Annex I

List of the names, pharmaceutical form, strengths of the veterinary medicinal products, animal species, route of administration, marketing authorisation holders in the Member States

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Belgium	Boehringer Ingelheim Animal Health Belgium SA Avenue Arnaud Fraiteurlaan, 15-23 1050 Brussels Belgium	Ronaxan 20 mg	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
Belgium	Boehringer Ingelheim Animal Health Belgium SA Avenue Arnaud Fraiteurlaan, 15-23 1050 Brussels Belgium	Ronaxan 100 mg	Doxycycline	100 mg	Tablets	Dogs	Oral use
Croatia	Boehringer Ingelheim Animal Health France SCS, 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan 100 mg, tablete za pse	Doxycycline	100 mg	Tablets	Dogs	Oral use
Croatia	Boehringer Ingelheim Animal Health France SCS, 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan 250 mg, tablete za pse	Doxycycline	250 mg	Tablets	Dogs	Oral use
Czech Republic	Boehringer Ingelheim Animal Health France SCS, 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan 100 mg tablety	Doxycycline	100 mg	Tablets	Dogs	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Czech Republic	Boehringer Ingelheim Animal Health France SCS, 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan 20 mg tablety	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
Denmark	Boehringer Ingelheim Animal Health Nordics A/S Strødamvej 52 2100 København Ø Denmark	Ronaxan Vet.	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
Denmark	Boehringer Ingelheim Animal Health Nordics A/S Strødamvej 52 2100 København Ø Denmark	Ronaxan Vet.	Doxycycline	100 mg	Tablets	Cats and dogs	Oral use
France	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan comprimes 20	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
France	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan comprimes 100	Doxycycline	100 mg	Tablets	Dogs	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
France	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan comprimes 250	Doxycycline	250 mg	Tablets	Dogs	Oral use
Germany	Boehringer Ingelheim Vetmedica GmbH Binger Strasse 173 55216 Ingelheim am Rhein Germany	Ronaxan 100	Doxycycline	100 mg	Tablets	Dogs	Oral use
Greece	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan, Δισκία 20 mg/tab	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
Greece	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan, Δισκία 100 mg/tab	Doxycycline	100 mg	Tablets	Dogs	Oral use
Greece	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan, Δισκία 250 mg/tab	Doxycycline	250 mg	Tablets	Dogs	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Ireland	Boehringer Ingelheim Vetmedica GmbH Binger Strasse 173 55216 Ingelheim am Rhein Germany	Ronaxan 100 mg Tablet	Doxycycline	100 mg	Tablets	Dogs	Oral use
Ireland	Boehringer Ingelheim Vetmedica GmbH Binger Strasse 173 55216 Ingelheim am Rhein Germany	Ronaxan 20 mg Tablet	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
Italy	Boehringer Ingelheim Animal Health Italia S.p.A Via Lorenzini n.8 Milano - 20139 Italy	Ronaxan, 20 mg compresse per cani e gatti	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
Italy	Boehringer Ingelheim Animal Health Italia S.p.A Via Lorenzini n.8 Milano - 20139 Italy	Ronaxan, 100 mg compresse per cani	Doxycycline	100 mg	Tablets	Dogs	Oral use
Italy	Boehringer Ingelheim Animal Health Italia S.p.A Via Lorenzini n.8 Milano - 20139 Italy	Ronaxan, 250 mg compresse per cani	Doxycycline	250 mg	Tablets	Dogs	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Lithuania	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan 20, tabletės	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
Lithuania	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan 100, tabletės	Doxycycline	100 mg	Tablets	Cats and dogs	Oral use
Luxembourg	Boehringer Ingelheim Animal Health Belgium SA Arianelaan 16 1200 Brussel Belgium	Ronaxan 20 mg	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
Luxembourg	Boehringer Ingelheim Animal Health Belgium SA Arianelaan 16 1200 Brussel Belgium	Ronaxan 100 mg	Doxycycline	100 mg	Tablets	Dogs	Oral use
Malta	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan tablets 100	Doxycycline	100 mg	Tablets	Dogs	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Malta	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan tablets 20	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
Norway	Boehringer Ingelheim Animal Health Nordics A/S Strødamvej 52 2100 Copenhagen Denmark	Ronaxan Vet	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
Norway	Boehringer Ingelheim Animal Health Nordics A/S Strødamvej 52 2100 Copenhagen Denmark	Ronaxan Vet	Doxycycline	100 mg	Tablets	Cats and dogs	Oral use
Portugal	Boehringer Ingelheim Animal Health, Unipessoal, Lda. Avenida de Pádua, nº 11 1800-294 Lisboa Portugal	Ronaxan 20 mg comprimidos para cães e gatos	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
Portugal	Boehringer Ingelheim Animal Health, Unipessoal, Lda. Avenida de Pádua, nº 11 1800-294 Lisboa Portugal	Ronaxan 100 mg comprimidos para cães	Doxycycline	100 mg	Tablets	Dogs	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Portugal	Boehringer Ingelheim Animal Health, Unipessoal, Lda. Avenida de Pádua, nº 11 1800-294 Lisboa Portugal	Ronaxan 250 mg comprimidos para cães	Doxycycline	250 mg	Tablets	Dogs	Oral use
Romania	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan 20 mg Tablet	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
Romania	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan 100 mg Tablet	Doxycycline	100 mg	Tablets	Dogs	Oral use
Romania	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan 250 mg Tablet	Doxycycline	250 mg	Tablets	Dogs	Oral use
Slovak Republic	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan 20 mg tablety	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Slovak Republic	Boehringer Ingelheim Animal Health France SCS 29 Avenue Tony Garnier 69007 Lyon France	Ronaxan 100 mg tablet	Doxycycline	100 mg	Tablets	Dogs	Oral use
Spain	Boehringer Ingelheim Animal Health España S.A.U. C/Prat de la Riba, 50 Sant Cugat del Valles Barcelona 08174 Spain	Ronaxan 20 mg comprimidos	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
Spain	Boehringer Ingelheim Animal Health España S.A.U. C/Prat de la Riba, 50 Sant Cugat del Valles Barcelona 08174 Spain	Ronaxan 100 mg comprimidos	Doxycycline	100 mg	Tablets	Dogs	Oral use
Sweden	Boehringer Ingelheim Animal Health Nordics A/S, Strødamvej 52, 2100 Copenhagen Ø, Denmark	Ronaxan vet.	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
Sweden	Boehringer Ingelheim Animal Health Nordics A/S, Strødamvej 52, 2100 Copenhagen Ø, Denmark	Ronaxan vet.	Doxycycline	100 mg	Tablets	Cats and dogs	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
The Netherlands	Boehringer Ingelheim Animal Health Netherlands B.V. Comensiusstraat 6 1817 MS Alkmaar The Netherlands	Ronaxan 100 mg, tablet voor honden en katten	Doxycycline	100 mg	Tablets	Cats and dogs	Oral use
The Netherlands	Boehringer Ingelheim Animal Health Netherlands B.V. Comensiusstraat 6 1817 MS Alkmaar The Netherlands	Ronaxan 20 mg, tablet voor honden en katten	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use
United Kingdom (Northern Ireland)[1]	Boehringer Ingelheim Animal Health UK Ltd, Ellesfield Avenue, Bracknell Berkshire RG12 8YS United Kingdom	Ronaxan 100 mg Tablet	Doxycycline	100 mg	Tablets	Dogs	Oral use
United Kingdom (Northern Ireland)[1]	Boehringer Ingelheim Animal Health UK Ltd, Ellesfield Avenue, Bracknell Berkshire RG12 8YS United Kingdom	Ronaxan 20 mg Tablet	Doxycycline	20 mg	Tablets	Cats and dogs	Oral use

