Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Twinox 200 mg/50 mg tablets for dogs

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substances

Amoxicillin (as amoxicillin trihydrate)	200 mg
Clavulanic acid (as potassium clavulanate)	50 mg

Excipient

Erythrosine (E127)	0.25 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Pale pink, rounded, one side scored, uncoated and divisible tablet.

4 CLINICAL PARTICULARS

4.1 Target Species

Dogs.

4.2 Indications for use, specifying the target species

Treatment of infections caused by micro-organisms sensitive to the combination amoxicillin/clavulanic acid, especially:
- dermatitis (superficial and deep pyoderma) caused by *Staphylococcus (pseud)intermedius*.
- urinary tract infections caused by *E. coli* and *Staphylococcus* spp.
- respiratory tract infections caused by *Streptococcus* spp.
- enteritis caused by *E. coli*.

4.3 Contraindications

- Do not use in animals with known hypersensitivity to penicillin or other substances of the beta-lactam group or to any of the excipients.
- Do not use in case of serious dysfunction of the kidneys accompanied by anuria and oliguria.
- Do not use in rabbits, guinea pigs, hamsters, chinchillas or gerbils.

4.4 Special warnings for each target species

None known.

4.5 Special precautions for use

i. Special precautions for use in animals

- Do not use in known cases of resistance to the combination.
- Official, national and regional antimicrobial policies with respect to the use of broad-spectrum antibiotics should be taken into account.
- Do not use in known cases of bacteria sensitive to narrow spectrum penicillins or to amoxicillin as a single substance.
- Due to likely variability (time geographical) in the occurrence of resistance of bacteria for the combination amoxicillin / clavulanic acid, bacteriological sampling and susceptibility testing are recommended.
- Use of the product deviating from the instructions given in the Summary of the Product Characteristics may increase the prevalence of bacteria resistant to the amoxicillin/clavulanate, and may decrease the effectiveness of treatment with β-lactam antibiotics.
- In animals with hepatic and renal failure, the dosing regimen should be carefully evaluated.

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

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

- Do not handle this product if you know you are sensitised, or if have been advised not to work with such preparations.
- Handle this product with great care to avoid exposure, taking all recommended precautions.
- If you develop symptoms following exposure such as a skin rash, seek medical advice immediately and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.
- Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

- Dose independent allergic reactions may occur, such as skin reactions or anaphylaxis. In those cases the treatment must be stopped immediately and a symptomatic treatment should be given.
- Gastro-intestinal disturbances (diarrhoea, vomiting, …) may occur after administration of the product.

4.7 Use during pregnancy, lactation or lay

Laboratory studies in rats and mice have not produced any evidence of teratogenic or foetotoxic effects. No studies have been conducted in pregnant or lactating dogs. Use only according to the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Chloramphenicol, macrolides, sulfonamides and tetracyclines may inhibit the antibacterial effects of penicillins.
The potential for allergic cross-reactivity with other penicillins should be considered.
Penicillins may increase the effect of aminoglycosides.

4.9 Amounts to be administered and administration route

Oral use.

Amounts to be administered:
The recommended dose rate is 10 mg amoxicillin/2.5 mg clavulanic acid per kg bodyweight (= 12.5 mg of combined active substances) twice a day by the oral route in dogs, i.e. 1 tablet per 20 kg body weight every 12 h.

Body weight (kg)	**Number of tablets (twice daily)**
< 8	Use 40 mg/10 mg tablets
(8.1 – 10.0)	½
(10.1 – 20.0)	1
(20.1 – 30.0)	1 ½
(30.1 – 40.0)	2
> 40	Use 400 mg/100mg tablets

In case of complicated infections, especially respiratory infections, a better cure rate is obtained with a double dose, up to 25 mg of the combination of the active substances per kg weight, twice daily.

Treatment duration:
In the majority of cases, a treatment of 5 to 7 days is sufficient.
For chronic and refractory infections, longer courses of antibacterial therapy may be required. Treatment length should be adapted by the veterinarian, and should be long enough to ensure complete bacteriological cure.

