HOSPIMAX
Maximising Life

Grafsporin™

Cyclosporine 25 mg, 50 mg,100 mg Capsules

Time Tested Immunosuppressant

Grafsporin

Product Description:

- Grafsporin25: Each soft gelatin capsule contains CyclosporineI.P.25 mg
- Grafsporin 50: Each soft gelatin capsule contains CyclosporineI.P.50 mg
- Grafsporin100: Each soft gelatin capsule contains CyclosporineI.P.100 mg

General Information:

Cyclosporine is a calcineurin inhibitor known for its immunomodulatory properties that prevent organ transplant rejection and treat various inflammatory and autoimmune conditions. It is isolated from the fungus *Beauveria nivea*.It has been approved for use by the FDA in 1983.

Indication & Usage:

Solid Organ Transplantation

Grafsporincapsules are indicated inthe prevention of graft rejection following solid organ transplantation and in the treatment oftransplant rejection in patients previously receiving other immunosuppressive agents.

Bone Marrow Transplantation

Grafsporincapsules are indicated inthe prevention of graft rejection following bone marrow transplantation and the prevention ortreatment of graft-versus-host disease (GVHD).

Psoriasis

Grafsporincapsulesare indicated for the treatment of severepsoriasis in patients for whom conventional therapy is ineffective or inappropriate.

Rheumatoid Arthritis

Grafsporincapsules are also indicated for the treatment ofsevere active rheumatoid arthritis in patients for whom classical slow-acting antirheumaticagents are inappropriate or ineffective.

Nephrotic Syndrome

Grafsporincapsules are indicated in adults and children forsteroid dependent and steroid resistant nephrotic syndrome due to glomerular diseases such asminimal change nephropathy; focal and segmental glomerulosclerosis, or membranousglomerulonephritis. Grafsporincan be used to induce remissions and to maintain them. It canalso be used for maintenance of steroid induced remissions, allowing withdrawal of, or reductionin the dosage of steroids.

DOSAGE AND ADMINISTRATION

- **Solid organ transplantation**
  - Treatment to be initiated within 12 hours prior to surgery
  - **Starting Dose**: 10 to 15mg/kg given in two divided doses, 12 hours apart for 1-2 weeks post-operatively
  - **Maintenance Dose:** Maintenance dose is about 2 to 6 mg/kg given in two divided doses.
  - When given with other immunosuppressants (e.g. with corticosteroids or as part ofa triple or quadruple drug therapy), lower doses (e.g. 3 to 6 mg/kg given in two divided doses 12hours apart for the initial treatment) may be used.

- **Bone marrow transplantation**
  - 12.5 – 15 mg/kg given intwo divided doses, 12 hours apart, and should be continued for at least 3 months (and preferablyfor 6 months) before the dose is gradually decreased to zero by one year after transplantation.
- **Psoriasis**
  - Dose Titration for Induction of Remission, the recommended initial dose is 2.5 mg/kg/day givenin two divided oral doses, 12 hours apart.If there is no improvement after one month, the daily dose may be gradually increased. Doseadjustments should be made in increments of 0.5 to 1.0 mg/kg/day body weight per month andtotal daily dose, depending on monitoring of drug tolerance, should not exceed 5 mg/kg/day.
- **Rheumatoid Arthritis**

  For the first 6 weeks of treatment, the recommended initial dose is 2.5 mg/kg/day orally given intwo divided doses, 12 hours apart. If necessary, the daily dose may then be increased graduallyas **tolerability**but, depending onmonitoring of drug tolerance, should not exceed 5 mg/kg/day.

- **Nephrotic Syndrome**

- In patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg/day. If therenal function is normal (except for proteinuria), the recommended initial dose is given BID intwo divided oral doses, 12 hours apart:

- 3.5mg/kg/day for adults
- 4.2mg/kg/day for children

Mechanism of action:

Cyclosporine is a potent immunosuppressive agent with a narrow therapeutic range which hasbeen shown in man to prolong the survival of allogenic transplants.