1 For the United Kingdom, as from 1 January 2021, EU Law applies only to the territory of Northern Ireland (NI) to the extent foreseen in the Protocol on Ireland/NI.

Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet

Overall summary of the scientific evaluation of Ronaxan and its associated names (see Annex I)

1. Introduction

Ronaxan and its associated names are tablets containing 20 mg, 100 mg or 250 mg doxycycline hyclate as active substance. Doxycycline is a second generation, broad-spectrum cycline belonging to the tetracycline family. It is active against a large number of gram-positive and gram-negative pathogens including strains resistant to first generation tetracyclines.

On 12 August 2019, Germany sent a referral notification under Article 34(1) of Directive 2001/82/EC to the European Medicines Agency (the Agency) for Ronaxan and its associated names. Germany referred the issue due to divergent national decisions having been taken by the EU Member States resulting in discrepancies in the product information for Ronaxan and its associated names.

The main areas of disharmony in the existing product information relate to target species, indications and posology.

The Committee for Medicinal Products for Veterinary Use (CVMP) was requested to give its opinion on this matter and to harmonise the product information for Ronaxan and its associated names.

2. Discussion of data available

This referral concerns Ronaxan 20 mg, 100 mg and 250 mg tablets.

Summary of product characteristics (SPC) section 4.1 Target species

For Ronaxan 20 mg tablets, all products concerned were authorised for target species 'dogs and cats', but small differences in the wording for target species 'dogs' existed. Therefore, the harmonisation of target species 'dogs and cats' was considered acceptable.

For Ronaxan 100 mg tablets the harmonisation to 'dogs and cats' was an extension to the target species cat in some Member States. Since Ronaxan has been registered for use in cats for a long period of time without concerns regarding lack of efficacy or safety as based on pharmacovigilance data, this harmonisation was also considered acceptable.

Ronaxan 250 mg tablets were authorised for use in dogs in all products concerned by this referral and thus no amendment was proposed by the marketing authorisation holder (MAH) since it was already harmonised.

SPC section 4.2 Indications for use, specifying the target species

Indication for respiratory infections

The proposed indication for dogs was: '*For the treatment of acute and chronic upper respiratory tract infections and canine infection respiratory disease complex including rhinitis, tonsillitis and bronchitis associated with Bordetella bronchiseptica, Pasteurella multocida, Pasteurella spp.'*

The proposed indication for cats was: '*For the treatment of acute and chronic upper respiratory tract infections including rhinitis, tonsillitis and bronchitis associated with Bordetella bronchiseptica, Pasteurella multocida, Pasteurella spp.'*

In support of the proposed indication for respiratory infections, the MAH referred to minimum inhibitory concentration (MIC) data on doxycycline for the target pathogens, pharmacokinetic/pharmacodynamic

(PK/PD) data including a new analysis included in the MAH expert report, and clinical data presented in the initial marketing authorisation applications and in published literature.

Susceptibility data were extracted from surveillance programs in France (Resapath reports)[2], Germany (BVL-reports)[3], and the Compath study II (Morrissey, *et al* 2016)[4]and III conducted by the Centre Européen d'Etudes pour la Santé Animale (CEESA) group, including data from up to 12 European countries). The latter was considered the most relevant data as it included MIC distributions from several countries.

There are no established clinical breakpoints for *Pasteurella* spp. and *Bordetella bronchiseptica* in cats and dogs, but compared to the tentative epidemiological cut-off values of 1 µg/ml for doxycycline for *Pasteurella multocida* and epidemiological cut-off values of 1 µg/ml for tetracycline for *Bordetella bronchiseptica* available from European Committee on Antimicrobial Susceptibility Testing, the presented MICs for isolates from dogs and cats with respiratory disease collected within the last 5 years were representative for the wild type population (MIC_{90} generally ≤0.25 µg/ml for *Pasteurella* spp. and *P. multocida* and ≤1 µg/ml for *Bordetella bronchiseptica*). There were also no significant trends of reduced susceptibility noted over time based on comparisons of MIC data from Compath II (data from 2013-2014) and Compath III (data from 2017-2018), annual Resapath reports from 2013 to 2018[2], and BVL reports from 2006/2007 to 2018.

According to the new PK/PD analysis provided by the MAH, the recommended dosage would allow treating target bacteria presenting a MIC <0.03 µg/ml in cats and <0.125 µg/ml in dogs. Using these cut-offs, treatment efficacy would only be partial against the target pathogens in dogs (68% of *B. bronchiseptica* and 82% of *Pasteurella* spp. from dogs with respiratory infections displayed a MIC <0.125 µg/ml in the Compath III data) and not supported in cats (no isolate of *Pasteurella* spp. from cats with respiratory infections displayed a MIC <0.03 µg/ml in the Compath III data). This was considered to be of some concern, but it was also acknowledged that there may be some specific features of the respiratory tract that are not taken into account in the PK/PD-analysis such as potentially higher drug concentrations in epithelial lining fluid, as it has been indicated for the tetracycline-class representative tigecycline in humans (Rodvold, *et al* 2017)[5].

