



ORAL CYCLOMUN®

REGISTRATION NUMBER Q-0790-140

Ciclosporine 10%

FORMULATION:

Ciclosporine 100 mg

Vehicle q.s. 1 mL

Dosage size: 50 mL



Ciclomun oral is an oral immunosuppressive solution.

Indications:

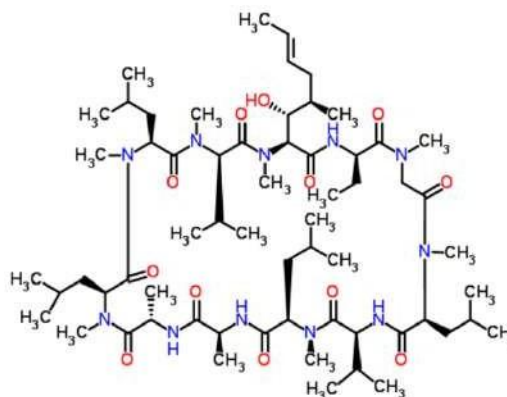
Immunosuppressant, auxiliary in the treatment of atopic dermatitis, anal furunculosis. For the treatment of autoimmune diseases such as immune-mediated hemolytic anemia, cutaneous lupus.

It is recommended as a long-term treatment, especially when chronic inflammatory processes such as allergies or autoimmune skin diseases have developed, such as: sebaceous adenitis, unknown feline alopecia, chronic resistant pemphigus, idiopathic facial dermatitis and other autoimmune diseases such as autoimmune thrombocytopenia, autoimmune hemolytic anemia, meningoencephalitis of unknown etiologies, inflammatory bowel disease, among others.

Cyclosporine, also known as Cyclosporin A, is an orally active immunosuppressive agent Cyclosporine, a cyclic peptide composed of 11 amino acids obtained from a fungus (*Tolypocladium inflatum* Gams).

Action mode:

Cyclosporine induces immunosuppression by inhibiting the first phase of T cell activation. In this phase, transcriptional activation of some products occurs (interleukins IL-2, IL3 and IL-4, TNF-alpha and interferon gamma) that allow the cell progresses from the G0 phase to the G1 phase. it does not reduce hematopoiesis and does not alter the functioning of phagocytes.



It also does not act on glucocorticoid receptors. Cyclosporine binds to an immunophilin called cyclophilin (immunophilins are proteins distributed throughout all cellular compartments that bind immunosuppressants). Next, the cyclophilin-cyclosporine complex binds to the **phosphatase calcineurin**, an enzyme that is activated by calmodulin and calcium. Calcineurin catalyzes the dephosphorylation reactions necessary for the transcription of lymphokines and therefore, the activation of T cells. For this reason, the inhibition of calcineurin results in the blockage of nuclear factor transduction signals of the cells T activated. Proteins whose transcription is inhibited include interleukin-4, CD40 ligand, and those required for Y cell activation (IL-2 and interferon gamma). Cyclosporine does not affect the production of antibodies that are independent of T cells.

In any case, the immunosuppressive effect of Cyclosporine is selective on the T₄ lymphocyte.

Pharmacokinetic Properties

The absorption of cyclosporine is very varied, it can be between 23-45%, it should not be given with food since its absorption decreases up to 20%, it is absorbed in the duodenum. The time until the maximum blood level (T_{max}) of cyclosporine that is achieved is 1.2 +/- 0.3 hours. Cyclosporine is widely distributed in all tissues, including skin with a stable volume of distribution of 3.5 L/kg. In the blood, 33-47% is in plasma, 4-9% bound to lymphocytes, 5-12% bound to granulocytes and 41-58% bound to erythrocytes. At high concentrations, the binding capacity of leukocytes and erythrocytes becomes saturated. In plasma, approximately 90% is bound to proteins, primarily lipoproteins.

Cyclosporine is converted to approximately 15 metabolites. Evidence suggests that extensive metabolism occurs primarily via the cytochrome P-450-dependent monooxygenase system in the liver. The main catabolic pathways are mono- and dihydroxylation as well as N-demethylation in various parts of the molecule. Medications known to inhibit or stimulate the cytochrome P-450-dependent enzyme system have been determined to increase or decrease the level of cyclosporine. All metabolites that have been identified to date contain the intact peptide of the parent drug. No metabolite has more than 10% of the immunosuppressive activity of the parent drug. Excretion occurs primarily via the biliary tract with only 6% of the oral dose via urine and only 0.1% of unchanged cyclosporine being excreted in the urine.

There is great variability in the data reported on the terminal half-life of cyclosporine from the evaluation or trial applied and the target population. The terminal half-life extended from 6.3 hours in healthy subjects to 20.4 hours in patients with severe liver disease. In felines it is 6.8 hours or up to 40 hours in healthy felines. The terminal half-life in patients with kidney transplants was approximately 11 hours (range of 2-25 hours).

Dosage and route of administration: Oral

For the treatment of atopic dermatitis: The recommended daily oral dose of cyclosporine is 5 mg/kg body weight, equivalent to 1 mL per 20 kg body weight (0.1 ml per 2 kg body weight) for 30 days or until observed the decrease in clinical signs. The dose can be modified at the discretion of the Veterinarian and the clinical response.

The dose can be divided into 2 doses per day.

Administer **CICLOMUN ORAL®** by oral route of administration, without food, at least 2 hours before or after feeding.

Once the clinical signs of atopic dermatitis are satisfactorily controlled, **CICLOMUN ORAL®** can be administered every 3 to 4 days. The veterinarian will adjust the frequency of administration to the response obtained at that time.

