Catofos® B9+B12

Injectable Solution

Stimulating organic phosphorus with hematopoietic vitamins

agrovetmarket s.a.

FORMULATION

Each 100 mL contains:

Phosphonous acid [1-(n-Butilamine)-1-methyl ethyl](Butaphosphan)..... 10 g

Vitamin B_9 (folic acid) ..... 1.5 g

Vitamin B_{12} (cyanocobalamin)..... 5 mg

Excipients.....q.s.ad.....100 mL

Each 100 mL of the solution contains 1.73 of phosphorous

GENERAL INFORMATION

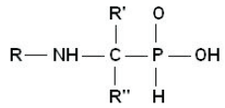
Catofos® B9+B12 provides a balanced combination of a high-available organic phosphorus (butaphosphan), vitamin B_9 (folic acid) and vitamin B_{12} (cyanocobalamin) in a single injection. Its components may be applied to animals presenting frank deficiency (or likely to contract it) or may be used as a preventive agent in high production or competition animals.

The three components of **Catofos® B9+B12** stimulates the metabolism as a whole, specially the energetic metabolism.

The deficiencies of phosphorus, vitamin B_{12} or folic acid may cause loss of energy, muscle functional deficiencies and low athletic performance. **Catofos® B9+B12** is the unique component able to fight these deficiencies within a single injection.

Butaphosphan - Organic Phosphorus

C_7-H_{18}-N-O_2-P



CAS Nº: 17316-67-5 MW: 179.20

The components of organic phosphorous, as presented in **Catofos® B9+B12**, influences on almost all the assimilation processes of the organism. In addition, they are involved in a countless number of enzymatic and anabolic reactions. Butaphosphan has a positive effect in the liver, musculature, energy metabolism and serum levels of phosphorus. It also increases the reaction characteristic of smooth muscle organs (digestive tract, uterus, etc.). Due to their purely physiological action, the organic compounds of phosphorus are far beyond tonics used to this date, and do not produce unexpected side effects.

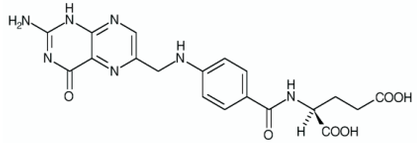
When the injections of **Catofos® B9+B12** are applied at regular intervals during training, they are a source of phosphorous which can be incorporated in high-energy phosphate complexes into body tissues, especially muscles.

Phosphorus is the most important mineral in the activity of the cell, and it is the major component of adenosine triphosphate (ATP)- the source of energy for cells, including working muscles.

Phosphorus is also the major structural mineral in the bone and acts as buffer in the blood and urine, maintaining the body pH.

Folic Acid (B_9) and cyanocobalamin (B_{12})

Folic Acid and cyanocobalamin (specially the last one) have a virtual participation in all the metabolic reactions.



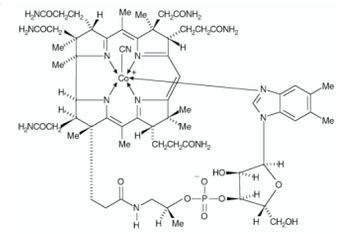
C_{19}-H_{19}-N_7-O_6

CAS Nº:59-30-3 MW:441.40

Due to its vitamin B_9 and vitamin B_{12} (folic acid) content, **Catofos® B9+B12** promotes the metabolism of carbohydrates and lipids in such a way that it influences positively on body growth, red cells formation and shows a protective action on the liver.

Cyanocobalamin (Vitamin B_{12})

$C_{63}H_{88}CoN_{14}O_{14}P$



CAS Nº: 13115-03-2 M.W.:1355.38

Vitamin B_{12} is one of the most important components for DNA synthesis. A lack of vitamin B_{12} blocks the maturing process and nuclear division. The halt of erythrocytes in the bone marrow causes megaloblastic (pernicious) anemia; therefore, vitamin B_{12} is an antianemic because it is involved in the synthesis of proteins and red cells. It is also a general stimulant of the organism and has neutrophic factors, nourishing nerve tissues.

