ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Kesium 500 mg / 125 mg Chewable tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Active substances:

Amoxicillin (as amoxicillin trihydrate)	500.00 mg
Clavulanic acid (as potassium clavulanate)	125.00 mg

Excipients:

Qualitative composition of excipients and other constituents
Pig liver powder
Yeast
Crospovidone (type A)
Povidone K 25
Hypromellose
Microcrystalline cellulose
Silica, colloidal anhydrous
Magnesium stearate

Clover-shaped scored beige chewable tablet. The tablets can be divided into four equal parts.

3. CLINICAL INFORMATION

3.1. Target species:

Dogs.

3.2. Indications for use for each target species:

For the treatment of the following infections caused by β-lactamase producing strains of bacteria sensitive to amoxicillin in combination with clavulanic acid and where clinical experience and/or sensitivity testing indicates the veterinary medicinal product as the drug of choice:

- Skin infections (including superficial and deep pyodermas) associated with *Staphylococcus* spp.
- Urinary tract infections associated with *Staphylococcus* spp., *Streptococcus* spp*., Escherichia coli* and *Proteus mirabilis*.
- Respiratory tract infections associated with *Staphylococcus* spp*., Streptococcus* spp*. and Pasteurella* spp.
- Digestive tract infections associated with *Escherichia coli*.
- Infections of the oral cavity (mucous membrane) associated with *Pasteurella* spp*., Streptococcus* spp. and *Escherichia coli.*

3.3. Contraindications

Do not use in cases of hypersensitivity to penicillins, to other substances of the β-lactam group or to any excipients.
Do not use in animals with serious dysfunction of the kidneys accompanied by anuria and oliguria.
Do not administer to gerbils, guinea pigs, hamsters, rabbits and chinchillas. Do not use in horses and ruminating animals.
Do not use where resistance to this combination is known to occur.

3.4. Special warnings

None.

3.5. Special precautions for use

Special precautions for safe use in the target species
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.
It is advised that upon initiating therapy appropriate sensitivity testing is performed and that therapy is continued only after susceptibility to the combination has been established.
Use of the veterinary medicinal 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 beta-lactam antibiotics
In animals with hepatic and renal dysfunction, the dosing regimen should be carefully evaluated and the use of the veterinary medicinal product based on a risk/benefit evaluation by the veterinary surgeon.
Caution is advised in the use in small herbivores other than those in the section 3.3.

The potential for allergic cross-reactions with other penicillin derivates and cephalosporins should be considered.
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 may lead to cross-reactions to cephalosporins and vice versa. Allergic reactions to these substances may occasionally be serious.

Do not handle this veterinary medicinal product if you know you are sensitised, or if you have been advised not to work with such preparations.

Handle this veterinary medicinal product with great 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.

Special precautions for the protection of the environment
Not applicable

3.6. Adverse events

Dogs

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Gastrointestinal signs (e.g. diarrhoea or vomiting) [1] Allergic reaction (e.g. allergic skin reaction, anaphylaxis) [2]

[1] Treatment may be discontinued depending on the severity of the undesirable effects and a benefit/risk evaluation by the veterinary surgeon.

[2] In these cases, administration should be discontinued, and a symptomatic treatment given.

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

Pregnancy and lactation:
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.

3.8. Interaction with other medicinal products and other forms of interaction

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.

3.9. Administration routes and dosage

Oral use.

The recommended dose of the product is 10 mg amoxicillin / 2.5 mg clavulanic acid per kg body weight twice a day by the oral route in dogs, *i.e.* 1 tablet per 50 kg body weight every 12 h, according to the following table:

Body weight (kg)	Number of tablets to be administered twice daily
> 9 to 12.5	¼
12.6 to 20	Use the 200 mg / 50 mg
20.1 to 25	½
25.1 to 37.5	¾
37.6 to 50	1
50.1 to 62.5	1¼
62.6 to 75	1½

In refractory cases the dose may be doubled to 20 mg of amoxicillin / 5 mg clavulanic acid per kg bodyweight twice daily, at the clinician's discretion.

The chewable tablets are flavoured and are accepted by a majority of dogs. The chewable tablets can be administered directly into the mouth of the animals or added to a small quantity of food.

Duration of therapy
The majority of routine cases respond to 5 – 7 days of therapy.
In chronic cases, a longer case 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.

To ensure the correct dosage, body weight should be determined as accurately as possible.

Instruction on how to divide the tablet: Put the tablet on an even surface, with its scored side facing down (convex face up). With the tip of the forefinger, exert slight vertical pressure on the middle of the tablet to break it along its width into halves. Then, in order to obtain quarters, exert slight pressure on the middle of one half with the forefinger to break it into two parts.

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

In case of overdose diarrhoea, allergic reactions or further symptoms like central nervous excitation manifestations or cramps could appear. Symptomatic treatment should be initiated when necessary.

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 ATC vet code:

QJ01CR02

4.2. Pharmacodynamics

Amoxicillin is a β-lactam antibiotic and its structure contains the β-lactam ring and thiazolidine ring common to all penicillins. Amoxicillin shows activity against susceptible Gram-positive bacteria and Gram-negative bacteria.

