CLAVASEPTIN P 50 MG CLAVASEPTIN P 250 MG CLAVASEPTIN P 500 MG CLAVASEPTIN P 62,5 MG CLAVASEPTIN P 750 MG	FR_V_0407_001-004_DC
VETOQUINOL	
Publicly available assessment report	

anses
AGENCE NATIONALE DU
MEDICAMENT VETERINAIRE

FRENCH AGENCY FOR FOOD, ENVIRONNEMENTAL AND OCCUPATIONAL HEALTH SAFETY

FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS

14 RUE CLAUDE BOURGELAT – PARC D'ACTIVITES DE LA GRANDE MARCHE JAVENE – CS 70611 – 35306 FOUGERES

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

CLAVASEPTIN P 50 MG
CLAVASEPTIN P 250 MG
CLAVASEPTIN P 500 MG
CLAVASEPTIN P 62,5 MG
CLAVASEPTIN P 750 MG

This PuAR was produced by former RMS (UK) till 2019.

FR (new RMS) has updated this PuAR in 2024 following a major variation (see POST-AUTHORISATION PROCEDURES)

Last update: 19/11/2024.

CLAVASEPTIN P 50 MG CLAVASEPTIN P 250 MG CLAVASEPTIN P 500 MG CLAVASEPTIN P 62,5 MG CLAVASEPTIN P 750 MG	FR_V_0407_001-004_DC
VETOQUINOL	
Publicly available assessment report	

PRODUCT SUMMARY

EU procedure number	FR_V_0407_001-004_DC
Name, strength and pharmaceutical form	CLAVASEPTIN P 50 MG tablet CLAVASEPTIN P 250 MG tablet CLAVASEPTIN P 500 MG tablet CLAVASEPTIN P 62,5 MG tablet CLAVASEPTIN P 750 MG tablet
Applicant	Vetoquinol S.A. Magny Vernois 70200 Lure France
Active substance(s)	Amoxicillin trihydrate Clavulanic acid
ATC vetcode	QJ01CR02
Target species	for dogs and cats
Indication for use	In dogs: treatment of infections caused by bacteria susceptible to amoxicillin in combination with clavulanic acid (including beta-lactamase producing strains), in particular: • Skin infections (including deep and superficial pyodermas, wounds, abscesses) caused by *Staphylococcus* spp, *Streptococcus* spp, and *Pasteurella* spp. • Respiratory tract infections (sinusitis, rhino-tracheitis, bronchopneumonia) caused by *Staphylococcus* spp, and *E. coli*. • Infections of the oral cavity (mucous membranes) caused by *Streptococcus* spp, and *Pasteurella* spp. • Urinary tract infections (nephritis, cystitis) caused by *E. coli*, *Klebsiella* spp and *Proteus mirabilis.* • Digestive tract infections, especially gastroenteritis caused by *E. coli.* In cats: treatment of infections caused by bacteria susceptible to amoxicillin in combination with clavulanic acid (including beta-lactamase producing strains), in particular:

	• Skin infections (including deep and superficial pyodermas, wounds, abscesses) caused by *Staphylococcus* spp, *Streptococcus* spp and *Pasteurella* spp. • Respiratory tract infections (sinusitis, rhino-tracheitis, bronchopneumonia) caused by *Staphylococcus* spp and *E. coli*. • Infections of the oral cavity (mucous membranes) caused by *Streptococcus* spp, and *Pasteurella* spp. • Urinary tract infections (nephritis, cystitis) caused by *E. coli*, *Pasteurella* spp, *Klebsiella* spp and *Proteus mirabilis.* • Digestive tract infections, especially gastroenteritis caused by *E. coli.*

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original applications	Applications in accordance with Article (1)(a)(ii) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	29 September 2010
Date product first authorised in the Reference Member State	18 June 2004
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, DK, EL, ES, FI, HU, IE, IT, LT, LU, LV, NL, ~~NO~~, PL, PT, RO, SK, SL, SE, UK(NI)

CLAVASEPTIN P 50 MG CLAVASEPTIN P 250 MG CLAVASEPTIN P 500 MG CLAVASEPTIN P 62,5 MG CLAVASEPTIN P 750 MG	FR_V_0407_001-004_DC
VETOQUINOL	
Publicly available assessment report	

I. SCIENTIFIC OVERVIEW

Clavaseptin 50 mg (40 mg/10 mg) Palatable Tablets for Dogs and Cats, Clavaseptin 250 mg (200 mg/50 mg) Palatable Tablets for Dogs and Clavaseptin 500 mg (400 mg/100 mg) Palatable Tablets for Dogs contain the active substances amoxicillin (as amoxicillin trihydrate) and clavulanic acid (as potassium clavulanate) in the ration 4:1. These products were granted National Marketing Authorisations in the UK in June 2004. Clavaseptin 50 mg Palatable Tablets for Dogs and Cats are indicated for use in dogs and cats, whereas Clavaseptin 250 mg Palatable Tablets for Dogs and Clavaseptin 500 mg Palatable Tablets for Dogs are only indicated for use in dogs.

