ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

STRENZEN 500/125 mg/g powder for use in drinking water for pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

Active substance
Amoxicillin 500 mg
(equivalent to 573.88 mg of Amoxicillin trihydrate)

Clavulanic acid 125 mg
(equivalent to 148.88 mg of Potassium clavulanate)

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

3. PHARMACEUTICAL FORM

Powder for use in drinking water.
Yellowish to yellow fine powder.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs

4.2 Indications for use, specifying the target species

Treatment of clinical

- respiratory tract infections caused by *Actinobacillus pleuropneumoniae, Pasteurella multocida, Streptococcus suis.*
- gastrointestinal infections caused by *Clostridium perfringens, Escherichia coli* and *Salmonella* Typhimurium

where the causative pathogens are beta-lactamase-producing strains of bacteria susceptible to amoxicillin in combination with clavulanic acid and where clinical experience and/or susceptibility testing indicates the combination as the drug of choice.

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 rabbits, guinea pigs, hamsters, chinchillas, gerbils or small herbivores.
Do not use in known cases of resistance to the combination of amoxicillin and clavulanic acid.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

The uptake of medication by animals can be altered as a consequence of illness. In case of insufficient uptake of water animals should be treated parenterally.
Use of the product should be based on susceptibility testing and should take into account official national and regional policies with respect to the use of broad-spectrum antibiotics. Do not use in cases of bacteria susceptible to narrow spectrum penicillins or to amoxicillin as a single substance. Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to amoxicillin and clavulanic acid, and may decrease the effectiveness of treatment with other beta-lactam antibiotics, due to the potential for cross resistance.
Due to the resistance rate detected in porcine *E. coli* isolates to amoxicillin/clavulanic acid in some countries, the product should be used for the treatment of infections caused by *E. coli* only after susceptibility testing has been carried out. Administration of the product should not be used as a method to control non-clinical *Salmonella* infections in pig herds. It is strictly recommended, that the product should not be used as a tool of *Salmonella* control programmes.
In the case of a history of MRSA on a farm it is inappropriate to use a combination of amoxicillin and clavulanic acid as there is a likelihood to co-select for MRSA.
The use of the product should be combined with good management practices e.g. good hygiene, proper ventilation, no overstocking.

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 product if you know you are sensitised or if you 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, 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.
Avoid inhalation of dust. Wear either a disposable half-mask respirator conforming to European Standard EN149 or a non-disposable respirator to European Standard EN140 with a filter to EN143.
Wear gloves during preparation and administration of medicated water.
Wash any exposed skin after handling the product or medicated water.
Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

It is known that adverse reactions including mild gastrointestinal signs (diarrhoea and vomiting) and allergic reactions (skin reactions, anaphylaxis) may occur after administration of penicillins.

Anal and perineal erythema, anal irritation and diarrhoea occur rarely.

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

Pregnancy and lactation:
Laboratory studies in rats and mice have not produced any evidence of mutagenicity, teratogenic and foetotoxic effects.
The safety of the veterinary medicinal product has not been established during pregnancy and lactation.
Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

In general, penicillins may be inhibited by the antibiotics with bacteriostatic action such as macrolides, sulfonamides and tetracyclines. No specific data on interaction of the combination have been described in the veterinary literature available. Neomycin given orally inhibits the intestinal absorption of penicillin. Penicillins may increase the effect of aminoglycosides.

4.9 Amounts to be administered and administration route

Administration in drinking water.

Give 10 mg of amoxicillin (in the form of trihydrate) and 2.5 mg of clavulanic acid (in the form of potassium salt) per kg of body weight twice daily, i.e. 2 g of product per 100 kg body weight twice daily. Treat for 5 days.

For the calculation of the amount to be administered every 12 hours the following formula can be used:
Number of pigs x average body weight (kg) x dose rate (0.02 g of product / kg body weight) twice daily.
During the twice daily treatment periods, medicated drinking water should be the only water supply available. After all the medicated drinking water has been consumed, resume the supply of unmedicated water.

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

The intake of medicated drinking water depends on the clinical conditions of the animals as well as on the weather/temperature. In order to obtain the correct dosage, the concentration of the product should be adjusted accordingly.

For bulk medication twice daily: Half of the calculated total daily dosage of the product is scattered onto the surface of tepid water (approximately 20 °C) and stirred until evenly dispersed. Add the required amount of water to achieve a concentration of 0.6 g – 3.0 g of product per liter of drinking water and stir for 20 minutes to reach full solubility.

The administration of the medicated drinking water should be repeated every 12 hours.

Do not administer the product through a dosing pump (proportioner).
Do not use a water acidifier simultaneously.
Prepare a fresh solution prior to use.
After reconstitution the medicated drinking water has to be consumed within 24 hours.

Do not use the product with water systems composed of metal.

4.10 Overdose

In case of severe hypersensitive reactions, the treatment should be discontinued and corticosteroids and adrenaline should be administered. Treatment should be symptomatic in other cases of adverse reactions.