β-lactam antibiotics prevent the bacterial cell wall from forming by interfering with the final stage of peptidoglycan synthesis. They inhibit the activity of transpeptidase enzymes, which catalyse cross-linkage of the peptidoglycan polymers that form the cell wall. They exert a bactericidal action but cause lysis of growing cells only.

Clavulanic acid is one of the naturally occurring metabolites of the streptomycete *Streptomyces clavuligerus.* It has a structural similarity to the penicillin nucleus, including possession of a beta-lactam ring. Clavulanic acid is a β-lactamase inhibitor acting initially competitively but ultimately irreversibly. Clavulanic acid will penetrate the bacterial cell wall binding to both extracellular and intracellular β-lactamases.

Amoxicillin is susceptible to breakdown by β-lactamase and therefore combination with an effective β-lactamase inhibitor (clavulanic acid) extends the range of bacteria against which it is active to include β-lactamase producing species.

In vitro potentiated amoxicillin is active against a wide range of clinically important aerobic and anaerobic bacteria including:

Gram-positive:
Staphylococcus spp. (including β-lactamase producing strains)
Streptococcus spp.

Gram-negative:

Escherichia coli (including most β-lactamase producing strains)

Pasteurella spp.
Proteus spp.

Resistance is shown among *Enterobacter* spp., *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus*. A trend in resistance of *E. coli* is reported.
Resistance to β-lactam antibiotics is mainly mediated by β-lactamases which hydrolyze antibiotics such as amoxicillin.
According to the CLSI standard (CLSI, July 2013)., Amoxicillin-clavulanate MICs breakpoints (µg/mL) were determined for *Staphylococcus* spp*.,* and *Escherichia coli* strains in dogs (skin and soft tissue), as:
Sensitive ≤ 0.25/0.12 µg/mL; Intermediate: 0.5/0.25 µg/mL; Resistant ≥ 1/0.5µg/ml.

4.3. Pharmacokinetics

After oral administration in dogs, amoxicillin and clavulanic acid are rapidly absorbed. 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.

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).

After single oral administration of 17 mg/kg amoxicillin and 4.3 mg/kg clavulanic acid in dogs:
- The maximal plasma concentration (Cmax) of amoxicillin (8.6 µg/mL) was observed 1.5 hour following administration.
- The maximal plasma concentration (Cmax) of clavulanic acid (4.9 µg/mL) was observed 54 minutes following administration.

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 divided tablet portions remaining after 36 hours should be discarded.

5.3. Special precautions for storage

Do not store above 25°C.
Divided tablets should be stored in the blister pack.

5.4. Nature and composition of immediate packaging

(PA-AL-PVC – aluminium heat sealed) containing 6 tablets per blister.
Cardboard box of 6 tablets.
Cardboard box of 12 tablets.
Cardboard box of 96 tablets.
Cardboard box of 144 tablets.
Cardboard box of 240 tablets.
Cardboard box of 480 tablets.

Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal product 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

7. MARKETING AUTHORISATION NUMBER

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: {DD/MM/YYYY}

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

{mm/yyyy}

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)

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE
Cardboard box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Kesium 500 mg / 125 mg Chewable tablets

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains:
Active substances:

Amoxicillin (as amoxicillin trihydrate)	500.00 mg
Clavulanic acid (as potassium clavulanate)	125.00 mg

3. PACKAGE SIZE

Cardboard box of 6 tablets
Cardboard box of 12 tablets
Cardboard box of 96 tablets
Cardboard box of 144 tablets
Cardboard box of 240 tablets
Cardboard box of 480 tablets

4. TARGET SPECIES

Dogs

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Oral use.

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp. {mm/yyyy}
Any divided tablet portions remaining after 36 hours should be discarded.

9. SPECIAL STORAGE PRECAUTIONS

Do not store above 25°C.
Divided tablets should be stored in the blister pack.

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

11. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only

12. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children

13. NAME OF THE MARKETING AUTHORISATION HOLDER

14. MARKETING AUTHORISATION NUMBERS

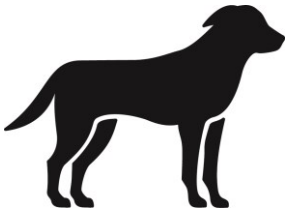
15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
Blister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Kesium



2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

500 mg of amoxicillin (as amoxicillin trihydrate)/ 125 mg of clavulanic acid (as potassium clavulanate)

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {MM/YYYY}

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Kesium 500 mg / 125 mg Chewable tablets for dogs

2. Composition

Each tablet contains:
Active substances:

Amoxicillin (as amoxicillin trihydrate)	500.00 mg
Clavulanic acid (as potassium clavulanate)	125.00 mg

Clover-shaped scored beige chewable tablet. The tablet can be divided into four equal parts.