The clinical studies performed for Ronaxan as part of the initial marketing authorisation applications and that are of relevance for the respiratory indication, included 14 uncontrolled trials performed in 1984 and 1985, including 31 dogs and 101 cats seen as outpatients in the practices of various expert clinicians or at the National Veterinary Schools in Nantes and Toulouse as well as one comparative trial where cats and dogs were treated with either Ronaxan or amoxicillin. Animals were treated with a daily dose of 10 mg per kg bodyweight (bw) for a duration of 3 to 30 days. An overall total cure rate of 85% was reported, marked improvement in 13% and 2% failure. However, the support for efficacy gained

[2] Resapath. French surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin, 2013 annual report. ANSES
Resapath. French surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin, 2014 annual report. ANSES
Resapath. French surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin, 2015 annual report. ANSES
Resapath. French surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin, 2016 annual report. ANSES
Resapath. French surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin, 2017 annual report. ANSES
Resapath. French surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin, 2018 annual report. ANSES
[3] GERM-Vet: German Resistance Monitoring 2011/2012 (2015). Federal Office of Consumer Protection and Food Safety (BVL), Berlin, Germany.
GERM-Vet (2017) German resistance monitoring. Berichte zur Resistenzmonitoringstudie 2014 und 2015. BVL-Report 11.5 Federal Office of Consumer Protection and Food Safety (BVL).
[4] Morrissey I. *et al* (2016). Antimicrobial susceptibility monitoring of bacterial pathogens isolated from respiratory tract infections in dogs and cats across Europe: ComPath results. Veterinary microbiology. 2016 Aug 15; 191:44-51.
[5] Rodvold KA, Hope WW, Boyd SE. Considerations for effect site pharmacokinetics to estimate drug exposure: concentrations of antibiotics in the lung. Current Opinion in Pharmacology. 2017 Oct 1;36:114-23.

from these trials was considered limited due to shortcomings of the study design (lack of a control group, insufficiently described inclusion/exclusion of study animals and efficacy endpoints, lack of bacteriological diagnosis, and non-uniform treatment duration).

The MAH also referred to published literature[6],[7],[8],[9],[10],[11]. None of the six cited references presented clinical efficacy data considered to be of relevance for the proposed indication. However, it was acknowledged that the provided literature supported the use of tetracyclines to treat respiratory tract disease in dogs and cats. The latter was also confirmed by the international society for companion animal infectious diseases (ISCAID) which recommends the use of doxycycline (at the proposed dose of 10 mg per kg bw) as a first line treatment for acute and chronic bacterial upper respiratory infection in cats and dogs (Lappin *et al.* 2017)[12].

Although the efficacy data provided was considered limited, the CVMP considered that in the frame of an Article 34 referral, an indication may be retained on the basis of well-established use together with lack of evidence to show a risk, such as new pharmacovigilance information in relation to suspected lack of expected efficacy. Ronaxan has been authorised for treatment of respiratory infections in cats and dogs in all Member States where Ronaxan is authorised with a reported global rate of suspected lack of expected efficacy of 0.02 affected animals per 10,000 treated animals based on pharmacovigilance data between 1 January 1999 and 31 October 2020. Furthermore, it was acknowledged that doxycycline at the proposed dosage is recommended as a first line treatment for respiratory tract infections in dogs and cats in international antimicrobial use guidelines (Lappin *et al* 2017)[12]. Based on this, it was concluded that the indication for treatment of respiratory infections for both target species could be accepted.

The harmonised indication proposed by the MAH was however not considered fully appropriate due to the following:

Neither the indication for canine infectious respiratory disease complex (CIRDC) nor bronchitis were included in any nationally authorised SPC. These additions could not be accepted since the purpose of an Article 34 referral is to harmonise the differences between the product information in the different Member States, and therefore it is not possible to add new indications which were not previously authorised in any Member State.

The proposed harmonised indication included acute and chronic upper respiratory tract infections. Since no differentiation was made between acute and chronic infections in the majority of the nationally authorised SPCs, the proposal to broaden the indication to specifically identify acute and chronic respiratory infections was not considered appropriate.

Given that an indication against *Pasteurella* spp. was proposed, a separate indication against *P. multocida* was not considered necessary.

The suggested deletion of lower respiratory tract infections was considered questionable, since antimicrobial treatment of respiratory infections is often indicated only when the infection affects the lower respiratory tract.

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[6] Barragry TB (1994). Veterinary drug therapy, Lea & Febiger.
[7] Jameson PH *et al* (1995). Comparison of clinical signs, diagnostic findings, organisms isolated, and clinical outcome in dogs with bacterial pneumonia: 93 cases (1986-1991), JAVMA, 206, 2, 206-209.
[8] Arpaillange C. *et al* (2001). Traitement de la toux chez le chien et le chat, Le nouveau praticien vétérinaire. 183, 21-22 (French - translated).
[9] Merton (2001). Small animal clinical pharmacology and therapeutics (Book), W.B. Saunders Company.
[10] Watson ADJ *et al* (2001). Systemic antibacterial drug use in dogs in Australia, Aus. Vet. J, 2001, 79, 11, 740- 746.
[11] Carter *et al* (2003). A concise guide to infectious and parasitic diseases of dogs and cats. International Veterinary Information Service (www.ivis.org), Ithaca, New-York, USA.
[12] Lappin MR, *et al.* (2017). Antimicrobial use Guidelines for Treatment of Respiratory Tract Disease in Dogs and Cats: Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases. J Vet Intern Med. 2017 Mar;31(2):279-294.

Based on the above, the CVMP agreed on the following indication for both target species in the harmonised SPC: '*For the treatment of respiratory tract infections including rhinitis, tonsillitis and bronchopneumonia caused by Bordetella bronchiseptica and Pasteurella spp. susceptible to doxycycline.'*

Indication for skin infections

The proposed indication for dogs was: '*For the treatment of acute and subacute superficial skin infections including purulent dermatitis, associated with Staphylococcus spp.'*

The proposed indication for cats was: '*For the treatment of acute and subacute superficial skin infections including purulent dermatitis associated with Pasteurella multocida, Pasteurella spp., Staphylococcus spp'.*

In support of the proposed indications for skin infections, the MAH referred to MIC data on doxycycline for the target pathogens, PK/PD-data, and clinical data presented in the initial marketing authorisation applications and in published literature.

Susceptibility data were mainly presented from the Compath III study conducted by the CEESA group including data from up to 12 European countries, but also from French surveillance programs (Resapath reports 2013-2018)[2].