Cyclosporine is a calcineurin inhibitor that inhibits T cell activation.Its binding to the receptor cyclophilin-1 inside cells produces a complex known as cyclosporine-cyclophilin. This complex subsequently inhibits calcineurin, which in turn stops the dephosphorylation as well as the activation of the nuclear factor of activated T cells (NF-AT) that normally cause inflammatory reactions. NF-AT is a transcription factor that promotes the production of cytokines such as IL-2, IL-4, interferon-gamma and TNF-alpha, all of which are involved in the inflammatory process. Specifically, the inhibition of IL-2, which is necessary for T cell activation or proliferation, is believed to be responsible for cyclosporine's immunosuppressive actions.In addition to the above, the inhibition of NF-AT leads to lower levels of other factors associated with T helper cell function and thymocyte development.

Pharmacokinetic:

Absorption: It provides improved dose linearity in cyclosporine exposure(AUC_B), a more consistent absorption profile and less influence from concomitant food intakeand from diurnal rhythm. These properties combined yield a lowerwithin-patient variability in pharmacokinetics of cyclosporine and a stronger correlation betweentrough concentration and total exposure (AUC). As a consequence of theseadvantages, the time schedule of administration does not require that meals beconsidered. In addition, Grafsporin produces a more uniform exposure to cyclosporinethroughout the day and from day to day on a maintenance regimen.
The absorption of cyclosporine occurs mainly in the intestine.Absorption of cyclosporine is highly variable with a peak bioavailability of 30% sometimes occurring 1-8 hours after administration with a second peak observed in certain patients.The absorption of cyclosporine from the GI tract has been found to be incomplete, likely due to first pass effects.Cmax in both the blood and plasma occurs at approximately 3.5 hours post-dose.

Distribution:

The distribution of cyclosporine in the blood consists of 33%-47% in plasma, 4%-9% in the lymphocytes, 5%-12% in the granulocytes, and 41%-58% in the erythrocytes. The reported volume of distribution of cyclosporine ranges from 4-8 L/kg. It concentrates mainly in leucocyte-rich tissues as well as tissues that contain high amounts of fat because it is highly lipophilic.

About 50% of the administered dose is taken up by erythrocytes while about 34% is bound to lipoproteins.

Metabolism:

Cyclosporine is primarily metabolized by the hepatic mono-oxygenase multiple forms ofcytochrome P-450. Metabolites and unchanged drug are excreted into bile.Since cyclosporine is primarily eliminated by hepatic metabolism, its clearance is impaired inpatients with liver disease and in liver transplant recipients in the early post-operative phase. Ona bodyweight basis, pediatric patients appear to clear the drug more rapidly as compared toadults. Therefore, children may require more frequent and larger doses of cyclosporine toachieve therapeutic blood levels. The metabolism of cyclosporine is also significantlyinfluenced by changes in the activity of the hepatic drug metabolising system; for example, theinduction of the cytochrome P-450 enzyme system by barbiturates, phenytoin and rifampicinmarkedly accelerated the elimination of cyclosporine, potentially causing inadequateimmunosuppression and acute rejection.

Excretion:

The major route of elimination of cyclosporine is through the bile. Less than 1 % of anadministered dose of cyclosporine is excreted in the bile as parent drug. More than 44% of acyclosporine dose appears in the bile as metabolites when measured by RIA.

Enterohepatic recirculation of parent drug is thus very low. Hepatic functional impairment canreduce total clearance of parent drug and/or metabolite. Renal excretion is a minor pathway withonly 6 % of an oral dose excreted in urine; only 0. 1 % is excreted as unchanged drug.

Use in Specific Population:

Pregnancy: However, there are no adequate data in pregnant women and, therefore, should not be used during pregnancy unless the expected benefit to themother outweighs the potential risk to the foetus.

Nursing Women: Cyclosporine passes into breast milk. Mothers receiving treatment with cyclosporineshould not breast feed. Because of the potential of cyclosporine to cause serious adverse drug reactions in breastfed newborns/infants, a decisionshould be made whether to abstain from breast-feeding or to abstain from using the medicinaldrug, taking into account the importance of the medicinal product to the mother.