Folic acid is essential for the production of red cells - cells carrying oxygen throughout the body to be used in the production of energy (ATP). Folic acid is a component of the vitamin B group, necessary for metabolic processes. The lack of folic acid causes megaloblastic anemia. At the end of the treatment with folic acid, a complete hematological remission will be achieved reaching a proper reticulocyte response, increase of erythrocytes, hemoglobin and ulterior disappearance of the megaloblastic hyperplasia of bone marrow.

PHARMACOKINETICS AND PHARMACODYNAMICS

Butaphosphan

Once injected, it is rapidly distributed throughout the blood serum covering the requirements of phosphorus at a muscle level. It is quickly excreted in the urine (70%) and a small percentage in the feces.

Butaphospan provides the necessary organic phosphorus to the body. Phosphorus is the most important mineral involved in the cell activity since it is the main component of adenosine triphosphate (ATP) - the source of energy for cells, including working muscles.

Phosphorus is a major structural mineral of bones and acts at the blood level, maintaining the body pH.

When there is permanent athletic functioning, the body requires great quantities of energy to produce muscle contraction. Energy is extracted from the oxygen, carbohydrates, fats and proteins by cells. Once in the cells, they chemically react to oxygen under the influence of enzymes, thus producing energy. This energy is used to form ATP.

ATP is the ultimate source of energy for all muscle contraction. It contains three phosphate groups. During exercise, ATP becomes ADP. This reaction produces great quantities of energy, thus fueling muscular contraction. Phosphates stored in muscles in the form of creatine phosphate serve as a reserve energy store.

Cyanocobalamin (vitamin B_{12})

Vitamin B_{12} belongs to the group of hydrosoluble vitamins. Cyanocobalamin may be rapidly absorbed when administered by intramuscular or subcutaneous route, reaching a maximum blood concentration after 4 or 5 hours. It is stored in the liver and eliminated by glomerular filtration in the urine.

Today, it is known that vitamin B_{12} is related to a series of substances called cobalamins, which contain cobalt in their molecule. In turn, cobalamins are derived from a fundamental substance called cobamide which contains trivalent cobalt.

Strictly speaking, vitamin B_{12} is a cyanocobalamin containing a cyanide group attached to the cobalt, meanwhile the hydroxocobalamin contains a hydroxyl group (also attached to the cobalt); both the cyanocobalamin and the hydroxocobalamin have the same therapeutic activity. In nature, the unique original source is found in certain microorganisms that grow in the soil, water or intestinal lumen. The man depends on exogenous sources of vitamin B_{12} because what he synthesizes in the colon is not available to be absorbed; therefore, it is obtained when animal subproducts are ingested.

Although it is widely known that this vitamin takes part in intracellular metabolic routes, the exact role of Vitamin B_{12} at a metabolic level has not been yet determined, but it is essential for cell growth and replication, in lipid metabolism (weak lipotropic action promoting the mobilization of fat reserves), DNA formation (essential component for the animal growth and development) and normal maturing of erythrocytes. For that reason, its therapeutic action is important for macrocytic or megaloblastic anemia, providing the required antianemic factor necessary for a normal erythropoiesis. Likewise, it is known that vitamin B_{12} is required for myelin synthesis and to maintain the integrity of the neuronal tissue.

Cyanocobalamin and hydroxocobalamin are easily absorbed when administered by intramuscular or subcutaneous route. When administered orally, normal individuals may absorb it at 70%. In order to cause ileum absorption, the "Castle's intrinsic factor" is necessary, which when combined with vitamin B_{12} it can be easily absorbed as a B_{12} complex.