The repeat use applications for Clavaseptin 50 mg, 250 mg and 500 mg Palatable Tablets were submitted in accordance with Article 13a of Directive 2004/28/EC.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC. The product is safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.

The overall benefit/risk analysis is in favour of granting a marketing authorisation.

FR (new RMS) has updated this PuAR in 2024 following a major variation (see POST-AUTHORISATION PROCEDURES).

CLAVASEPTIN P 50 MG CLAVASEPTIN P 250 MG CLAVASEPTIN P 500 MG CLAVASEPTIN P 62,5 MG CLAVASEPTIN P 750 MG	FR_V_0407_001-004_DC
VETOQUINOL	
Publicly available assessment report	

II. QUALITY ASPECTS

A. Composition

The products contain the active substances amoxicillin (as amoxicillin trihydrate) and clavulanic acid (as potassium salts) and excipients brown iron oxide (E172), crospovidone, povidone K25, silicon dioxide, microcrystalline cellulose, liver aroma, yeast aroma, magnesium stearate and hypromellose.

The products are supplied in cartons of 10, 20, 50, 100, 120, 150, 200, 250, 300, 400, 500, 600, 750 and 1000 tablets presented in aluminium/aluminium strip pack each containing 10 tablets. Declarations have been provided indicating that the materials comply with European Pharmacopoeia requirements in respect of suitability for food and pharmaceutical use.

The choice of formulation is justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European Guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The supporting data for amoxicillin trihydrate and potassium clavulanate have been provided in the form of EDQM[2] Certificate of Suitability. It is considered that the manufacturing process is adequately controlled and the active substance specifications have been suitably justified.

There are nine excipients used in the formulation and each has been used previously in veterinary medicines. Crospovidone, povidone K25, microcrystalline cellulose, magnesium stearate, hypromellose, have monographs in the European Pharmacopoeia and each complies with the requirements of the current edition of the Ph. Eur. Silicon Dioxide is the subject of a monograph in the German Pharmacopoeia (DAB). The colorant brown iron oxide E172 comply with the requirements of Directive 95/45/EC and is certified for food and pharmaceutical use.

The applicant provided raw material specifications for liver aroma and yeast aroma comprising tests of appearance, identity, pH, solubility and loss on drying. This is considered acceptable.

CLAVASEPTIN P 50 MG CLAVASEPTIN P 250 MG CLAVASEPTIN P 500 MG CLAVASEPTIN P 62,5 MG CLAVASEPTIN P 750 MG	FR_V_0407_001-004_DC
VETOQUINOL	
Publicly available assessment report	

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

There are no intermediate products.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

G. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf-life. The shelf-life of the veterinary medicinal product as packaged for sale is 2 years.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

CLAVASEPTIN P 50 MG CLAVASEPTIN P 250 MG CLAVASEPTIN P 500 MG CLAVASEPTIN P 62,5 MG CLAVASEPTIN P 750 MG	FR_V_0407_001-004_DC
VETOQUINOL	
Publicly available assessment report	

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics:
Amoxicillin is an aminobenzylpenicillin from the betalactam penicillin family which prevents the bacterial cell wall formation by interfering with the final step of peptidoglycan synthesis.

Clavulanic acid is an irreversible inhibitor of intracellular and extracellular ÿ-lactamases which protects amoxicillin from inactivation by many betalactamases.

Amoxicillin/clavulanate has a wide range of activity which includes betalactamase producing strains of both Gram-positive and Gram-negative aerobes, facultative anaerobes and obligate anaerobes.

