1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Twinox 200 mg/50 mg chewable tablets for cats and dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains:

Active substances:

Amoxicillin 200 mg (equivalent to 229.6 mg amoxicillin trihydrate)
Clavulanic acid 50 mg (equivalent to 59.6 mg potassium clavulanate)

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Cellulose, microcrystalline	
Magnesium stearate	
Silica, colloidal anhydrous	
Sodium starch glycollate (type A)	
Dried autolyzed yeast	
Erythrosine aluminium lake, E127	3.06 mg

Pink mottled tablets, round, with a break line on one side.
The tablet can be divided into halves.

3. CLINICAL INFORMATION

3.1 Target species

Cats and dogs.

3.2 Indications for use for each target species

Dogs:
For the treatment of
- Skin infections (including deep and superficial pyoderma).
- Soft tissue infections (including anal sacculitis and abscesses).
- Urinary tract infections.
- Respiratory infections.
- Intestinal infections.
- Periodontal infections in addition to mechanical or surgical periodontal therapy.

Cats:
For the treatment of
- Skin infections (including superficial pyoderma).
- Soft tissue infections (including abscesses).
- Urinary tract infections.
- Respiratory infections.

- Intestinal infections.
- Periodontal infections in addition to mechanical or surgical periodontal therapy.

3.3 Contraindications

Do not use in rabbits, guinea pigs, hamsters, gerbils, chinchillas or other small herbivores.

Do not use in cases of hypersensitivity to the active substances, other substances of the beta-lactam group or to any of the excipients.

Do not administer to horses or ruminating animals.

Do not use in animals with severe renal impairment with anuria or oliguria.

3.4 Special warnings

Cross-resistance has been shown between amoxicillin/clavulanic acid and other antibiotics belonging to the beta-lactam group. Use of the veterinary medicinal product should be carefully considered when susceptibility testing has shown resistance to other antimicrobials in the beta-lactam group because its effectiveness may be reduced.
When susceptibility testing has shown resistance to sole beta-lactam, but susceptibility to combination of amoxicillin/clavulanic acid has been confirmed, treatment with the veterinary medicinal product might nevertheless be considered.

Do not use in cases of suspected or confirmed methicillin resistant *S. aureus* (MRSA) and methicillin resistant *S. pseudintermedius* (MRSP) infections, as such isolates should be considered resistant to all beta-lactams including amoxicillin/clavulanic acid combinations.

The veterinary medicinal product has no effect against infections caused by *Pseudomonas* spp. due to its inherent resistance.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use of the product should be based on identification and susceptibility testing of the target pathogen(s). 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 product should be in accordance with official, national and regional antimicrobial policies.

An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

Narrow spectrum antibiotic therapy with a lower risk of antimicrobial resistance selection should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach. Pharmacokinetics of the active substances in the target tissue might be considered as well.

The routine use of systemic antibiotics for intestinal infections is not recommended.

Oral treatment with antibiotics can result in disturbance of gastrointestinal flora, especially in case of long-term treatment.

In case of renal or hepatic insufficiency, the use of the veterinary medicinal product should be subject to a benefit-risk assessment by the responsible veterinarian.

The chewable tablets are flavoured. In order to avoid any accidental ingestion, store tablets out of reach of the animals.

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

Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins can lead to cross reactions with cephalosporins and vice versa. Allergic reactions caused by these substances may occasionally be serious.

People with known hypersensitivity to the active substance should avoid contact with the veterinary medicinal product. Wear gloves when handling this product to avoid skin contact.

If you develop symptoms such as a skin rash and persistent eye irritation after exposure to the veterinary medicinal product, seek medical advice immediately and show the package leaflet or label to the physician. Swelling of the face, lips or eyes or difficulty breathing, are more serious symptoms that require urgent medical attention.

Wash hands after use.

To prevent children from accessing the veterinary medicinal product, only the required number of tablets should be removed from the blister pack and only when required. Store any unused portion of the tablet in the opened blister pack and return it into the carton immediately after use. The carton should be stored out of the sight and reach of children. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Dogs and cats:

Common (1 to 10 animals / 100 animals treated):	gastrointestinal disorder[1] (e.g. vomiting, diarrhoea)
Uncommon (1 to 10 animals / 1 000 animals treated):	hypersalivation anorexia[1, 2], lethargy
Very rare (<1 animal / 10 000 animals treated, including isolated reports):	hypersensitivity reaction[3] (e.g. allergic skin reaction, anaphylaxis)

[1] Depending on the severity of the adverse event treatment should be discontinued and symptomatic treatment initiated based on the benefit-risk assessment by the responsible veterinarian.
[2] Very rare (<1 animal / 10 000 animals treated, including isolated reports) in cats.
[3] May be serious. Immediate discontinuation of the veterinary medicinal product is required. Countermeasures to be taken in case of an allergic reaction:

- anaphylaxis: administer epinephrine (adrenaline) and glucocorticoids.
- allergic skin reactions: administer antihistamines and/or glucocorticoids.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.

Pregnancy and lactation:

In laboratory studies (rat, mouse), signs of embryotoxicity or teratogenicity could only be detected at high doses.
Use only according to the benefit-risk assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

The bactericidal effect of amoxicillin may be inhibited by the concomitant use of bacteriostatic antimicrobials.

Penicillins may increase the effect of aminoglycosides.

3.9 Administration routes and dosage

Oral use.

Dosage: 10 mg amoxicillin and 2.5 mg clavulanic acid/kg bodyweight every 12 hours.

