For Veterinary Use Only.

Bioksal®%24

Concentrated Oral Solution

Veterinary Systemic Antibacterial

COMPOSITION

Bioksal 24% concentrated Oral solution is a clear, yellow colored, odorless viscous solution containing 200 mg sulphachloropyridazine and 40 mg trimethoprim in each ml.

PHARMACOLOGICAL PROPERTIES

Bioksal 24% concentrated Oral Solution is a concordant combination prepared on the base of sulphachloropyridazine and trimethoprim synergism intended for use in the treatment of infections arising from Gram negative and Gram positive microorganisms in broiler chicken and turkey and young ruminants in which rumination has not started yet.

Sulphonamides essentially displays bacteriostatic effect. Due to its similarity with PABA (Para-amino benzoic acid) in chemical structure sulphonamide competes on the basis of cell and consequently substitutes PABA and inhibits the normal metabolism of the bacteria. Generally, sulphonamides are used in combination with trimethoprim of other DAP (Diaminopyrimidine) derivatives. As a result of an inhibition performed by trimethoprim at another stage on bacterial basis, the growth of the bacteria is inhibited with double blockage. Its antimicrobial efficiency is based on the deterioration of the folic acid synthesis of its active ingredients required for the maintenance of the activity and reproduction of the bacteria. While sulphachloropyridazine inhibits the dihydropteroic acid step, trimethoprim inhibits the synthesis of tetrahydrofolic acid and forms the synergic bactericide activity. The following are the bacteria which are sensitive to sulphonamide+trimethoprim combinations:

-Gram positive aerobes: Staphylococcus aureus, Streptococcus sp., Actimomyces sp., Corynebacterium sp., Listeria monocytogenes, Erysipelothrix rhusiopathie,

-Gram negative aerobes: Enterobacteriaceae (E.coli, Salmonella sp., Klebsiella sp., Proteus sp., Yersinia sp.), Pasteurella sp., Haemophilus sp., Actinobacillus sp., Bordetellasp.,

-Anaerobes: Certain Clostridium sp., Bacteroides sp., Fusobacterium sp., Chlamydia sp., Actinomyces sp.,

Moderately sensitive bacteria are certain Mycobacterium sp. and certain Nocardia sp.. Rickettsia sp., Leptospira sp., Pseudomanas aeruginosa, Mycoplasma sp. are considered as resistant. Bioksal 24% Concentrated Oral Solution permeates into blood following absorption within an hour after oral administration and maintains its efficient concentration for 12 hours. The plasma half life of trimethoprim in calf is 11.3± 0.56 hours whereas that of sulphachloropyridazine is 13.1 ± 0.86 hours.

AREA OF USE/INDICATIONS

Bioksal 24% concentrated Oral Solution is used for bacteria originated diarrhea, coli septicemia, bronchopneumonia, polyarthritis, calf diphtheria and umbilical cord infections in Calf-sheep and goat; whereas for bacteria originated diarrhea, coli septicemia, air sac infections, salpingitis, cholera, coryza and staphylococci infections in broiler chickens and turkeys.

USAGE AND DOSAGE

Orally administered to calf, sheep, goats and broiler chickens and turkey in which rumen activity has not started yet. Bioksal 24% Concentrated Oral Solution is administered to domestic animals at the dose of 24-30mg active

ingredient/kg. It is acceptable to administer the solution to calf, sheep and goats by adding into water, milk or feed ensuring that 1 ml is for 10 kg live weight calculated on the basis of 0.1ml Bioksal 24%/kg live weight. The oral pomp in the 100 and 200 ml packages ejects 1ml per each press. The total daily dose should be splitted-up and administered in the morning and evening. the solution is administered for 5-7 days by observing the course of the infection. The practical dose is 100-125 ml/1000 kg live weight in broiler chicken and turkeys.

SPECIFIC CLINICAL INFORMATION AND SPECIAL WARNINGS FOR TARGET SPECIES:

It should not be used in calf, sheep and goats for the purpose of systemic treatment in which rumen activities have started due to its negative effects for rumen flora. Water restriction should not be applied for the animals during sulphonamide administration.