Fertility: There is a limited data on the effect of cyclosporineon human fertility. No impairment in fertilitywas demonstrated in studies in male and female rats

Renal Impairment: Cyclosporine undergoes minimal renal elimination and its pharmacokinetics is not affected byrenal impairment. However, due to itsnephrotoxic potential, a careful monitoring of the renal functionis recommended

Hepatic Impairment: Cyclosporine is extensively metabolized by the liver. The terminal half-life varied between 6.3hours in healthy volunteers to 20.4 hours in severe liver disease patients. Dose reduction may be necessary in patients with severeliver impairment to maintain blood levels within the recommended target range

Paediatric Use: Cyclosporineis not recommended in children of non-transplant indications other than nephroticsyndrome. Pediatric patients have similar adverse drug reaction profiles as those in the adults.
Clinical studies in patients with nephrotic syndrome have included children from one year of ageusing standard cyclosporine dosage. In several studies, pediatric patients required higher doses ofcyclosporine per kg body weight than those used in adults.

Geriatric Use: Experience with cyclosporine in the elderly is limited, but no particular problems have beenreported following the use of the drug at the recommended dose. However, factors sometimesassociated with aging, in particular impaired renal function, necessitate careful supervision andmay necessitate dosage adjustment.

Contraindication: Patients who are hypersensitive to cyclosporine or any of its excipients.
Also contraindicated in the treatment of psoriasis and rheumatoid arthritispatients under the following circumstances: abnormal renal function; uncontrolledhypertension; malignancy (except non-melanoma skin cancer); uncontrolled infection;primary or secondary immunodeficiency excluding autoimmune disease.

Warning & Precaution:

Cyclosporine capsules should beprescribed only by physicians who are experienced in immunosuppressive therapy andmanagement of transplant patients
Appropriate patient and laboratory monitoring is essential to prevent, reverse or minimize thefollowing adverse events: nephrotoxicity; hypertension; the development of malignancies andlymphoproliferative disorders; increased risk of infections; hepatotoxicity; lipoproteinabnormalities; neurotoxicity.

Cyclosporine wholeblood concentrations as well as the effectiveness and the adverse events related to cyclosporineshould be appropriately monitored in all patients

Cardiovascular: Patients receiving cyclosporine may develop hypertension, and regular monitoring of bloodpressure is required.
Endocrine and Metabolism: Many transplant patients have hyperlipidemia and cyclosporine may contribute to the genesis ofthis problem. It is advisable to perform lipid determination before treatment and after the firstmonth of therapy. If lipids are increased, restriction of dietary fat should be considered.

Hyperkalemia/Hyperuricemia/Hypomagnesemia: Cyclosporine enhances the risk of hyperkalemia, especially in patients with renal dysfunction. Caution is also required when cyclosporine is co-administeredwith potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin IIreceptor antagonists and potassium containing drugs as well as in patients on a potassium richdiet. Control of potassium levels in these situations is advisable.

Caution is required in treating patients with hyperuricemia

Cyclosporine enhances the clearance of magnesium. This can lead to symptomatic hypomagnesemia, especially in the peri-transplant period.Control of serum magnesium levels is therefore recommended inthe peri-transplant period, particularly in the presence of neurological symptoms/signs

Hepatotoxicity: Cyclosporine may also cause dose-dependent, reversible increases in serum bilirubin and in liverenzymes. Close monitoring of parameters that assess hepatic function is required. Abnormal values maynecessitate dose reduction

Adverse Reactions:

Various adverse reaction related to Cyclosporine are as follows

- Infections and Infestations
- Neoplasms benign, malignant and unspecified (including cysts and polyps)
- Blood and Lymphatic System disorders: Leucopenia
- Cardiovascular disorders: hypertension, flushing
- Gastrointestinal tract disorders: nausea, vomiting, abdominal discomfort
- General disorders and administration site conditions: pyrexia, edema
- Metabolism and nutrition disorders: anorexia**,** hyperglycemia
- Nervous system disorders: tremor, headache, convulsions, paresthesia
- Skin and subcutaneous tissue disorders:hirsutism&acne
- Renal and Urinary disorders:renal dysfunction

Therapeutic Drug Monitoring:

In transplant patients, routine monitoring of cyclosporine trough blood levels is required toavoid adverse effects due to high levels and to prevent organ rejection due to low levels

Routine monitoring of cyclosporine blood levels is also required when switching a patient fromone oral cyclosporine formulation to another. The results obtained will serve as a guide fordetermining the actual dosage required to achieve the desired target concentration in individualpatients.

Target Trough Levels		
RIA Method (Radioimmunoassay)	**Blood ng/mL**	**Plasma/serum ng/mL**
Monoclonal specific Polyclonal non-specific	100-400 150-1500	50-200 50-300