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In the treatment of perianal fistulas, 5 - 7.5 mg/kg every 12 hours is recommended, until there is improvement.

As an auxiliary in the treatment of furunculosis: It is recommended to start with 10 mg/kg/day complemented with ketoconazole 5 mg/kg daily for 2 days, rest is allowed and the plasma levels of cyclosporine are reviewed, which should be maintained at 240-400 ng/mL, it should be continued for up to 8 weeks, but the plasma concentration of cyclosporine should be checked weekly.

For chronic asthma in felines, it is recommended to start with a dose of 10 mg/kg every 12 hours, and it is recommended to check plasma levels weekly, maintaining them at 500 to 1000 ng/mL.

Precautions

Side effects such as vomiting, diarrhea and gingival hypertrophy may be observed during prolonged treatment greater than 10 mg/kg daily. Clinical improvement is usually seen in course of 4 weeks. If no response is obtained within the first 8 weeks, discontinue treatment. Treatment for at least 12 weeks or up to 4 weeks after lesion resolution is recommended to minimize recurrence. Concurrent antibiotics or analgesia may be required. Recurrence can be managed with another course of treatment with **CICLOMUN ORAL®**.

Contraindications:

- Known hypersensitivity to cyclosporine.
- In patients with abnormal kidney or liver function or kidney failure.
- In pregnant animals, since embryotoxicity and fetotoxicity have been seen in laboratory animals
- In lactating animals, it must be handled with great care, since it is eliminated through milk.
- In uncontrolled infections or any type of malignant tumor.

Drugs that reduce cyclosporine concentrations

Barbiturates, carbamazepine, oxcarbazepine, phenytoin; intravenous sulfadimidine, rifampicin, orlistat, Hypericum perforatum (Hypericum or St. John's wort), ticlopidine, sulfinpyrazone, terbinafine.

Drugs that increase cyclosporine concentrations

Antibiotics of the macrolide family (e.g. azithromycin, and clarithromycin), ketoconazole, fluconazole, itraconazole, voriconazole, diltiazem, nicardipine, verapamil, metoclopramide, danazol, methylprednisolone (high doses), allopurinol, amiodarone, cholic acid and derivatives, protease inhibitors, imatinib, colchicine, nefazodone.

Ketoconazole is used to maintain high levels of cyclosporine at a dose of 2.5 to 5 mg/kg, which is recommended to be given with food to avoid digestive problems.

Drug interactions

Those that cause a potential increase in nephrotoxicity during coadministration of a drug that may produce nephrotoxic synergy, renal function (particularly serum creatinine) should be closely monitored. If renal dysfunction is significant, the dose of the co-administered medication should be reduced or another therapeutic option should be considered. Caution should be exercised when using cyclosporin with other drugs that produce nephrotoxic synergy such as: aminoglycosides (gentamicin and tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (sulfamethoxazole), non-steroidal anti-inflammatory drugs (incl. diclofenac, naproxen, sulindac), melphalan, histamine H2 receptor antagonists (e.g. cimetidine, ranitidine), methotrexate.

Coadministration with tacrolimus should be avoided due to the increased risk of nephrotoxicity.

In people, it has been determined that the co-administration of diclofenac and cyclosporine causes a significant increase in the bioavailability of diclofenac, the consequence of which may be reversible renal dysfunction, but it must be remembered that in canines and even more so in felines, diclofenac is not easily metabolized, so this combination is not recommended. This does not happen with other non-steroidal anti-inflammatory drugs (NSAIDs). In the case of NSAIDs with significant first-pass metabolism (e.g. diclofenac), the dose should be lower than that which would be used in patients not treated with cyclosporine.

Interactions that cause increased concentrations of other drugs: Cyclosporine is also an inhibitor of the CYP3A4 form and of P-glycoprotein (drug efflux transporter protein) and may increase plasma concentrations of co-administered drugs that are substrates of these drugs. Cyclosporine may reduce the clearance of digoxin, colchicine, prednisolone

Pregnancy and lactation: Its use is not recommended. In rabbits and rats, it has been teratogenic and hembryotoxic, and part of its elimination is through milk.



OVERDOSE: The oral LD₅₀ of cyclosporine is 2329 mg/kg in mice, 1480 mg/kg in rats and > 1000 mg/kg in rabbits, while the intravenous LD₅₀ is 148 mg/kg in mice, 104 mg/kg in rats and 46 mg/kg in rabbits.

Treatment: General supportive measures and symptomatic treatment should be undertaken in all cases of overdose. Forced emesis and gastric lavage may be useful in the first hours after ingestion. Cyclosporine is not significantly dialyzable and cannot be removed by charcoal hemoperfusion.

Warnings AND/OR Restrictions:

Do not use in cases of hypersensitivity to cyclosporine. Do not administer to canines less than six months old or weighing less than 2 kg. Do not use in felines under 1.4 kg. Do not vaccinate with live viruses during treatment and up to two weeks before and after treatment. Once opened, the product is stable for up to 6 months. Keep in a cool, dry place in a range within 15-30°C and protected from direct sunlight. Keep out of reach of children and pets. Avoid contact with hands and eyes. Discontinue immediately if adverse reactions occur. Product for exclusive use in Veterinary Medicine

SPECIES: Canines and Felines.

Dosage size: 50 mL

Consult a Doctor of Veterinary Medicine.
(Exclusive information for Doctors of Veterinary Medicine).
Responsible for content: Technical Department.