Veterinary Package Insert

TP-AMOCLAVU 500/125 MG/G WATER SOLUBLE POWDER

PRODUCT DESCRIPTION
White, off-white to slightly yellow colour powder, which contains 574mg of amoxicillin trihydrate (500mg of amoxicillin) and 149mg of clavulanate potassium (125mg of clavulanic acid) per gram in sachet.

PHARMACODYNAMICS & PHARMACOKINETICS
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 (Penicillin-binding proteins), 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.

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.

INDICATION
In pigs:

Treatment of clinical infections:

- Respiratory tract infections caused by *Actinobacillus pleuropneumoniae , Pasteurella multocida, Streptococcus suis* ,

- Gastrointestinal infections caused by *Clostridium perfringens , Escherichia coli.* and *Salmonella Typhimurium.*

In which the causative organisms are bacterial strains producing amoxicillin / clavulanic acid sensitive beta-lactamases, and for which clinical experience and / or sensitivity tests indicate that this combination is the treatment of choice.

TARGETED SPECIES
Pigs.

RECOMMENDED DOSAGE AND ADMINISTRATION
The product is recommended for oral administration in drinking water.

Administer 10 mg of amoxicillin (as trihydrate) and 2.5 mg of clavulanic acid (as potassium salt) per kg body weight twice daily, i.e 2 g of product per 100 kg body weight twice a day. Treat for 5 days.

For the calculation of the dose to be administered every 12 hours, the following formula can be used: Number of pigs x average live weight (kg) x frequency of administration (0.02 g product / kg live weight twice per day). Do not administer water other than medicated water during the twice-daily treatment period. After all medicated drinking

water has been consumed, resume the unmedicated water supply.

To ensure a correct dosage, the weight of the animals should be determined as accurately as possible; this will prevent any underdosing.

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

For bulk preparation twice a day: half of the calculated total daily product dose is dispersed in warm water (approximately 20 ° C) and stirred until uniform dispersion. Add the amount of water needed to reach the concentration of 0.6 g - 3.0 g of product per liter of medicated water and mix for 20 minutes until completely solubilized.

Administration of the medicated water should be repeated every 12 hours.

Do not administer the product with a dosing pump. Do not use simultaneously with an acidifier.

Prepare a new solution before each use. After reconstitution, the medicated drinking water must be consumed within 24 hours.

CONTRAINDICATIONS

Do not use in animals with known hypersensitivity to penicillin or other substances in 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 if there is known resistance to amoxicillin / clavulanic acid.

WARNINGS & PRECAUTIONS.

Special warnings for each target species
Any.

Special precautions for use in animals
The intake of the drug by animals may be affected by the disease. In case of insufficient intake of water, the animals must be treated parenterally.

The use of this product should be based on susceptibility testing and should take into account national and regional recommendations for the use of broad-spectrum antibiotics. Do not use in cases of narrow-spectrum penicillin-sensitive bacteria or amoxicillin monotherapy. Use of the product that does not comply with the recommendations of the insert may increase the prevalence of bacteria resistant to amoxicillin and clavulanic acid, and may reduce the effectiveness of other beta-lactam treatment due to the risk of cross resistance.

Based on the amoxicillin / clavulanic acid resistance reported in *E. coli* isolates in pigs in some countries, this product should only be used for the treatment of *E. coli* infections after completion. sensitivity tests.

This product should not be used as a method to control non-clinical Salmonella infections in swine herds. It is strictly recommended that this product not be used as a tool for salmonella control programs.

In case of a history of MRSA on a farm, the use of amoxicillin / clavulanic acid is inappropriate, given the risk of selection for MRSA.

The use of the product should be associated with the application of good practices, including good hygiene, adequate ventilation, and the absence of overcrowding.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Penicillins and cephalosporins can cause hypersensitivity (allergy) after injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may cause cross reactions to cephalosporins and vice versa. Allergic reactions to these substances can sometimes be serious.

Do not handle this product if you are allergic to these preparations or if you have been advised not to use them.

Handle this product with extreme caution to prevent exposure by taking all recommended precautions.

If you develop symptoms after exposure to the product, including rash, seek medical advice and show this warning to the doctor. Swelling of the face, lips or eyes, or breathing difficulties are more serious symptoms that require emergency medical care.

Avoid inhaling dust. Wear a disposable half-mask respirator or a non-disposable respirator with particulate filter.

Wear gloves during preparation and administration of medicated water. Wash exposed skin after handling the product or medicated water. Wash hands after use.

INTERACTIONS WITH OTHER MEDICATIONS

In general, penicillins can be inhibited by bacteriostatic antibiotics such as macrolides, sulfonamides and tetracyclines. No specific data concerning the association's interaction has been reported in the available veterinary scientific

literature. Neomycin administered orally inhibits the intestinal absorption of penicillin.

Penicillins can increase the effect of aminoglycosides.

PREGNANCY AND LACTATION

Laboratory studies in rats and mice have not demonstrated mutagenicity, teratogenic or foetotoxic effects. The safety of this veterinary medicinal product has not been established during pregnancy or lactation. The use of the drug should be done only after evaluation of the benefit / risk ratio established by the veterinarian.

ADVERSE EFFECTS

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

Anal and perianal erythema, anal irritation and diarrhea are rarely reported.

The frequency of adverse events is defined as follows:

- very common (adverse effects in more than 1 animal in 10 treated animals)

- frequent (between 1 and 10 animals out of 100 treated animals)

- uncommon (between 1 and 10 animals per 1000 treated animals)

- rare (between 1 and 10 animals out of 10,000 treated animals)

- very rare (less than one in 10,000 animals treated, including isolated cases)

OVERDOSE & TREATMENT

In case of severe allergic reactions, stop treatment and give corticosteroids and adrenaline. In other cases of adverse reactions, give symptomatic treatment.

WITHDRAWAL PERIOD

Meat & Offal: 1 day

MAXIMUM RESIDUAL LIMIT (MRL)

Substance/ Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
Amoxicillin	Muscle, liver, kidney, fat (all food producing species)	50
Clavulanic acid	Muscle, liver, kidney, fat	200

STORAGE CONDITION

Store below 30°C. Protect from direct sunlight.

SHELF LIFE

2 years.

After 1st opening, reconstitution or dilution, use within 24 hours.

PACKING

100g
1kg

THYE PHARMA SDN. BHD.
(manufacturer & product registration holder)
No.2 Lorong Industri Ringan Permatang Tinggi 8,
Kawasan Industri Ringan Permatang Tinggi,
14000 Bukit Mertajam,
Pulau Pinang.

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