Pharmacokinetics
After oral administration at the recommended dose in dogs and cats, the absorption of amoxicillin and clavulanic acid is fast.
In dogs, the maximum plasma concentration of amoxicillin of 8.5 µg/ml is reached in 1.4 h and the maximum plasma concentration of clavulanic acid of 0.9 µg/ml is reached in 0.9h.
In cats, the maximum plasma concentration of amoxicillin of 6.6 µg/ml is reached in 1.8 h and the maximum plasma concentration of clavulanic acid of 3.7 µg/ml is reached in 0.75h. Elimination is also fast.
After repeated oral administration of the recommended dose in dogs and cats, there is no accumulation of amoxicillin or clavulanic acid and the steady state is reached rapidly after first administration.

Variation FR/V/xxxx/WS/152 (2024):
To justify the addition of claims and harmonisation with the reference product Synulox (or its generics) as well as the addition of a detailed list of target pathogens and updates to various SPC sections, the data presented by the Applicant include *in-vivo* bioequivalence studies in dogs and cats and an *in-vitro* bioequivalence study to compare the dissolution profiles of the five Clavaseptin formulations.

Toxicological Studies

The applicant has provided a review of published literature which shows that relevant toxicity issues have been addressed with regard to single and repeated dose toxicity, and other appropriate parameters.

Single dose toxicity:
Single dose toxicity studies were performed in rats and mice. The $_{LD504}$ values (mg/kg body weight) for both test compounds in the rat and mouse by various routes of administration are presented in the table below:

Species	Route	Sex	Potassium clavulanate	Amoxicillin
Mouse	Oral	Male	4.526 (3.223-6.355)	>15.000
		Female	6.933 (6.229-7.716)	>15.000
	s.c.	Male	2.185 (1.877-2.544)	6.433 (6.125-6.757)
		Female	2.276 (1.832-2.827)	8.264 (7.560-9.034)
	i.p.	Male	1.531 (1.313-1.785)	3.925 (3.708-4.155)
		Female	1.720 (1.631-1.814)	4.118 (3.993-4.247)
Rat	Oral	Male	9.695 (8.986-10.460)	>15.000
		Female	7.936 (7.182-8.769)	>15.000
	s.c.	Male	1.781 (1.720-1.845)	5.259 (4.779-5.788)
		Female	1.398 (1.254-1.558)	3.487 (2.968-4.070)
	i.p.	Male	1.432 (1.323-1.550)	3.878 (3.285-4.576)
		Female	1.399 (1.344-1.457)	2.774 (2.439-3.155)

Repeated dose toxicity:
Repeated dose toxicity studies were conducted in rats and beagle dogs. NOEL[5] has been identified as being 30 mg/kg and 90 mg/kg in a 35 day subacute toxicity study for potassium clavulanate and amoxicillin respectively and 20 mg/kg/day and 60 mg/kg/day in a 6 month chronic toxicity study for potassium clavulanate and amoxicillin respectively in dogs.

A NOEL of 30 mg/kg for potassium clavulanate 150 mg/kg/day for amoxicillin in a 26 week chronic toxicity study in rats.

Reproductive Toxicity, including Teratogenicity:
Reports of studies on reproductive toxicity/teratogenicity were provided. A study conducted in rats in the organogenesis period at dose levels of 10, 50 and 400 mg/kg potassium clavulunate and 30, 150 and 1200 mg/kg amoxicillin showed no abnormalities in gestation period and birth. Another study in rats showed no abnormalities of gestation period or at parturition at dose levels of 10, 50 and 400 mg/kg potassium clavulunate and 30, 150 and 1200 mg/kg amoxicillin.

Mutagenicity:
Reports of studies on mutagenic potential were provided. In a GLP-compliant study, the mutagenic potential of potassium clavulanate:amoxicillin trihydrate (1:4) was investigated in *Salmonella typhimurium* and *E.coli.* The study concluded that potassium clavulanate:amoxicillin trihydrate (1:4) was not mutagenic when tested at concentrations extending into the toxic range. Another study was conducted to assess the mutagenic potential of potassium clavulanate:amoxicillin trihydrate (1:4) in the mouse lymphoma L5178Y cell line, clone-3.7.2.C scoring for forward mutations at the thymidine kinase locus. The study was fully compliant with the requirements of GLP. It was concluded that potassium clavulanate:amoxicillin trihydrate (1:4) is mutagenic in mouse lymphoma L5178Y cells, when tested for an extended exposure period at concentrations extending into the toxic range.

