoided as they reduce doxycycline availability.

Overdose (symptoms, emergency procedures, antidotes)

Vomiting may occur in dogs with 5 times the recommended dose. Increased levels of ALT, GGT, ALP and total bilirubin were reported in dogs at 5-fold overdose.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Medicines should not be disposed of via wastewater or household waste.

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

To be completed nationally.

15. OTHER INFORMATION

Pack sizes:

1 x 10 tablets, 2 x 10 tablets or 10 x 10 tablets.

Not all pack sizes may be marketed.