Intracelular vitamin B_{12} can be found as two active coenzymes: methylcobalamin and deoxyadenosylcobalamin. The second one is a co-factor of mitochondrial mutase which catalyzes isomerization between methylmalonyl CoA and succinyl CoA, important reaction in the metabolism of carbohydrates and lipids. The methylcobalamin supports methionine synthetase activity, which is essential for folate metabolism. The folate-cobalamin interaction is essential for the synthesis of purines and pyrimidines, and therefore DNA. The methionine synthetase reaction is highly responsible for controlling the recycling of folate cofactors, the maintenance of intracellular contractions of folypolyglutamates and, through the synthesis of methionine and its product, for the s-adenosylmethionine and the maintenance of several methylation reactions. When there is a deficiency of vitamin B_{12} or folate, the decrease of methionine synthesis and s-adenosylmethionine interfere with protein biosynthesis, with several methylation reactions and with the synthesis of polyamides. Active coenzymes methylcobalamin and deoxyadene-sylcobalamin are essential for cell proliferation and replication.

Methylcobalamin is necessary for the formation of methionine and its methylation derivative and for polyamine synthesis. Active coenzymes methylcobalamin and deoxyadene-sylcobalamin are essential for cell proliferation and replication. Methylcobalamin is necessary for the formation of methionine and its s-adenosylmethionine from homocysteine. The isomerization of l-methylmalonil CoA to succinil CoA requires deoxyadenosylcobalamin.

Folic Acid (Vitamin B_{12})

Folic acid is an essential component of animal diet. The lack of it causes a defective DNA synthesis in the whole cell aiming at reaching chromosome replication and division. Due to the fact that tissues with greater index of cell renewal present more alterations, the hematopoietic system is especially sensitive to folic acid deficiency. Folic acid is rapidly absorbed in the gastrointestinal tract, especially close to the small intestine, the duodenum. There is a small absorption in the distal part of jejunum and practically not a single one at the distal ileum.

In the epithelial cells, the polyglutamates are reduced to dihydrofolates and tetrahydroholates. They bind to plasmatic proteins or to non-methyladed analogues and are transported in the form of methyltetrahydrofolate. The plasmatic levels range from 3 to 21 milimicrograms/mL and straight forwardly reflect the dietetic ingestion.

Erythrocyte folate (normal, 160 to 640 milimicrograms/mL in whole blood corrected by hematocrit value of 45%) is a safer indicator of the state of folate in tissues. Its absorption requires the transportation and the action of a pteroyl-gamma-glutamyl carboxypeptidase associated to mucous cells membranes. The duodenum mucus and the proximal jejunum are rich in dihydrophosphate reductase, and are capable to methylate almost all the absorbed phosphate (see metabolism).

The availability by oral or injectable route varies from 49.3 to 96.7%. C_{max} and T_{max} vary depending on the administered dose. The administration of 5 gm by oral route during 9 days produced an average C_{max} of 243 ± 33 ng/ml at T_{max} of 2.24 hours. Other

reports state that the necessary time to reach maximum concentration (T_{max}) is between 60 and 90 minutes. Once absorbed, the phosphate is rapidly distributed throughout the tissues as methyltetrahydrofolate attached to plasmatic proteins. It is distributed throughout the body tissues and mainly to the liver (50%) and is stored in cells as polyglutamates. It is concentrated in the central nervous system.

The folate has enterohepatic circulation and passes to breast milk. Therapeutically administered folic acid enters in great quantities and unaltered to portal circulation, because it is a poor substrate for the reduction of dihydrofolate reductase. It is converted to its metabolically active form 5-methyltetrahydrofolate in the plasma and especially in the liver.

Around 20% of folate (natural form) ingested is eliminated without absorbing, along with 60 to 90 mcg. non reabsorbed of the bile. The oral ingestion and the enterohepatic cycle of the vitamin maintain a permanent provision of methyltetrahydrofolate. Folate has an intestinal first-pass metabolism, meanwhile the synthetic form (folic acid) concentrate it mainly in the liver, which reduces and methylates the folic acid actively, take it to the bile to be reabsorbed in the intestine and then take it to the tissues (the importance of this enterohepatic cycle is evidenced in studies performed on animals).