User Safety

CLAVASEPTIN P 50 MG CLAVASEPTIN P 250 MG CLAVASEPTIN P 500 MG CLAVASEPTIN P 62,5 MG CLAVASEPTIN P 750 MG	FR_V_0407_001-004_DC
VETOQUINOL	
Publicly available assessment report	

The applicant has provided a user safety assessment in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the VMP.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in accordance with VICH guidance which showed that no further assessment is required. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided a number of literature references and data generated in-house with the amoxicillin/clavulanic acid combination which indicate that amoxicillin is a semi-synthetic penicillin with activity against a range of Gram-positive and Gram-negative bacteria. It acts by interfering with the final stage of peptidoglycan synthesis and thus prevents proper formation of the bacterial cell wall which results in cell lysis. Amoxicillin is susceptible to breakdown by beta-lactamase enzymes produced by some bacteria.

Clavulanic acid has structural similarities with penicillin and possesses a beta-lactam ring. It has little intrinsic antibacterial activity, but it is able to destroy some staphylococcal beta-lactamases and many chromasomally and plasmid-mediated beta-lactamases produced by Gram-negative bacteria. Used in combination, clavulanic acid protects amoxicillin from breakdown by beta-lactamases and thus broadens its antibacterial spectrum.

The applicant also provided published literature which indicates that the combination of amoxicillin and clavulanic acid has a wide spectrum of antimicrobial activity, which includes beta-lactamase producing strains of both Gram-positive and Gram-negative aerobes and both facultative and obligate anaerobes. The applicant conducted an in vitro study to evaluate the kinetics of bacterial killing. This was carried out with an amoxicillin/clavulanic acid combination at a ratio of 2:1 on two strains of bacteria isolated from cats. Bacterial killing rates were evaluated using a broth dilution technique and concentrations of 0, 1, 2, 4 and 8 times the MIC for the organisms. The results showed time dependent activity of the combination with a bactericidal effect at 4x and 8x the MIC against the strains tested.

MIC data was provided in relation to pathogens relevant to the proposed clinical conditions. These were based partly on the published literature and also on work carried out with isolates from cases treated in the clinical trials.

The applicant also provided a number of references detailing the absorption, distribution, metabolism and excretion of the actives amoxicillin and clavulanate in rats and mice. The Applicant has also provided references detailing the pharmacokinetic profiles of amoxicillin and clavulanate in man and in dogs.

Absorption of both amoxicillin and clavulanic acid is good after oral administration, although the later is absorbed slightly more slowly in the dog. Absorption does not appear to be affected by the simultaneous administration of food or antacids in man. However, milk can decrease the absorption of clavulanic acid slightly. There is no evidence of accumulation with either antibiotic following repeated administrations in healthy human subjects.

The distribution of amoxicillin and clavulanic acid in body tissues and fluids is similar to other beta-lactam antibiotics. Studies in laboratory rats indicated that both agents are widely distributed in the body with varying concentrations in the different organs. In most cases the levels were considerably lower than those in the plasma and were very low in the brain. However, concentrations were high in the liver in the case of amoxicillin and high in the kidney with clavulanic acid. This was thought to be due to the presence of bile or urine in the respective tissues. Studies in infection models in mice indicated significant levels of both antibiotics at the various sites of infection. These included pneumonia, peritonitis, muscle lesions, abscesses and pyelonephritis. Furthermore, the ability of clavulanic acid to protect amoxicillin *in vivo* was confirmed by the efficacy of the combination in the treatment of the infections studied, most of which were refractory to treatment with amoxicillin alone.

With regard to metabolism and elimination, amoxicillin is largely excreted unchanged in the urine (60-75%) by proximal tubular excretion. Some hydrolysis of the beta-lactam ring occurs with this antibiotic and the subsequent metabolites are also excreted via the same route. Clavulanic acid is more extensively metabolised and this has been studied in both rats and dogs. In both species there were two major metabolites and these were excreted in the urine. Between 30 and 50% of the clavulanic acid administered was excreted unchanged in the urine via glomerular filtration.

The applicant also provided supportive studies. One study was conducted to evaluate the plasma kinetic of amoxicillin and clavulanic acid in dogs following repeated oral administration of the product. Another study was conducted to evaluate the plasma kinetics of amoxicillin and clavulanic acid in cats following repeated oral administrations of the product. These studies established the important related parameters in the two species. Both amoxicillin and clavulanic acid were rapidly absorbed from the product in dogs and cats and also eliminated rapidly. There was no indication of accumulation over the 7 day dosing period.

