ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Clavucill 200 mg/50 mg (DE, DK, ES, FR, NL, PL, PT, RO, SE, BE)
Tablets for dogs.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet (900 mg) contains:
- Active substances: Amoxicillin (as amoxicillin trihydrate) 200 mg/tablet
  Clavulanic acid (as potassium clavulanate) 50 mg/tablet
- Excipients: 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 tablet with a diameter of 14.5 mm.
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
Dogs
Treatment of infections caused by micro-organisms sensitive for the combination amoxicillin/clavulanic acid, especially:
- dermatitis (superficial and deep pyoderma) caused by *Staphylococcus (pseud)intermedius*.
- urinary tract infections caused by *E. coli*.
- 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 case of known 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 case of bacteria sensitive to narrow spectrum penicillins or to amoxicillin as single substance.
- Whenever possible, the product should only be used based on susceptibility testing. Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria

resistant to the amoxicillin/clavulanate, and may decrease the effectiveness of treatment with β-lactam antibiotics, due to the potential for cross resistance.
- 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.
- People with known hypersensitivity to penicillins should avoid contact with the veterinary medicinal product.
- 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)
- Gastro-intestinal disturbances (diarrhoea, vomiting, …) may occur uncommonly 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.
- Dose independent allergic reactions may very rarely occur, such as skin reactions or anaphylaxis. In those cases the treatment must be stopped immediately and a symptomatic treatment should be given.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reactions during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

4.7 Use during pregnancy or lactation
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 12h.

Body weight (kg)	Number of tablets (twice daily)
< 8	Use 50 mg
(8.1 – 10.0)	½
(10.1 – 20.0)	1
(20.1 – 30.0)	1 ½
(30.1 – 40.0)	2
> 40	Use 500 mg 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
Not applicable.

5. PHARMACOLOGICAL 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 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 pseudintermedius*, 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 particulars

Amoxicillin is well absorbed after oral intake. The mean bioavailability associated with the tablets is of approximately 53% 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 mean bioavailability associated with the tablets is of approximately 43% in dogs. 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 were summarized in the following table:

Parameter	*Mean value*	
	Amoxicillin	Clavulanic acid
C_{max} (µg/mL)	12,49	4,23
T_{max} (hr)	1,18	0,97
$t_{1/2}$ (hr)	1,57	0,63
AUC_{∞} (µg.h/ml)	31,1	5,54

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- Colloidal silica, anhydrous
- Sodium starch glycolate, type A
- Microcrystalline cellulose (E460)
- Erythrosine (E127)
- Magnesium stearate (E572)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Any divided tablet portion remaining after 24 hours should be discarded.

6.4. Special precautions for storage
Do not store above 25°C.
Divided tablets should be stored in the blister pack.

6.5 Nature and composition of immediate packaging
Alu-Alu-blister packs consisting of aluminium foil (Polyester / Aluminium foil / LD Polyethylene), heat sealed, in strips of 10 tablets. Cartons containing 10, 100 or 250 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 products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date of last renewal:

10 DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE
Delivery: veterinary prescription only.