UNDESIRED/SIDE EFFECTS

Treatment safety is narrowed down in case of folic acid deficiency in patients. Also it has negative effects on hemopoietic system. In this case, reduction is observed in the number of platelets and erythrocytes whereas an enhancement in the number of megablasts. Hypersensitivity reactions may occur in certain animals. A crystal formation may be caused in the urinary system of all species. Therefore, this factor should be taken into consideration during the administration to severely dehydrated animals. In order to moderate the effects toward the kidneys a healthy hydration of the patient should be ensured and urinary alkalinization should be consulted when required.

It has toxic effects on homeopathic system and kidneys. It should be used with special care in newborn animals. Long term administration may lead to hepatoxicity and hypothyroidism. As sulphonamides enhance the bleeding tendency the treatment should be supported with vitamin K. Long term administration in dogs may result in keratoconjunctivitis. They may cause deterioration in blood table, non-septic polyarthritis and idiosyncratic intoxication characterized by skin eruption in all dog types, particularly in Doberman-Pinscher. Also diarrhea, vomiting, Steven Johnson Syndrome, hepatitis, anemia, impaired blood clotting, granulocytopenia, sulphemoglobinemia are included in the undesired effects.

DRUG INTERACTIONS

It may create an antagonist effect with local anesthetics such as procain, benzocain, butacain containing para-aminobenzoic acid (PARA), and with penicillin G. Also, the effects of sulphonamides are weakly antagonized by the B complex group vitamins such as nicotinamide, folic acid, choline and their primary substances such as glutamic acid, methionine and valine, and also isoleucine, arginine, lysine and some other amino acids. In case they are administered with or following diuretics (Thiazide and furosemid), they may cause a serious reduction in the number of platelets. This is particularly important for the patients with coronary failure and may lead to mortality.

SYMPTOMS OF OVERDOSE, PRECAUTIONS AND ANTIDOTE

Although trimethoprim is better tolerated in overdose, the administration of sulphonamides in overdoses for long periods, the insufficient level of fluid intake or dehydration state catalyzes crystalluria formation. The primary toxic effects of sulphonamides in kidneys are anorexia and depression. In more serious cases certain symptoms are seen such as haematuria, the presence of sulphonamide crystals in the urine, whitish hardening of the urethra hole, albuminuria, enhancement of urea and nitrogen values in the blood, renal colic, anuria and hydronephrosis. In case of crystallization formation in kidneys, infuse bicarbonate or Ringer lactate solution, develop alkalosis and

ensure its excretion through kidneys, and induce drinking plenty of water.

WARNINGS ON DRUG RESIDUES IN FOOD

Withholding period (WHP); Calf, sheep and goats and broiler chickens and turkeys should not be sent for slaughter during the treatment and before 14 days and 10 days, respectively, after the final administration. The drug should not be used in turkeys and chickens whose eggs are offered for human consumption.

CONTRAINDICATIONS

Antibiotics which are used for treatment should not be administered to ruminants in which rumen activity has started. It is contraindicated in animals with serious liver or renal failure, in cases of aciduria and in the animals with known sensitivity to sulphonamides.

GENERAL WARNINGS

Consult your veterinary surgeon before using and in case an unexpected effect is observed. Keep out of reach of children.

STORAGE CONDITIONS AND SHELF LIFE

Store at room temperature of (15-25℃) away from sun light. Shelf life is 2 years as of the production date.

COMMERCIAL PRESENTATION FORM INDICATING THE QUALITY AND QUANTITY OF THE PACKAGE

Offered for sale in 100, 200, 500,1000 and 2500 L high-density polyethylene, white colored plastic packages. 100 ml and 200 ml packages are placed in cardboard boxes with dosator attachable to the bottle that ejects 1 ml Bioksal oral solution in each pumping process.

PLACE AND CONDITIONS OF SALE

Sold with Veterinary Surgeon's prescription in pharmacies and veterinary surgeries. (VSP)

APPROVAL DATE OF PACKAGE INSERT 07.04.2008

MINISTRY OF AGRICULTURE AND RURAL AFFAIRS MARKETING AUTHORIZATION DATE – NO

07.04.2008-19/099

NAME AND ADDRESS OF MARKETING AUTHORIZATION OWNER:

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