Tolerance in the Target Species of Animals

The applicant has provided reference to tolerance studies conducted with the Clavaseptin Palatable Tablets in dogs and cats. A study was conducted to evaluate the tolerance of amoxicillin and clavulanic acid tablets after repeated oral administrations in dogs at dose levels of 12.5 and 37 mg/kg twice daily for 14 days. The dogs were divided into different groups. The control group received a suitable number of placebo tablets daily. All animals were subjected to clinical monitoring using an objective scoring system. No mortalities occurred during the study. The study concluded that the amoxicillin/clavulanic acid tablets were well tolerated by dogs at up to three times the recommended dose rate when administered twice daily for 14 days.

Another study was conducted to evaluate the tolerance of amoxicillin and clavulanic acid tablets after repeated oral administration in cats. A suitable number of cats were divided into different groups. The test product was amoxicillin/clavulanic acid tablets containing 40 mg amoxicillin and 10 mg clavulanic acid. The test product was administered to cats at dose levels of 12.5 and 37.5 mg/kg twice daily for 28 days. The control group received a suitable number of placebo tablets daily. All animals were subjected to clinical monitoring using an objective scoring system. No mortalities occurred during the study. The study concluded that the amoxicillin/clavulanic acid tablets were well tolerated by cats at up to three times the recommended dose rate when administered twice daily for 28 days.

Resistance

The applicant has provided an overview of the published literature on amoxicillin/clavulanic acid which included reference to this section. Resistance to the combination of amoxicillin and clavulanic acid occurs intrinsically in some micro-organisms and it can also develop following exposure of bacteria to beta-lactam antibiotics.

IV.B Clinical Studies

The applicant conducted two clinical trials with Clavaseptin Palatable Tablets; one in dogs and the other in cats. These were controlled, blinded, randomised, multi-centre studies designed to evaluate and compare the efficacy and safety of the test and pioneer products. The pioneer products, Synulox Palatable Tablets 50 mg, Synulox Palatable Tablets 250 mg and Synulox Palatable Tablets 500 mg, have been authorised in the European Community for more than 10 years. Both studies were conducted in accordance with VICH Good Clinical Practice guidelines and the analyses were in line with EMEA/CVMP statistical principles. The trial in dogs compared the Clavaseptin Palatable Tablets 50, 250 and 500 mg and the corresponding Synulox Palatable Tablets in the treatment of periodontal infections in dogs. The trial in cats compared the Clavaseptin 50 mg Palatable Tablet presentation and Synulox 50 mg Palatable Tablet in the treatment of skin and soft tissue infections in cats. The trial protocols and methodology were well planned. The animals used in these trials were representative of the target population and both the numbers and their distribution per group were appropriate. The studies established no statistically significant

differences in efficacy between Clavaseptin 50, 250 and 500 mg Palatable Tablets and Synulox Palatable Tablets.

Variation FR/V/xxxx/WS/152 (2024):
To justify the addition of claims and harmonisation with the reference product Synulox (or its generics) as well as the addition of a detailed list of target pathogens and updates to various SPC sections, the data presented by the Applicant include *in-vivo* bioequivalence studies in dogs and cats and an *in-vitro* bioequivalence study to compare the dissolution profiles of the five Clavaseptin formulations.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit-risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

CLAVASEPTIN P 50 MG CLAVASEPTIN P 250 MG CLAVASEPTIN P 500 MG CLAVASEPTIN P 62,5 MG CLAVASEPTIN P 750 MG	FR_V_0407_001-004_DC
VETOQUINOL	
Publicly available assessment report	

POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the VMP. The current SPC is available in the Union Product Database (UPD).

This section contains information on significant changes, which have been made after the original procedure, which are important for the quality, safety or efficacy of the VMP.

Sequence of significant variations

Changes to Part 3 and/or Part 4 of the dossier (safety/efficacy)

Summary of change (Application number)	Supporting information	Approval date
G.I.7.a - SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one **(FR/V/xxxx/WS/152)**	This application aimed at • updating the list of indications and target pathogens for each target species, based on a review of the reference product Synulox indications and of recent susceptibility data of target pathogens, • updating the SPC to the current guidelines as shown on EMA website Guideline on SPC for veterinary medicinal products containing antimicrobial substances: EMA/CVMP/383441/2005-Rev.1 Corr1 QRD 9. To justify the addition of claims and harmonisation with the reference product Synulox (or its generics) as well as the addition of a detailed list of target pathogens and updates to various SPC sections, the data presented by the Applicant include *in-vivo* bioequivalence studies in dogs and cats, an *in-vitro* bioequivalence study to compare the dissolution profiles of the five Clavaseptin formulations and a review of the recent susceptibility and epidemiological data for target pathogens.	12/11/2024