For staphylococci in dogs, the Clinical and Laboratory Standards Institute (CLSI) established clinical breakpoints for doxycycline for skin and soft tissue infections caused by *Staphylococcus pseudintermedius* as follows: ≤0.125 µg/ml for susceptible, 0.25 for intermediate, and ≥0.5 for resistant. Based on these breakpoints, 40.5% of isolates of the *S. intermedius* group presented in the Compath III study (n=440) were considered resistant. The high level of resistance was also confirmed by published data from France (Ganiere *et al*. 2005)[13] and Denmark (Maaland *et al*., 2013)[14] indicating a proportion of resistance in *S. pseudintermedius* from dogs of 46% (total n=50) and approximately 40% (total n=93), respectively (data based on isolates collected between 2002-2012). According to data from Resapath for *S. pseudintermedius* from skin and soft tissue infections from dogs, the proportion of strains classified as sensitive decreased from 90% (n=58) in 2017 to 60% (n=62) in 2018.

For cats, the MICs for *P. multocida* and *Pasteurella* spp. from skin infections were similar to those reported for respiratory infections (MIC_{50}=0.12 µg/ml and MIC_{90}=0.25 µg/ml). The reported MIC_{50} and MIC_{90} for staphylococci were 0.06 µg/ml and 0.5 µg/ml for *S. aureus* (n=48), 0.06 µg/ml and 0.25 µg/ml for *S. felis* (n=33) and for coagulase-negative staphylococci (n=44), and 0.06 µg/ml and 4 µg/ml for the *S. intermedius* group (n=24). There are no available breakpoints for cats, but based on the PK/PD-analysis provided, the recommended dosage would allow treating target bacteria presenting a MIC<0.03 µg/ml in cats. Using this cut-off, treatment efficacy was not supported in cats.

The clinical studies performed for Ronaxan as part of the initial marketing authorisation applications included 43 dogs treated for pyoderma or "pseudo-pyoderma" and 22 dogs and 10 cats treated for abscesses, fistulas or infected wounds. The treatment duration varied between 5 and 20 days. The response rate was 56% for pyoderma and 69% for abscesses, fistulas or infected wounds. The support for efficacy for the proposed indications gained from these trials was considered very limited due to shortcomings of the study design (lack of a control group, insufficiently described inclusion/exclusion of study animals and efficacy endpoints, lack of bacteriological diagnosis, and non-uniform treatment

[13] Ganiere JP, Medaille C, Mangion C. (2005). Antimicrobial drug susceptibility of Staphylococcus intermedius clinical isolates from canine pyoderma. Journal of Veterinary Medicine, Series B. 2005 Feb;52(1):25-31.
[14] Maaland MG, Papich MG, Turnidge J, Guardabassi L, (2013). Pharmacodynamics of doxycycline and tetracycline against Staphylococcus pseudintermedius: proposal of canine-specific breakpoints for doxycycline. Journal of clinical microbiology. 2013 Aug 21:JCM-01498.

duration). Moreover, no cats with pyoderma were included and the response rate to treatment of canine pyoderma was considered low.

The MAH also referred to published literature but none of the four cited references presented clinical efficacy data of relevance for the proposed indication. It was also noted that the ISCAID guidelines for superficial bacterial folliculitis in dogs (Hillier *et al* 2014)[15] do not recommend doxycycline as a first line treatment but as a second line treatment option. In addition, the treatment duration recommended in the above-mentioned guidelines for superficial canine pyoderma is substantially longer than the one authorised for Ronaxan for skin infections (i.e. 21 days compared to 5-10 days).

Ronaxan was not authorised for treating skin infections in the majority of the Member States where the product is authorised. For dogs, susceptibility data showed that doxycycline resistance in the main target pathogen is common (40.5% for the *S. pseudintermedius* group) and widespread in Europe. There was a scarcity of clinical data to support efficacy for the proposed indication for use and in addition, uncertainty whether the authorised treatment duration would be sufficient. For cats, the proposed skin indication was not supported by the PK/PD data provided and clinical data relevant for the proposed indication was lacking. The efficacy of Ronaxan at the proposed dosing regimen for the proposed indication in dogs and cats was considered to have been inadequately supported which was regarded to be of special concern for an antimicrobial considering the risk of resistance development. Based on this, the CVMP considered that the benefit-risk balance for the proposed skin indications in dogs and cats is negative and these indications should be omitted.

Indication for ehrlichiosis

Treatment of vector-borne disease associated with *Ehrlichia canis* was authorised in a number of Member States and its approval was based on literature data.

In support of the indication for the treatment of vector-borne disease associated with *E. canis* in dogs, the MAH referred to efficacy data from published literature including both experimental and natural infections. Eight reports were available with dogs experimentally infected with *E. canis*[16],[17],[18],[19],[20],[21],[22],[23]. Group sizes were generally small and treatment schedules varied between studies. In only two of the reports, the proposed posology for treatment with doxycycline was used. In these two studies, 8 out of 10 dogs and 4 out of 5 dogs, respectively, were cured (as verified by negative polymerase chain reaction (PCR) analysis). In the remaining studies, doxycycline was administered at lower doses, or divided in two daily doses, or with shorter duration of treatment. No control groups were included in these experimental studies.

Due to the shortcomings in the study design and reporting, these experimental studies were considered supportive only for the proposed indication of treatment of vector-borne disease associated

[15] Hillier A, Lloyd DH, Weese JS, Blondeau JM, Boothe D, Breitschwerdt E, et al. (2014). Guidelines for the diagnosis and antimicrobial therapy of canine superficial bacterial folliculitis (Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases). Veterinary Dermatology. 2014 Jun;25(3):163-e43.
[16] Iqbal et al. (1994). Reisolation of Ehrlichia canis from blood and Tissues of dogs after Doxycycline Treatment. Journal of clinical microbiology 32, 1644-1649.
[17] Breitschwerdt E., Hegarty B., Hancock S. (1998). Doxycycline hyclate treatment of experimental canine ehrlichiosis followed by challenge inoculation with two Ehrlichia canis strains. Antimicrobial agents and chemotherapy 42, 362-368.
[18] Harrus et al. (1998). Therapeutic Effect of Doxycycline in Experimental Subclinical Canine Monocytic Ehrlichiosis: Evaluation of a 6-Week Course. Journal of clinical microbiology 36, 2140-2142.
[19] Eddlestone et al. (2007). Doxycycline Clearance of Experimentally Induced Chronic Ehrlichia canis Infection in Dogs. Journal of Veterinary Internal Medicine 21(6), 1237-1242.
[20] Gaunt S. *et al.* (2010). Experimental infection and co-infection of dogs with Anaplasma platys and Ehrlichia canis: hematologic, serologic and molecular findings. Parasites & Vectors 3, 10.
[21] Harrus *et al.* (2004). Comparison of Simultaneous Splenic Sample PCR with Blood Sample PCR for Diagnosis and Treatment of Experimental Ehrlichia canis Infection. Antimicrobial agents and chemotherapy 48, 4488- 4490.
[22] McClure J *et al.* (2010). Efficacy of a Doxycycline Treatment Regimen Initiated during Three Different Phases of Experimental Ehrlichiosis. Antimicrobial Agents and Chemotherapy 54(12), 5012-5020.
[23] Fourie et al. (2015). The efficacy of a generic doxycycline tablet in the treatment of canine monocytic ehrlichiosis Journal of the South African Veterinary Association 86(1), 1193.