Folate metabolites are excreted in the urine and the excess folate in the body is excreted unaltered in the urine. Folate is also eliminated through breast milk in normal quantities to cover the requirements of the offspring. During pregnancy and breastfeeding, around 50 ng/day of folic acid is excreted in breast milk. Bile excretion after administering folic acid by oral route is found in a range from 15 to 400 ng/mL with the highest concentration after 120 minutes of its administration. Folic acid is part of Vitamin B, which mode of action consists in intervening in several metabolic processes, including the synthesis of purines and pirimidines, favoring the DNA synthesis. Once the substance gains entry into a cell through a process of receptor mediated endocytosis, the methyltetrahydrofolate acts as a methyl donor for the formation of methylcobalamin in the conversion of homocysteine to methionine. This reaction requires vitamin B_{12} as cofactor.

Folic acid and those of its kind and unstable compounds, 50% to 90% may be destroyed through boiling and canning. At a clinical level, the earliest sign of folic acid deficiency is the megaloblastic anemia, in which the defective DNA synthesis produces a morphological abnormality characteristic in bone marrow precursor cells.

This defect produces abnormal macrocytic erythrocytes, where the patient develops severe anemia. Within the first 48 hours from the beginning of the therapy, the megaloblastic erythropoiesis disappears and meanwhile erythropoiesis is being performed, the plasma concentration of iron regulates. The reticulocytes count starts to elevate the second or third day and reaches a maximum level between the fifth and seventh day (reflecting the proliferating state of the marrow). The hematocryte starts to elevate during the second week of the therapy. The exact mechanism through which the folic acid prevents the defective neural closure is unknown, but it is considered that folic acid corrects the abnormal homocysteine metabolism. Folate deficiency has been associated to the following disorders: abortion, placental abruption, neural tube defects, neuropathy and psychiatric alterations.

The high concentrations have been related to teratogenic effects (ventricular septal alterations, defective neural tube closure), as well as to cardiovascular diseases due to affectation of coagulation systems and of vascular endothelial integrity.

TARGET SPECIES
Formulation developed and exclusively tested to be used in cattle, horses, swine, camelids, sheep, goats, dogs, cats and poultry.

THERAPEUTIC INDICATIONS
Catofos® B9+B12 is indicated when a phosphorus supplement is required to improve the condition of the animal and optimize its production, provided that the concomitant administration of the 2 vitamins present in the formula is required.

Specific cases include:
- Acute metabolic disorders and diseases.
- Hypocalcaemia (related to calcium therapy), loss of appetite and breast feeding performance, acetonemia (related to specific therapy), physical exhaustion, stress conditions, offspring weaknesses and diseases, joint disorders and skeletal muscles (related to specific treatment), intoxications (related to specific treatment), cannibalism in birds and bird flu hysteria.
- Chronic diseases and chronic metabolic disorders.
- Development disorders, cachexia, malnutrition, parasitism (related to antiparasitic drugs), lower productive and/or physical performance, nerve disorders (related to specific therapy), excess of work, fatigue and physical exhaustion.
- Anemia: Primary: macrocyclic or megaloblastic, providing the necessary antianemic factor for normal erythropoiesis; anemia arising from serious parasitism, hemorrhages and other secondary factors.
- Prevention of reproductive diseases and other disorders.
- Prevention of metabolic diseases related to delivery (in line with the prevention of reproductive and fertility problems). We can mention: hypocalcemia, ketosis, ovarian cyst. Deficiencies of **Catofos® B9+B12** components have demonstrated to cause abortion, placental abruption, neural tube defects, neuropathy and psychiatric alterations.
- Treatment of healthy animals.
- To improve the muscle performance in race horses, fighting cocks, fighting bulls, dogs and other amusement and sports animals; to improve the reproductive potential of males and females; in dairy cows submitted to intense work of high production; to improve the general condition of animals; and to prepare animals to participate in expositions.

ROUTE OF ADMINISTRATION AND DOSAGE
To be administered by intravenous, intramuscular and subcutaneous route. Shake well before using:

* Cattle and horses	10-25 mL
* Dairy cows before delivery	20 mL in the 6th and 4th weeks before delivery.
* Calves, colt	5-12 mL
* Sheep, camelids and goats	2.5 – 5 mL
* Swine	2.5- 10 mL
* Piglets, pigs	1 – 2.5 mL
* Dogs	0.5 – 5 mL
* Cats	0.5 – 1 mL
* Hens, chickens, fighting cocks	0.5 – 1 mL

Volumes over 20 mL shall be divided into two points of application if applied by intramuscular or subcutaneous route.

