Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Twinox 400 mg/100 mg chewable tablets for dogs

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains:
Active substances:

Amoxicillin (as amoxicillin trihydrate)	400	mg
Clavulanic acid (as potassium clavulanate, diluted)	100	mg

Excipients:
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 Target Species

Dogs.

4.2 Indications for use, specifying the target species

For the treatment of infections caused by bacteria susceptible to amoxicillin and clavulanic acid including: skin disease (including deep and superficial pyodermas); soft tissue infections (abscesses and anal sacculitis); dental infections (e.g. gingivitis); urinary tract infections; respiratory disease (involving upper and lower respiratory tract); enteritis.

4.3 Contraindications

Do not administer to gerbils, guinea pigs, hamsters, rabbits and chinchillas. Do not use in horses and ruminants.
Do not use in cases of serious dysfunction of the kidneys accompanied by anuria and oliguria.
Do not use in cases of hypersensitivity to penicillins or other substances of the β-lactam group or to any excipients.
Do not use in cases of known resistance to the combination of amoxicillin and clavulanic acid.

4.4 Special warnings for each target species

This product is not indicated for cases involving *Pseudomonas* spp.

4.5 Special precautions for use

Special precautions for use in animals
Whenever possible, the amoxicillin/clavulanic acid combination should only be used based on susceptibility testing.
Official, national and regional antimicrobial policies should be taken into account when the product is used.
Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to amoxicillin/clavulanic acid and may decrease the effectiveness of treatment with other penicillins, due to the potential for crossresistance.
A trend in resistance of *E. coli* is reported, including multidrug-resistant *E. coli*.
In animals with hepatic and renal dysfunction, the dosing regimen should be carefully evaluated and the use of the product based on a risk/benefit evaluation by the veterinary surgeon.
Caution is advised in the use in small herbivores other than those in section 4.3.
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 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 you have been advised not to work with such preparations.

Handle this product with care to avoid exposure, taking all recommended precautions.

If you develop symptoms following exposure such as a skin rash, you should seek medical advice and show the doctor this warning. Swelling of the face, lips or eyes or difficulty with breathing, are more serious symptoms and require urgent medical attention.

Wash hands after use.

To avoid accidental ingestion, particularly by a child, unused part-tablets should be returned to the open blister space, inserted back into the outer packaging and kept in a safe place out of the sight and reach of children.

4.6 Adverse reactions (frequency and seriousness)

Very rarely, hypersensitivity reactions to penicillins may occur in treated animals; in these cases, administration should be discontinued and a symptomatic treatment given.

Very rarely, gastro-intestinal disturbances (diarrhoea, vomiting, ...) may occur after administration of the product. Treatment may be discontinued depending on the severity of the undesirable effects and a benefit/risk evaluation by the veterinary surgeon.

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 mice have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.

The safety of the product has not been assessed in pregnant and lactating bitches.

In pregnant and lactating animals, use only according to the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interactions

Chloramphenicol, macrolides, sulfonamides and tetracyclines may inhibit the antibacterial effect of penicillins because of the rapid onset of bacteriostatic action. Penicillins may increase the effect of aminoglycosides.

4.9 Amounts to be administered and administration route

Administration: for oral use.

Dosage rate and frequency: 10 mg amoxicillin and 2.5 mg clavulanic acid/kg body weight (i.e. 12.5 mg of combined active substances per kg bodyweight), twice daily (corresponding to 25 mg of combined active substances per kg per day).

The following table is intended as a guide to dispensing the product at the recommended dose rate:

Bodyweight (kg)	Number of tablets per dose twice daily
≤30.0	Use 40 mg/10 mg or 200 mg/50 mg tablet(s)
30.1-40.0	1
40.1-60.0	1 ½
60.1-80.0	2

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

If the animal does not accept the tablet from hand or bowl, then the tablets may be crumbled and added to a little food and fed immediately.

Duration of therapy: The majority of routine cases respond to between 5 and 7 days therapy. In chronic cases, a longer course of therapy is recommended. In such circumstances, overall treatment length must be at the clinician's discretion but should be long enough to ensure complete resolution of the bacterial disease.

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

Mild gastrointestinal symptoms (diarrhoea, nausea and vomiting) may occur after overdose of the product and symptomatic treatment should be initiated when necessary.

4.11 Withdrawal period(s)

Not applicable.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterials for systemic use, combinations of penicillins, incl. beta-lactamase inhibitors.
ATC vet code: QJ01CR02.

5.1 Pharmacodynamic properties

Amoxicillin is an aminobenzylpenicillin from the beta-lactam penicillin family. It interferes with the synthesis of peptidoglycan, an important component of bacterial cell walls. Therefore, it prevents bacterial cell wall formation.
Clavulanic acid binds irreversibly with beta –lactamase and prevents it from inactivating amoxicillin.
Therefore, amoxicillin/clavulanic acid combination has a notably broad spectrum of bactericidal activity against bacteria commonly found in dogs.