with *E. canis* in dogs. Nevertheless, dogs with clinical signs of canine monocytic ehrlichiosis (CME) in these experimental studies, seemed to improve clinically within a few days of start of the treatment with doxycycline.

Four reports of studies with naturally infected dogs were presented. In one of these studies (Breitschwerdt *et al.* (1998b)[24]), doxycycline treatment appeared to cure the four *E. canis*-infected dogs (as verified by negative PCR). However, one dog was again PCR positive at 6 months follow-up and re-infection could not be ruled out. Dogs in this study seemed to respond clinically to the treatment.

In another study (Sainz *et al.* (2000)[25], diagnosis was made based on serology which was considered a shortcoming of this study since diagnosis was not confirmed by PCR, and *Ehrlichia* spp. are known to show cross-reactivity on serology, and infection with species other than *E. canis* could therefore not be excluded. 32 out of the 93 dogs included were treated with doxycycline at the proposed dosage. Dogs with non-specific signs usually improved within a short period of time (i.e. 1–2 days) and platelet counts returned to normal. No data on clearance of *E. canis* was presented.

The third study (Van der Krogt (2010)[26] included 50 dogs with suspected *E. canis*-infection from the island of Curacao. Diagnosis was made based on clinical signs, haematology and/or a quick test for immunoglobulin G antibodies. Not all included cases were thus confirmed to actually have an infection with *E. canis*. Dogs were treated with doxycycline (5- 10 mg per kg bw per day) for a period of one to three weeks. No definite conclusions could be drawn from this study due to unclarities concerning the diagnosis and treatment lengths in relation to the outcome (very few dogs were available for follow-up analyses).

The fourth report (Villaescusa *et al.* (2015)[27] included 20 dogs with CME, naturally infected with *E. canis*. Diagnosis was based on clinical signs and serology or PCR. Dogs were treated according to the proposed posology and the majority of treated dogs recovered clinically.

Overall, the literature data cited by the MAH provided limited support for the proposed indication for *E. canis* in dogs. Relevant susceptibility data was lacking and there were no controlled clinical trials available in support of the indication. A few case series were available that seemed to indicate clinical improvement in dogs with acute or subclinical CME treated with doxycycline at the proposed dose. However, the CVMP acknowledged that Ronaxan has been indicated for the treatment of *E. canis* infections in several Member States without any concerns regarding reported lack of efficacy. Therefore, the CVMP concluded that the indication for the treatment of canine ehrlichiosis caused by *Ehrlichia canis* in dogs was acceptable for the harmonised SPC.

In support of the indication for treatment of vector-borne disease associated with *E. canis* in cats, the MAH referred to efficacy data from published literature consisting of seven reports[28],[29],[30],[31],[32],[33].

[24] Breitschwerdt, E., Hegarty, B., Hancock, S. (1998-bis). Sequential Evaluation of Dogs Naturally Infected with Ehrlichia canis, Ehrlichia chaffeensis , Ehrlichia equi, Ehrlichia ewingii, or Bartonella vinsonii. Journal of clinical microbiology 36, 2645-2651.
[25] Sainz A., Tesouro M., Amusategui I., Rodríguez F., Mazzucchelli F., Rodríguez M. (2000). Prospective Comparative Study of 3 Treatment Protocols Using Doxycycline or Imidocarb Dipropionate in Dogs with Naturally Occurring Ehrlichiosis Journal of Veterinary Internal Medicine 14(2), 134-139.
[26] Van der Krogt J. (2010). Ehrlichia canis infections on the island of Curaçao – An overview of the clinical picture and current diagnostics & therapies. Research report. 21 pages.
[27] Villaescusa A., García-Sancho M., Rodríguez-Franco F., Tesouro M., Sainz Á. (2015). Effects of doxycycline on haematology, blood chemistry and peripheral blood lymphocyte subsets of healthy dogs and dogs naturally infected with Ehrlichia canis. The Veterinary Journal 204(3), 263-268.
[28] Beaufils J., Martin-Granel J., Jumelle P., Barbault-Jumelle M. (1999). Ehrlichiose probable chez le chat : étude rétrospective sur 21 cas. Pratique médicale et chirurgicale de l'Animal de compagnie 34, 587-596 (French - translated).
[29] Breitschwerdt E., Abrams-Ogg A., Lappin M., Bienzle D., Jancock S., Cowan, *et al.* (2002). Moleculer evidence supporting Ehrlichia canis-like infection in cats. Journal of veterinary internal medicine 16, 642-649.
[30] Bjöersdorff *et al.* (1999). Feline granulocytic ehrlichiosis -a report of a new clinical entity and characterisation of the infectious agent Journal of Small Animal Practice 40(1), 20-24.

Three of the reports were case studies or small case series involving cats with granulocytic ehrlichiosis, caused by *Anaplasma phagocytophilum* and therefore, they were not considered relevant. Two of the reports were review papers and did not contain any proprietary data. Two reports remained for support of the proposed indication.

In the publication by Beaufils (1999)[28], a study including 11 cats with clinical signs and positive serology for *E. canis* is described. Seven cats were treated with doxycycline. Cats were clinically cured after a few days of treatment. It is known that antibodies to rickettsial infections can be detected by immunofluorescence and enzyme-linked immunosorbent assay (ELISA) techniques but that *E. canis* can cross-react with other *Ehrlichia* species. PCR was not used to confirm cases in this study which is considered a shortcoming.