If necessary, the injection may be applied on a daily basis. In cases of chronic problems, administer several times as the vet may deem convenient with intervals from 3 to 7 days half of the above indicated dose.

In healthy animals apply half of the above indicated doses.

ADDITIONAL PRECAUTIONS FOR THE ADMINISTRATION
Sterilize the injectable equipment with boiling water. Avoid using strong disinfectants in equipments.
Maintain cleanliness at all time.
Keep sharp and clean needles. Frequently replace them.
Use needles with the required length and caliber. For subcutaneous administration use the shortest needle (not longer than ½").
Avoid injectable administration in animals in rainy seasons or dusty conditions as possible.
Intramuscular administration in production animals shall be performed in the center of the neck. Subcutaneous injections shall be applied under the skin in the upper part of the neck behind the ear.

OBSERVATIONS
Do not pour in the same syringe or container any other substance not related to the product.
Keep it out of reach of children.
Follow asepsis and antisepsis indications before and after the application of the product.
Agrovet Market S.A. is not responsible for any damages that may arise from the improper use of the product.

CONTRAINDICATIONS
None when applied at the suggested dosage.

SIDE EFFECTS
None when applied at the suggested dosage. In animals sensitive to folic acid and/or cyanocobalamin or hydroxocobalamin may cause hypersensitivity or allergies and anaphylactic shock.

ALTERATIONS IN THE RESULTS OF LAB TESTS
Folic Acid
Folate reserves in the body are very limited. Serum levels of folic acid under 5 milimicrograms suggest the diagnosis, which may be confirmed through low levels of erythrocyte folate (normal values 160 to 640 milimicrograms).

DRUG INTERACTIONS
Folic Acid
Folic acid antagonist: methotrexate, pyrimethamine, triamterene. Compounds of trimethoprim, anticonvulsives (possibly increasing convulsions), cortisone and cloramphenicol.

Cyanocobalamin
The cloramphenicol reduces the hematopoietic response of vitamin B_{12}. Vitamin C may inactivate the vitamin B_{12}. H_2 blockers, the omeprazole, the colchicine, the neomicine, preparations of prolonged release potassium, aminosalicitic acid and its salts may decrease the absorption of vitamin B_{12}.

SAFETY – RESTRICTIONS OF USE DURING PREGNANCY AND LACTATION
Butaphosphan has an extremely low level of toxicity, which is evidenced in the intravenous DL50 in mice of 10,000 mg/kg, equal to 100 mL of **Catofos® B9+B12**, per kg. There are no restrictions to the indicated doses, however, we suggest you to have the application supervised by a vet.

It may be applied at any time of pregnancy (although the last three months must be handled very carefully and under professional supervision). It does not affect the fertility, pregnancy, fetal formation or the reproductive performance of studs.

WITHDRAWAL PERIOD
Milk: None
Meat: None

STORAGE
Keep the container within a cardboard box, in a cool and dry place, protected from light exposure. Do not expose to extreme temperatures. Keep out of the reach of children.

COMMERCIAL PRESENTATION
Vial x 20 mL, 50 mL, 100 mL and 250 mL

Reg. SENASA Perú: F.01.01.N.0552; Reg. Bolivia: 001500/06;
Costa Rica: Reg. MAG PE4-67-02-3402; Reg. Ecuador: 10AB-9520-SESA-U;
Reg. El Salvador: 2006-09-3504; Reg. Guatemala: 19-29-191-10983;
Reg. Honduras: PF-3882; Reg. Nicaragua: 6887-435-X;
Reg. Panamá: RF-3545-06; Reg. Rep. Dominicana: 5999;
Reg. Venezuela: MAT-SASA-M.I 12.257

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