In refractory respiratory tract infections, the dose can be doubled to 20 mg amoxicillin and 5 mg clavulanic acid/kg bodyweight every 12 hours and the treatment can be prolonged for up to 10 days.

Dosing instructions:

Bodyweight (kg)	**Number of tablets every 12 hours (10 mg amoxicillin and 2.5 mg clavulanic acid/kg bodyweight)**
> 8 – 10	0.5
> 10 – 20	1
> 20 – 30	1.5
> 30 – 40	2
> 40 – 50	2.5

Duration of treatment:
In most of the cases, a treatment duration of 5 to 7 days is sufficient.
For chronic cases, a longer course of therapy may be required.
Based on clinical trials, the following treatment durations are recommended:
Chronic skin infections, 10–20 days.
Chronic cystitis, 10–28 days.

Instructions for use:
To ensure a correct dosage, bodyweight should be determined as accurately as possible.

The tablets can be administered directly into the mouth of the animals or crumbled and added to a small quantity of food and fed immediately.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

Doses up to 40 mg amoxicillin and 10 mg clavulanic acid/kg and 60 mg amoxicillin and 15 mg clavulanic acid/kg administered twice daily for 5 days were tolerated well in young dogs and young cats, respectively.
No adverse events associated with overdoses other than those listed in section 3.6 were detected in the respective studies (for information on symptomatic treatment see also section on adverse events).

Due to the neurotoxicity of penicillins, overdosing might result in central nervous system symptoms and convulsions. In these cases, treatment with the veterinary medicinal product should be discontinued immediately and symptomatic treatment should be initiated.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance.

Not applicable.

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QJ01CR02

4.2 Pharmacodynamics

The veterinary medicinal product is an association of amoxicillin and clavulanic acid. Amoxicillin inhibits the cross-linking of the peptidoglycan layer through a selective and irreversible blockage of various enzymes involved in this process (primarily transpeptidases) and thus prevents the formation of an intact bacterial cell wall. This results in an osmotic imbalance that particularly affects bacteria in the logarithmic phase of growth which ultimately leads to bacterial cell lysis. The effect is therefore bactericidal and related to the time the susceptible organisms are exposed to supra-minimum inhibitory concentrations. Clavulanic acid has a similar structure to beta-lactam antibiotics such as amoxicillin. It has a weak antibacterial effect but, compared to amoxicillin, has a higher affinity for beta-lactamases, enzymes produced by Gram-positive and Gram-negative bacteria which inactivate beta-lactam antibiotics through the hydrolytic cleavage of their beta-lactam ring. When administered simultaneously with amoxicillin, clavulanic acid rapidly, progressively and irreversibly inactivates the beta-lactamases by forming a stable molecule-enzyme complex. This prevents inactivation of amoxicillin by beta-lactamases and, as a result, the spectrum of amoxicillin is broadened to include strains that have acquired resistance through secretion of plasmid-derived penicillinase, and strains that are naturally resistant through the production of chromosomally mediated beta-lactamases.
Other mechanisms of resistance to beta-lactams include the modification of the antibiotic target site (penicillin-binding proteins), efflux pumps and changes in the permeability of the outer membrane.

4.3 Pharmacokinetics

Following oral administration, amoxicillin is well absorbed from the gastrointestinal tract. In dogs, bioavailability is 60-70%. Following absorption, the highest concentrations are found in the kidneys (urine), bile and further in the liver, lungs, heart, and spleen.
Distribution of amoxicillin to the cerebrospinal fluid is low unless meningitis occurs.
Amoxicillin is excreted mainly by the kidneys (unchanged in the urine).
Clavulanic acid is well absorbed after oral administration and has pharmacokinetic properties similar to amoxicillin. Extracellular distribution of clavulanic acid is extensive, but permeation into milk and cerebrospinal fluid is very limited. Clavulanic acid is excreted unchanged by the kidneys.

In a study in dogs/cats administered the veterinary medicinal product at the dose of 10 mg of amoxicillin and 2.5 mg of clavulanic acid per kg bodyweight, the following results were obtained:

<u>Dogs</u>

- For amoxicillin, the time to reach maximum concentration (T_{max}) was approximately 1.37 hours, with a mean maximum concentration (C_{max}) 7.31 µg/ml. The mean terminal half-life was 1.21 hours.
- For clavulanic acid, a mean C_{max} of 1.33 µg/ml was achieved at approximately 1.02 hours. The mean terminal half-life was 0.83 hours.

Cats
- For amoxicillin, the T_{max} was approximately 1.59 hours, with a mean C_{max} 5.87 µg/ml. The mean terminal half-life was 1.18 hours.
- For clavulanic acid, a mean C_{max} of 3.16 µg/ml was achieved at approximately 0.70 hours. The mean terminal half-life was 0.81 hours.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Any unused half tablets should be returned to the blister pack and used within 12 hours.

5.3 Special precautions for storage

Do not store above 25 °C.
Store in the original package in order to protect from light and moisture.

5.4 Nature and composition of immediate packaging

Blister formed of an aluminium foil which consists of aluminum layer coated with OPA (Oriented Polyamide) film on one side and PE with desiccant on the other side and an aluminium sealing foil which consists of aluminium layer and PE coating.

Cardboard box with 1 blister of 10 tablets
Cardboard box with 2 blisters of 10 tablets
Cardboard box with 10 blisters of 10 tablets.
Cardboard box with 50 blisters of 10 tablets.

Not all pack sizes may be marketed.

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

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

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto

7. MARKETING AUTHORISATION NUMBER(S)

VPA10774/072/002

8. DATE OF FIRST AUTHORISATION

11/06/2021

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

07/09/2026

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).