In the publication by Breitschwerdt *et al.* (2002)[29], 3 cats naturally infected by *E. canis* (United States strains) and treated with doxycycline were included. All cats were negative for *E. canis* specific antibodies, but infection with *E. canis*-like organism was confirmed by PCR. Cats were treated with doxycycline at higher doses than currently proposed. All cats received other medications concomitantly, including prednisolone, which may influence the results. Cats improved clinically within a few days after treatment was initiated.

The data presented by the MAH provided very limited support for the proposed indication for treatment of *E. canis*-infection in cats. No PK or relevant PD data was available to support dose and efficacy and there were no controlled clinical trials available in support of the indication which relied on very few case reports. Data in one report only, including 11 cats, originate from Europe, and diagnosis in these cases was made only from serology and thus cross-reaction with other *Ehrlichia* spp. could not be excluded. Bacteriological cure after treatment is uncertain but presumably not complete in all treated cats. In account of these deficiencies, the CVMP concluded that the indication feline ehrlichiosis should be omitted.

SPC section 4.3 Contraindications

The MAH suggested a list of contraindications (hypersensitivity, renal or hepatic insufficiency, diseases associated with vomiting or dysphagia, known photosensitivity, use in puppies and kittens before completion of teeth enamel formation) that were all included in approved SPCs. The CVMP concluded that the list of contraindications was considered acceptable with minor adjustments according to the latest QRD template.

SPC section 4.4 Special warnings for each target species

The MAH proposed a special warning in the harmonised SPC regarding recommendations on treatment of *E. canis*, including a statement concerning the need to treat severe or chronic ehrlichiosis for a longer duration than 28 days. The text was derived from different sections from previously approved SPCs and the CVMP accepted it with minor amendments.

SPC section 4.5 Special precautions for use

The advice to administer tablets with food to avoid vomiting as suggested by the MAH was considered acceptable and already present in the SPCs of most Member States.

A statement that use of tetracyclines during the period of tooth development may cause teeth discolouration was considered acceptable.

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[31] Tarello W. (2002). Granulocytic Ehrlichia-like bodies in a cat with chronic oral disease: case report. Revue de Médecine Vétérinaire 153(6), 401-406.
[32] Tarello W (2005). Microscopic and clinical evidence for Anaplasma (Ehrlichia) phagocytophilum infection in Italian cats. Veterinary Record 156(24), 772.
[33] Lobetti R. (2017). Tick-Borne Diseases of the Cat. Advances in Small Animal Medicine and Surgery 30(11), 1-3.

Warnings regarding antimicrobial resistance were introduced in accordance with recommendations in the CVMP guideline on the SPC for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/SAGAM/383441/2005-Rev.1)[34].

The text proposed by the MAH for *'Special precautions to be taken by the person administering the veterinary medicinal product to animals'* was revised in accordance with the CVMP guideline on user safety for veterinary medicinal products and the latest QRD template and extended to also include information on the risk for cross-sensitisation and information on potential adverse effects in relation to accidental ingestion.

SPC section 4.6 Adverse reactions (frequency and seriousness)

Relevant adverse reactions stated in nationally authorised SPCs were included. A frequency of 'very rarely' was accepted for gastrointestinal adverse reactions, based on post-marketing pharmacovigilance data. In the absence of data from robust clinical studies, the CVMP concluded that a more representative frequency was likely to be available from pharmacovigilance data, given the widespread use of the product since its authorisation.

SPC section 4.7 Use during pregnancy, lactation or lay

The MAH suggested not to recommend the use of Ronaxan during pregnancy and in accordance with previously approved SPCs and this proposal was supported by the CVMP.

SPC section 4.8 Interactions

Regarding interaction with anti-epileptic drugs, it was suggested to include carbamazepine in addition to the barbiturates and phenytoin. Furthermore, it was noted that in some Member States, a warning that doxycycline may increase the effect of antithrombotic agents since tetracyclines depress the plasma activity of prothrombin was included in the SPCs. In addition, a general statement that multivalent cations (such as calcium, magnesium, aluminium, and iron) reduces absorption of doxycycline was suggested to be included, as stated in the SPCs in several Member States.

While no scientific literature has been provided in order to justify the proposed wordings above, the described interactions are well known in the veterinary practice. Therefore, the CVMP suggested to retain this information in the harmonised SPC.

SPC section 4.9 Amounts to be administered and administration route

Regarding the dosing regimen, the proposal for all indications was 10 mg per kg bodyweight per day for dogs and cats. The proposed treatment durations were 7 days for acute respiratory infections, 10 days for chronic respiratory infections, 21 days for skin infections, and 28 days for ehrlichiosis.

In support of the proposed dosage, the MAH referred to the PK/PD properties of doxycycline as presented in the initial marketing authorisation applications, a new PK/PD-analysis as well as published literature.

The new PK/PD-analysis by the MAH based on the dose of 10 mg per kg bw per day, demonstrated that a MIC of 0.125 µg/ml for dogs and 0.03 µg/ml for cats provided probability of target attainment of at least 90%.

For dogs, the PK/PD-analysis provided some support for efficacy of the dose of 10 mg per kg bw, although there were indications that a higher dose may be preferable, since the 0.125 µg/ml cut-off did not cover the entire wildtype population for the target pathogens. However, it was noted that this was also the case for the higher dose of 20 mg per kg bw that was authorised in two Member States.

[34] CVMP guideline on the SPC for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/SAGAM/383441/2005-Rev.1) - link

For cats, the PK/PD-analysis did not support the dose of 10 mg per kg bw due to higher protein binding in cats compared to dogs. In addition, with the higher dose of 20 mg per kg bw, the majority of the target pathogens have MICs above the PK/PD cut-off (0.06 µg/ml for the 20 mg/kg dose).

No clinical dose characterisation studies were available from the initial marketing authorisation applications. The dose of 10 mg per kg bw per day was used in the original clinical trials for treatment of respiratory and skin infections but no firm conclusions on efficacy could be drawn from these trials due to shortcomings in the study designs. Some support for the dose of 10 mg per kg bw per day could however be gained by the case series presented in support for the efficacy against canine ehrlichiosis. Moreover, it was also noted that a dose of 10 mg per kg bw per day is recommended in international consensus guidelines concerning treatment of respiratory infections (Lappin *et al*, 2017)[12].