3. Target species

Dogs

4. Indications for use

For the treatment of the following infections caused by β-lactamase producing strains of bacteria sensitive to amoxicillin in combination with clavulanic acid and where clinical experience and/or sensitivity testing indicates the veterinary medicinal product as the drug of choice:

- Skin infections (including superficial and deep pyodermas) associated with *Staphylococcus* spp..
- Urinary tract infections associated with *Staphylococcus* spp., *Streptococcus* spp*., Escherichia coli* and *Proteus mirabilis*.
- Respiratory tract infections associated with *Staphylococcus spp., Streptococcus spp. and Pasteurella* spp..
- Digestive tract infections associated with *Escherichia coli*.
- Infections of the oral cavity (mucous membrane) associated with *Pasteurella* spp*., Streptococcus* spp. *and Escherichia coli.*

5. Contraindications

Do not use in animals in cases of hypersensitivity to penicillins, or other substances of the β-lactam group or to any excipients.
Do not use in animals with serious dysfunction of the kidneys accompanied by anuria and oliguria.

Do not administer to gerbils, guinea pigs, hamsters, rabbits and chinchillas. Do not use in horses and ruminating animals.
Do not use where resistance to this combination is known to occur.

6. Special warnings

Special precautions for safe use in the target species:
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.
It is advised that upon initiating therapy appropriate sensitivity testing is performed and that therapy is continued only after susceptibility to the combination has been established.
Use of the veterinary medicinal 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
In animals with hepatic and renal dysfunction, the dosing regimen should be carefully evaluated and the use of the veterinary medicinal product based on a risk/benefit evaluation by the veterinary surgeon.
Caution is advised in the use in small herbivores other than those in the section "Contraindications".

The potential for allergic cross-reactions with other penicillin derivates and cephalosporins should be considered.
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 may lead to cross-reactions to cephalosporins and vice versa. Allergic reactions to these substances may occasionally be serious.

Do not handle this veterinary medicinal product if you know you are sensitised, or if you have been advised not to work with such preparations.

Handle this veterinary medicinal product with great 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.

Pregnancy and lactation:
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.

Interaction with other medicinal products and other forms of interaction:
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.

Overdose:
In case of overdose diarrhoea, allergic reactions or further symptoms like central nervous excitation manifestations or cramps could appear. Symptomatic treatment should be initiated when necessary.

7. Adverse events

Dogs:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):
Gastrointestinal signs (e.g. diarrhoea or vomiting) [1]
Allergic reaction (e.g. allergic skin reaction, anaphylaxis) [2]

[1] Treatment may be discontinued depending on the severity of the undesirable effects and a benefit/risk evaluation by the veterinary surgeon.

[2] In these cases, administration should be discontinued, and a symptomatic treatment given.

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system.

8. Dosage for each species, routes and method of administration

Oral use

The recommended dose of the product is 10 mg amoxicillin /2.5 mg clavulanic acid per kg body weight twice a day by the oral route in dogs, i.e. 1 tablet per 50 kg body weight every 12 h, according to the following table:

Body weight (kg)	**Number of tablets to be administered twice daily**
> 9 to 12.5	¼
12.6 to 20	Use the 200 mg / 50 mg
20.1 to 25	½
25.1 to 37.5	¾
37.6 to 50	1
50.1 to 62.5	1¼
62.6 to 75	1½

In refractory cases the dose may be doubled to 20 mg of amoxicillin / 5 mg clavulanic acid/kg bodyweight twice daily, at the clinician's discretion.

Duration of therapy

The majority of routine cases respond to 5 – 7 days of therapy.

In chronic cases, a longer case 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.

To ensure the correct dosage, body weight should be determined as accurately as possible.

9. Advice on correct administration

The chewable tablets are flavoured and are accepted by a majority of dogs. The chewable tablets can be administered directly into the mouth of the animals or added to a small quantity of food.
Instruction on how to divide the tablet: Put the tablet on an even surface, with its scored side facing down (convex face up). With the tip of the forefinger, exert slight vertical pressure on the middle of the tablet to break it along its width into halves. Then, in order to obtain quarters, exert slight pressure on the middle of one half with the forefinger to break it into two parts.

10. Withdrawal periods

Not applicable.

11. Special storage precautions

Keep out of the sight and reach of children.
Do not store above 25°C.
Divided tablets should be stored in the blister pack.
Any divided tablet portions remaining after 36 hours should be discarded.
Do not use after the expiry date stated on the blister and the carton.

12. Special precautions for disposal

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 applicable national collection systems. These measures should help to protect the environment.
Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorization numbers and pack sizes

(MA)

Pack sizes:
Cardboard box of 6 tablets
Cardboard box of 12 tablets
Cardboard box of 96 tablets
Cardboard box of 144 tablets
Cardboard box of 240 tablets
Carboard box of 480 tablets

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

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

16. Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:
(Name and address to be completed nationally)
Tel: +800 35 22 11 51
Email: pharmacovigilance@ceva.com

Manufacturer responsible for batch release:
Ceva Santé Animale
Boulevard de la Communication
Zone Autoroutière
53950 LOUVERNE
FRANCE

17. Other information