In vitro amoxicillin/clavulanic acid combination is active against a wide range of clinically important aerobic and anaerobic bacteria including:
Gram-positive: Staphylococci (including ß-lactamase producing strains); Streptococci.
Gram-negative: Escherichia coli (including most ß-lactamase producing strains); Klebsiellae; Pasteurellae.

Susceptibility and resistance for selected pathogens causing respiratory, urinary tract or skin infections and identified in European surveys were as follows:
Respiratory infections (reported in 2019)

Pathogen	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Resistance (%)
Staphylococcus pseudointermedius	0.12	0.12	
Streptococcus sp.	≤0.015	0.06	
Staphylococcus aureus	0.5	1	
*Escherichia coli**	4	8	0

*Breakpoints were derived from human breakpoints.

Urinary tract infections (reported in 2017 and 2019)

Pathogen	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Resistance (%)
Staphylococcus intermedius	0.12	0.25	3
Streptococcus canis	0.12	0.12	0
Escherichia coli	4	8	26

Skin infections (reported in 2016)

Pathogen	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Resistance (%)
Staphylococcus pseudointermedius	0.12	0.12	4.7
Staphylococcus aureus	0.25	1	26.7
*mec*A-positive staphylococci	16	32	82.0
Streptococcus spp.	0.12	0.12	/
Escherichia coli	4	8	99.1
Pasteurella spp.	0.25	0.25	/

The Clinical and Laboratory Standards Institute CLSI has set the MIC breakpoints based on disk-diffusion method (CLSI document VET01S, 5th ed, 2020) for the amoxicillin-clavulanate against staphylococci and streptococci causing skin and soft tissue infections and urinary tract infections in dogs as ≤0.25 / 0.12 µg/mL susceptible and ≥1 / 0.5 µg/mL resistant. For *E. coli* causing skin and soft tissue infections in dogs, the susceptible breakpoint is set at ≤0.25 / 0.12 µg/mL and for urinary tract infections as ≤8 / 4 µg/mL.
The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

- Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.
- Alteration of Penicillin-Binding Proteins (PBP), which reduce the affinity of the antibacterial agent for the target (methicillin resistant *S. aureus*, MRSA and *S. pseudintermedius*, MRSP).

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria. Resistance genes can be located on chromosomes (mecA, MRSA) or plasmids (LAT, MIR, ACT, FOX, CMY family beta-lactamases) and a variety of resistance mechanisms have emerged.
Pseudomonas aeruginosa and *Enterobacter* spp. may be regarded as intrinsically resistant to the combination. Resistance is shown among methicillin-resistant *Staphylococcus aureus*. A trend in resistance of *E. coli* is reported, including multidrug-resistant *E. coli*.

5.2 Pharmacokinetic particulars

Amoxicillin is well-absorbed following oral administration. In dogs the systemic bioavailability is 60-70%. Amoxicillin (pKa 2.8) has a relatively small apparent distribution volume, a low plasma protein binding (34% in dogs) and a short terminal half-life due to active tubular excretion via the kidneys. Following absorption, the highest concentrations are found in the kidneys (urine) and the bile, and then in liver, lungs, heart and spleen. The distribution of amoxicillin to the cerebrospinal fluid is low unless the meninges are inflamed.
Following the administration of the product in dogs, a mean C_{max} of 7.31 µg/ml was achieved for amoxicillin at approximately 1.37 hours. The mean terminal half-life for amoxicillin was 1.21 hours.
Clavulanic acid (pKa 2.7) is also well-absorbed following oral administration. The penetration to the cerebrospinal fluid is poor. The plasma protein binding is approximately 25% and the elimination half-life is short. Clavulanic acid is mainly eliminated by renal excretion (unchanged in urine).
Following the administration of the product in dogs, a mean C_{max} of 1.33 µg/ml was achieved for clavulanic acid at approximately 1.02 hours. The mean terminal half-life for clavulanic acid was 0.83 hours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Magnesium stearate
Silica, colloidal anhydrous
Sodium starch glycollate (type A)
Dried autolyzed yeast
Erythrosine aluminium lake, E127

6.2 Major incompatibilities

None known.

6.3 Shelf-life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years
Any unused half tablets should be returned to the blister pack and used within 24 hours.

6.4 Special precautions for storage

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

6.5 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.
Blister contains 6 tablets. Carton contains 12, 60 or 300 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal products 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

Krka, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER(S)

VPA10774/072/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 June 2021

10 DATE OF REVISION OF THE TEXT