In conclusion, the PK/PD-analysis provided some support for the dose of 10 mg per kg bw per day in dogs but not in cats. Increasing the dose to 20 mg per kg bw would not substantially increase the proportion of bacterial isolates that are considered 'susceptible' to doxycycline for dogs and cats and there would be a risk that an increased dose may lead to reduced gastrointestinal tolerance to the product (Savadelis *et al*, 2018)[35]. Based on this and the fact that the dose of 10 mg per kg bw per day was authorised in the majority of Member States where it has been used for a number of years in dogs and cats without any concerns regarding reports of lack of efficacy, the CVMP concluded that the dose of 10 mg per kg bw for the treatment of respiratory infections in dogs and cats and ehrlichiosis in dogs could be accepted.

Regarding treatment duration, it was not considered appropriate to broaden the respiratory indication to specifically identify acute and chronic respiratory infections and thus, the CVMP concluded that separate dosing recommendations for acute and chronic infections were not accepted. Based on the currently approved treatment durations, the CVMP concluded that the treatment duration for respiratory tract infections in dogs and cats should be stated as 5-10 days. This treatment duration would also permit clinical judgement to be made by the veterinary surgeon, without stipulating a longer treatment duration which might not be required.

For the skin infections, a treatment duration of 21 days was proposed by the MAH with reference to the recommendations by ISCAID (Hillier *et al.* 2014)[15]. This was a new treatment duration not included in any of the currently authorised SPCs and therefore could not be accepted within this procedure. However, the CVMP concluded that the benefit/risk balance for the indication for skin infections in cats and dogs is negative and any reference to this indication in the product information should be omitted.

For treatment of *E. canis* in dogs, the proposed treatment duration of 28 days as previously approved in several Member States was considered acceptable by the CVMP. Although deficiencies could be identified in the clinical data presented, the CVMP concluded that reasonable support for this treatment duration could be gained from the studies provided.

SPC section 4.10 Overdose

The suggested text by the MAH for SPC section 4.10 in the harmonised SPC for Ronaxan tablets was merged from SPCs in all Member States where Ronaxan is authorised. The data originated from the target animal safety studies included in the initial marketing authorisation applications. The CVMP considered the wording acceptable, with minor amendments.

[35] Savadelis MD, Day KM, Bradner JL, Wolstenholme AJ, Dzimianski MT, Moorhead AR. Efficacy and side effects of doxycycline versus minocycline in the three-dose melarsomine canine adulticidal heartworm treatment protocol. Parasites & vectors. 2018 Dec 1;11(1):671.

SPC section 5.1 Pharmacodynamic properties

The proposed text for this section was updated in accordance with the CVMP guideline on the SPC for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/SAGAM/383441/2005-Rev.1)[34]. Appropriate information was included regarding molecular genetics of acquired resistance and susceptibility data for target bacteria. The CVMP concluded that the proposed text was acceptable with amendments (i.e. addition of information on when the susceptibility data was collected, deletion of susceptibility data for target pathogens that are no longer included in the indications, deletion of the statement that co-resistance has not been detected, and deletion of the reference to PK/PD cut-offs since this information was considered difficult for the prescriber to interpret).

SPC section 5.2 Pharmacokinetics

The CVMP concluded that the MAH proposed text for this section with regards to absorption, distribution and elimination, was considered acceptable with amendments.

3. Benefit-risk assessment

Introduction

This benefit-risk evaluation is performed in the context of Article 34 of Directive 2001/82/EC, which is to harmonise within the EU the conditions of authorisation for the veterinary medicinal product Ronaxan and its associated names. The referral leads to full harmonisation of the product information. This evaluation focuses on issues in regard to the harmonisation that may change the benefit-risk balance.

Ronaxan are tablets containing 20 mg, 100 mg or 250 mg doxycycline hyclate as active substance. Doxycycline belongs to the tetracycline family and is active against a large number of gram-positive and gram-negative pathogens.

Benefit assessment

The following indications for Ronaxan can be supported based on the data provided:

Dogs:

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*.

Cats:

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

In support of the indication for the treatment of respiratory infections, the marketing authorisation holder provided a combination of *in vitro* susceptibility data, pharmacokinetic data, a PK/PD modelling approach, clinical efficacy data from the initial marketing authorisation application of Ronaxan and justifications from the literature.

The indication for treatment of ehrlichiosis in dogs was supported by published efficacy data.

The dosing regimen was supported by a PK/PD approach including up-to-date susceptibility data for the target bacteria and/or justifications from literature.

Risk assessment

The dosing regimens recommended have not been increased beyond what was already authorised and the indications have not been extended with regards to those already authorised. Therefore, the assessment of target animal safety, risk for the environment and user safety did not present new issues.

Risk management or mitigation measures

The harmonised product information of Ronaxan contains the information necessary to ensure safe and effective use of the product in the target animal species.

The warnings and precautions proposed in the product information are considered adequate to ensure the safety of the product to target animals and users.

The precautions for use in animals have been complemented to take into account the current recommendations on precautions regarding risks related to antimicrobial resistance. Moreover, information regarding resistance and susceptibility data for target bacteria has been updated in accordance with the CVMP guideline on the SPC for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/SAGAM/383441/2005-Rev.1)[34].

A statement that use of tetracyclines during the period of tooth development may lead to tooth discolouration was included in SPC section 4.6, and a contraindication in SPC section 4.3 not to use the product in puppies and kittens before completion of teeth enamel formation.

Evaluation and conclusions on the benefit-risk balance

Data has been provided to support that Ronaxan is efficacious for treating respiratory infections in dogs and cats and ehrlichiosis in dogs. The resistance situation for the target pathogens listed for the respiratory indication was considered favourable.

No data have been presented that may question whether Ronaxan is well tolerated by the target animals and presents risk for users and the environment when used as recommended. Appropriate precautionary measures have been included in the product information.

Having considered the grounds for referral and the data provided by the MAH, the CVMP concluded that the benefit-risk balance of the product remains positive subject to the recommended changes in the product information.

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Whereas

- the CVMP considered the scope of the referral was the harmonisation of the summary of product characteristics, labelling and package leaflet;
- the CVMP reviewed the summary of product characteristics, labelling and package leaflet proposed by the marketing authorisation holders and considered all the overall submitted data;

the CVMP has recommended the amendment of the marketing authorisations for Ronaxan and its associated names as referred in Annex I for which the summary of product characteristics, labelling and package leaflet are set out in Annex III.