4.11 Withdrawal period(s)

Meat and offal: 1 day

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, amoxicillin and enzyme inhibitor
ATC vet. code: QJ01CR02

5.1 Pharmacodynamic properties

The product is a combination of a beta-lactam antibiotic with a beta-lactamase inhibitor which restores the potency of amoxicillin against strains producing beta-lactamases.

Amoxicillin is a bactericidal antibiotic, which acts by inhibiting the synthesis of bacterial cell wall during bacterial multiplication. It inhibits cross-linkage between the linear peptidoglycan polymer chains in the cell wall of Gram-positive bacteria. Broad-spectrum penicillin antibiotic amoxicillin is active also against a limited range of Gram-negative bacteria where the outer layer of bacterial cell wall is made up of lipopolysaccharide and protein.

There are three principal mechanisms of resistance to beta-lactam antibiotics: production of beta-lactamases, alteration of the PBP, diminished outer membrane permeation. One of the most important is inactivation of penicillin antibiotics by beta-lactamase enzymes produced by certain bacteria. These enzymes cleave the penicillin beta-lactam ring and render the penicillin drug inactive.
Clavulanic acid acts as inhibitor of bacterial beta-lactamases. It prevents destruction of the beta-lactam ring and penicillins by beta-lactamase enzymes. The reaction is irreversible and both the enzyme and the clavulanate are destroyed while the antibiotic activity is preserved.
The role of the clavulanic acid in the combination is not only to act as a beta-lactamase inhibitor. Clinical efficacy is dependent upon a number of factors including not only intrinsic antibacterial properties but also a positive interaction with host defenses. After exposure to an antibacterial compound, the resulting alteration of cell wall integrity and changes in bacterial expression of surface proteins, surface charges and hydrophobicity can influence the rate of phagocytosis and the extent of intracellular killing of bacteria. An effect on the rates of phagocytosis and the intracellular killing functions of polymorphonuclear leucocytes was demonstrated in experimental studies.
Susceptibility and resistance patterns can vary with geographical area and bacterial strain, and may change over time.
Minimum inhibitory concentrations of the combination amoxicillin/clavulanic acid were determined in different bacterial strains:

Species (no. isolates/year)	**MIC range (µg/ml)**	**MIC_{50} (µg/ml)**	**MIC_{90} (µg/ml)**
P. multocida (152/'09-'12)	0.12 – 1.0	0.25	0.5
A. pleuropneumoniae (158/'09-'12)	0.12 –2.0	0.25	0.5
S. suis (151/'09-'12)	≤0.03-8.0	≤0.03	0.06
E. coli (213/'09-'12)	0.5 – ≥128	8.0	8.0
C. perfringens (89/'09-12)	0.03-32.0	0.5	4.0
Salmonella Typhimurium *(127/'09-12)*	1.0 -32.0	8.0	16.0

5.2 Pharmacokinetic particulars

The plasma pharmacokinetic properties of amoxicillin and clavulanic acid are relatively similar. Both compounds are stable in the acidic environment of the gastrointestinal tract.
After oral administration, amoxicillin and clavulanic acid are readily absorbed.
The absorption following oral administration does not appear to be inhibited by presence of food in the alimentary tract.
Both compounds distribute to tissue fluids (pleural, synovial, peritoneal fluids) and inflammatory exudates but do not penetrate the blood-brain barrier well.
Both compounds are largely eliminated by renal excretion.
Elimination half-lives of amoxicillin and clavulanic acid are not significantly different (i.e. 0.73 and 0.67 h respectively).
Repeated treatment does not appear to result in any accumulation of amoxicillin and clavulanic acid.
Therapeutic concentrations of amoxicillin and clavulanic acid are achieved approximately one hour after dosing and may persist for several hours after administration.
The mean p.o. bioavailability was found to be 22.8 % for amoxicillin and 44.7 % for clavulanic acid.
The mean maximum plasma concentrations (C_{max}) of amoxicillin and clavulanic acid were 3.14 and 2.42 mg⁄ L, and these were reached after 1.19 and 0.88 h respectively.
These pharmacokinetic parameters were obtained after administration of a combination of 20 mg/kg amoxicillin and 5 mg/kg clavulanic acid given as a single oral dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Citric acid
Mannitol

6.2 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 7 days.
Shelf life after dilution or reconstitution according to directions: 24 hours.

6.4. Special precautions for storage

Store below 25 °C.
Keep the container tightly closed in order to protect from moisture.
Store in a dry place.

6.5 Nature and composition of immediate packaging

Pack size 500g.
Product in a low density polyethylene (LDPE) bag packed in another polyethylene bag with desiccant sachet included in a Polypropylene container closed with tamper-evident push down lid.
Alternatively, the product is packaged in a laminated aluminum bag with a zipper closure.

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

Elanco Europe Ltd.
Lilly House,
Priestley Road,
Basingstoke, RG24 9NL,
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

Country specific information

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Country specific information

10 DATE OF REVISION OF THE TEXT

Country specific information

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.