To ensure a correct dosage, body weight should be determined as accurately as possible to avoid under-dosing.

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

Mild gastrointestinal symptoms (diarrhoea, vomiting) may occur more frequently after overdose of the product

4.11 Withdrawal Period(s)

Not applicable.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use**,** amoxicillin and enzyme inhibitor
ATCvet code: QJ01CR02.

5.1 Pharmacodynamic properties

Amoxicillin is a beta-lactam antibiotic, and as such interferes with the synthesis of cell wall peptidoglycan; it has a bactericidal activity on growing bacteria. It is considered as a broad-spectrum penicillin; it is active in vitro against many aerobic and anaerobic, Gram+ and Gram- bacteria, however it is inactivated in bacteria producing beta-lactamases. Susceptible bacterial species include: *Staphylococcus (pseud)intermedius*, β-haemolytic streptococci and *Escherichia coli*.
Clavulanic acid is a potent inhibitor of many β-lactamases produced by Gram positive and Gram negative bacteria, of plasmid or chromosomal origin. Inhibition is allowed by structural similarity with beta-lactams, and occurs through the formation of a stable molecule-enzyme complex. During this process, clavulanic acid is destroyed leading to the protection of amoxicillin against inactivation by these enzymes.

Acquired resistance may be high in *E. coli*. Resistance notably develops through the production of inhibitor-resistant beta-lactamases or the hyperproduction of beta-lactamases.

In some strains of *Staphylococcus aureus* (methicillin-resistant *S. aureus*, MRSA), and of *Staphylococcus (pseudo) intermedius*, resistance to all beta-lactams is conferred by the alteration of the cell wall target proteins (Penicillin-Binding Proteins). This is often associated to resistance to multiple other antimicrobial compounds.

Pseudomonas aeruginosa and *Enterobacter spp*. can be regarded as intrinsically resistant to the combination.

5.2 Pharmacokinetic properties

Amoxicillin is well absorbed after oral intake. The bioavailability associated with the tablets is 60-70% in dogs. Following absorption the highest concentrations are found in the kidneys (urine) and the bile, then the liver, the lungs, the heart and the spleen. The distribution of amoxicillin in the cerebrospinal fluid is limited, unless the meninges are inflamed.

Clavulanic acid is also well absorbed after oral administration. The distribution to the cerebrospinal fluid is limited, unless the meninges are inflamed. Clavulanic acid is excreted mainly through the kidneys (unchanged in the urine).

The main pharmacokinetic parameters after a single dose of 25 mg of the combination of active substances per kg body weight to dogs are summarised in the following table:

Parameter	*Mean value*	
	Amoxicillin	Clavulanic acid
C_{max} (µg/mL)	12.49	4.23
T_{max} (hr)*	1	1
$t_{1/2}$ (hr)	1.56	0.52
AUC_{∞} (µg.h/ml)	31.1	5.54

** median value*
***harmonic mean*

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Erythrosine (E127)
Silica, colloidal anhydrous
Sodium starch glycolate, type A
Microcrystalline cellulose
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf-life of halved tablets: 24 hours.

6.4 Special precautions for storage

Do not store above 25°C.
Any unused divided tablet portion should be returned to the blister, kept within the outer carton.

6.5 Nature and composition of immediate packaging

Alu-Alu-blister packs consisting of laminated aluminium foil (PE-aluminium-lacquer or PE-aluminium-PET), heat sealed, in strips of 10 tablets.
Cartons containing 10 tablets and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials

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

7 MARKETING AUTHORISATION HOLDER

VIRBAC
1ère avenue – 2065 m – L.I.D.
06516 Carros
FRANCE

8 MARKETING AUTHORISATION NUMBER(S)

VPA 10988/098/002

9 DATE OF THE FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th July 2015

10 DATE OF REVISION OF THE TEXT