Annex III

Summary of product characteristics, labelling and package leaflet

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 20 mg tablets for dogs and cats

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substance:
Doxycycline (as doxycycline hyclate)..... 20 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.
Light yellow to yellow, biconvex, round, scored tablets.
The tablets can be divided into two equal parts.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs and cats.

4.2 Indications for use, specifying the target species

Dogs
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*.

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

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 and kittens 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 2 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 aminoacetyl-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 (*number of strains tested*)**	**MIC_{50} (µg/ml)**	**MIC_{90} (µg/ml)**
Bordetella bronchiseptica	Dog – respiratory tract (*38*)	0.12	0.5
Bordetella bronchiseptica	Cat – respiratory tract (*11*)	0.12	0.12
Pasteurella spp.	Dog – respiratory tract (*27*)	0.12	0.25
Pasteurella spp.	Cat– respiratory tract (*77*)	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 and 48% in cats. Peak concentrations of 4.5 µg/ml (dogs) and 3.8 µg/ml (cats) 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 and 0.9 l/kg in cats, supporting that doxycycline diffuses from blood into tissues. Protein binding in dogs is reported as 91.75 % ± 0.63 and 91.4% in the literature. In cats a publication reports a protein binding of 98.35% (+/-0.24).
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 and 5.82 hours, in dogs and cats respectively. 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 2 blisters of 10 tablets
Cardboard box containing 5 blisters of 10 tablets
Cardboard box containing 10 blisters of 10 tablets
Cardboard box containing 50 blisters of 10 tablets
Cardboard box containing 100 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 2 x 10 tablets, 5 x 10 tablets, 10 x 10 tablets, 50 x 10 tablets and 100 x 10 tablets

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 20 mg tablets for dogs and cats
doxycycline hyclate

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains:
Doxycycline (as doxycycline hyclate)..... 20 mg

3. PHARMACEUTICAL FORM

Tablets

4. PACKAGE SIZE

2 x 10 tablets
5 x 10 tablets
10 x 10 tablets
50 x 10 tablets
100 x 10 tablets

5. TARGET SPECIES

Dogs and cats

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

<Invented name> 20 mg tablets for dogs and cats
doxycycline hyclate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim

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:
<Invented name> 20 mg tablets for dogs and cats

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

<Invented name> 20 mg tablets for dogs and cats
doxycycline hyclate

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

Each tablet contains:

Active substance:
Doxycycline (as doxycycline hyclate)..... 20 mg

Light yellow to yellow, biconvex, round, scored tablets.
The tablets can be divided into two equal parts.

4. INDICATION(S)

Dogs
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*.

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

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 and kittens 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 and cats.

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 2 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:
2 x 10 tablets, 5 x 10 tablets, 10 x 10 tablets, 50 x 10 tablets or 100 x 10 tablets.
Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 100 mg tablets for dogs and cats

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substance:
Doxycycline (as doxycycline hyclate)..... 100 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.
Light yellow to yellow, biconvex, round, scored tablets.
The tablets can be divided into two equal parts.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs and cats.

4.2 Indications for use, specifying the target species

Dogs
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*.

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

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 and kittens 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 10 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 aminoacetyl-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 (*number of strains tested*)**	**MIC_{50} (µg/ml)**	**MIC_{90} (µg/ml)**
Bordetella bronchiseptica	Dog – respiratory tract (*38*)	0.12	0.5
Bordetella bronchiseptica	Cat – respiratory tract (*11*)	0.12	0.12
Pasteurella spp.	Dog – respiratory tract (*27*)	0.12	0.25
Pasteurella spp.	Cat– respiratory tract (*77*)	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 and 48% in cats. Peak concentrations of 4.5 µg/ml (dogs) and 3.8 µg/ml (cats) 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 and 0.9 l/kg in cats, supporting that doxycycline diffuses from blood into tissues. Protein binding in dogs is reported as 91.75 % ± 0.63 and 91.4% in the literature. In cats a publication reports a protein binding of 98.35% (+/-0.24).
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 and 5.82 hours, in dogs and cats respectively. 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 or 50 tablets packed in a cardboard box.

Cardboard box containing 1 blister of 50 tablets
Cardboard box containing 2 blisters of 10 tablets
Cardboard box containing 5 blisters of 10 tablets
Cardboard box containing 10 blisters of 10 tablets
Cardboard box containing 50 blisters of 10 tablets
Cardboard box containing 100 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 50 tablets, 2 x 10 tablets, 5 x 10 tablets, 10 x 10 tablets, 50 x 10 tablets and 100 x 10 tablets

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 100 mg tablets for dogs and cats
doxycycline hyclate

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains:
Doxycycline (as doxycycline hyclate)..... 100 mg

3. PHARMACEUTICAL FORM

Tablets

4. PACKAGE SIZE

1 x 50 tablets
2 x 10 tablets
5 x 10 tablets
10 x 10 tablets
50 x 10 tablets
100 x 10 tablets

5. TARGET SPECIES

Dogs and cats

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 and 50 tablets

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 100 mg tablets for dogs and cats
doxycycline hyclate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim

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:
<Invented name> 100 mg tablets for dogs and cats

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

<Invented name> 100 mg tablets for dogs and cats
doxycycline hyclate

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

Each tablet contains:

Active substance:
Doxycycline (as doxycycline hyclate)..... 100 mg

Light yellow to yellow, biconvex, round, scored tablets.
The tablets can be divided into two equal parts.

4. INDICATION(S)

Dogs
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*.

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

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 and kittens 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 and cats.

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 10 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 50 tablets, 2 x 10 tablets, 5 x 10 tablets, 10 x 10 tablets, 50 x 10 tablets or 100 x 10 tablets.
Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

<Invented name> 250 mg tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substance:
Doxycycline (as doxycycline hyclate)..... 250 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.
Light yellow to yellow, biconvex, round, scored tablets.
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 aminoacetyl-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 (*number of strains tested*)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
Bordetella bronchiseptica	Dog – respiratory tract (*38*)	0.12	0.5
Pasteurella 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

<Invented name> 250 mg tablets for dogs
doxycycline hyclate

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains:
Doxycycline (as doxycycline hyclate)..... 250 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

<Invented name> 250 mg tablets for dogs
doxycycline hyclate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim

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:
<Invented name> 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

<Invented name> 250 mg tablets for dogs
doxycycline hyclate

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

Each tablet contains:

Active substance:
Doxycycline (as doxycycline hyclate)..... 250 mg

Light yellow to yellow, biconvex, round, scored tablets.
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.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.