Size 360 x 240 mm (Front)

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

CYCLOSPORINE CAPSULES IP 25 mg / 50 mg / 100 mg

CYCLOSPORINE ORAL SOLUTION USP 100 mg/ml

Panimun Bioral®

Panacea Biotec

Innovation in support of life

WARNING

Only physicians experienced in management of systemic immunosuppressive therapy for the indicated disease should prescribe **Cyclosporine**. At doses used in solid organ transplantation, only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should prescribe **Cyclosporine**. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient. **Cyclosporine**, a systemic immunosuppressant, may increase the susceptibility to infection and the development of neoplasia. In kidney, liver, and heart transplant patients **Cyclosporine** may be administered with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma and other neoplasms may result from the increase in the degree of immunosuppression in transplant patients.

For Psoriasis Patients

Psoriasis patients previously treated with PUVA and to a lesser extent, methotrexate or other immunosuppressive agents, UVB, coal tar, or radiation therapy, are at an increased risk of developing skin malignancies when taking Cyclosporine. Cyclosporine, the active ingredient in Cyclosporine, in recommended dosages, can cause systemic hypertension and nephrotoxicity. The risk increases with increasing dose and duration of cyclosporine therapy. Renal dysfunction, including structural kidney damage, is a potential consequence of cyclosporine, and therefore, renal function must be monitored during therapy.

COMPOSITION

Panimun Bioral Solution

(Cyclosporine Oral Solution USP 100 mg/ml)

Description

Pale yellow coloured, clear liquid.

Composition

Each ml contains:

Cyclosporine IP.....100 mg.

Palatable base

Panimun Bioral 25 mg

(Cyclosporine Capsules IP 25 mg)

Description

Reddish brown coloured, oval shaped, soft gelatin capsules, printed with “PB 25” in white ink, containing clear liquid.

Composition

Each soft gelatin capsule contains:

Cyclosporine IP..... 25 mg

Colour: Ferric Oxide Red

Panimun Bioral 50 mg

(Cyclosporine Capsules IP 50 mg)

Description

Coffee brown coloured, oblong shaped, soft gelatin capsules, printed with “PB 50” in white ink, containing clear liquid.

Composition

Each soft gelatin capsule contains:

Cyclosporine IP..... 50 mg

Colours: Ferric Oxide Red & Ferric Oxide Black

Panimun Bioral 100 mg

(Cyclosporine Capsules IP 100 mg)

Description

Reddish brown coloured, oblong shaped, soft gelatin capsules, printed with “PB 100” in white ink, containing clear liquid.

Composition

Each soft gelatin capsule contains:

CyclosporineIP..... 100 mg

Colour: Ferric Oxide Red

DOSAGE FORM

Capsule / Oral Solution

INDICATIONS

Transplant Indication

Organ transplantation

Cyclosporine is indicated in the prevention of graft rejection following organ kidney, liver, heart, combined heart-lung, lung, or pancreas transplantation and in the treatment of transplant rejection in patients previously receiving other immunosuppressive agents.

Bone-marrow transplantation

Cyclosporine is indicated in the prevention of graft rejection following bone marrow transplantation and the prevention or treatment of graft-versus-host disease (GVHD).

Non-Transplant Indication

Psoriasis

Cyclosporine is indicated for patients with severe psoriasis, in whom the conventional therapy is ineffective or inappropriate.

Rheumatoid arthritis

Cyclosporine is indicated for the treatment of severe active rheumatoid arthritis in patients for whom classical slow-acting antirheumatic agents are inappropriate or ineffective.

Nephrotic syndrome

Cyclosporine can be used to induce remissions and to maintain the patients of steroid-dependent and steroid resistant nephrotic syndrome due to glomerular diseases such as minimal change nephropathy, focal and segmental glomerulosclerosis or membranous glomerulonephritis. Cyclosporine can also be used for maintenance of steroid induced remissions, allowing withdrawl of, or reduction in the dosage of steroids.

Atopic Dermatitis

Cyclosporine Capsules and Cyclosporine Oral Solution are indicated for the short term treatment (8 weeks) of patients with severe atopic dermatitis in whom conventional therapy is ineffective or inappropriate.

DOSE AND METHOD OF ADMINISTRATION

Dosage

The daily dose of Cyclosporine should always be given in two divided doses (BID). It is recommended that Cyclosporine be administered on a consistent schedule with regard to time of day and relation to meals. Grapefruit and grapefruit juice affect metabolism, increasing blood concentration of cyclosporine, thus should be avoided.

Due to the differences in bioavailability between different oral formulations of Cyclosporine, it is important that prescribers, pharmacists and patients be aware that substitution of Cyclosporine with any other oral formulation of Cyclosporine is not recommended as this may lead to alterations in Cyclosporine blood levels. For this reason it may be appropriate to prescribe by brand.

Transplantation Indications:

Organ transplantation

Treatment with Cyclosporine Soft Gelatin Capsules or Cyclosporine Oral Solution should be initiated within 12 hours before transplantation at a dose of 10 to 15mg/kg body weight given in two divided doses.

As a general rule, treatment should continue at a dose of 10 to 15mg/kg per day given in two divided doses for one to two weeks post-operatively. Dosage should then be gradually reduced until a maintenance dose of about 2 to 6mg/kg per day is reached. This total daily dose should be given in two divided doses. Dosage should be adjusted by monitoring Cyclosporine trough levels and kidney function.

When Cyclosporine is given with other immunosuppressant's (e.g. with corticosteroids or as part of a triple or quadruple drug therapy), lower doses (e.g. 3 to 6mg/kg per day given orally in two divided doses) may be used for the initial treatment. For trough level monitoring, whole blood is preferred, measured by a specific analytical method. Target trough concentration ranges depend on organ type, time after transplantation and immunosuppressive regimen.

Bone marrow transplantation/prevention and treatment of graft-versus-host-disease (GVHD)

If Cyclosporine Soft Gelatin Capsules or Cyclosporine Oral Solution are used to initiate therapy, the recommended dose is 12.5 to 15mg/kg per day, given in two divided doses, starting on the day before transplantation .However Intravenous route is preferred for initiation of therapy.

Maintenance treatment should continue using Cyclosporine Soft Gelatin Capsules or Cyclosporine Oral Solution at a dosage of 12.5mg/kg per day, given in two divided doses, for at least three and preferably six months before tailing off to zero. In some cases it may not be possible to withdraw Cyclosporine until a year after bone marrow transplantation. Higher doses of Cyclosporine may be necessary in the presence of gastro-intestinal disturbances which might decrease absorption.

If GVHD develops after Cyclosporine is withdrawn it should respond to reinstitution of therapy. Low doses of Cyclosporine should be used for mild, chronic GVHD.

Non-transplantation Indications

Psoriasis

Due to the variability of this condition, treatment must be individualized. To induce remission, the recommended initial dose of Cyclosporine is 2.5mg/kg a day given orally in two divided doses. If there is no improvement after 1 month, the daily dose may be gradually increased, but should not exceed 5mg/kg. Treatment should be discontinued if sufficient response is not achieved within 6 weeks on a daily basis of 5mg/kg per day, or if the effective dose is not compatible with the safety guidelines given below. Initial doses of 5mg/kg per day of Cyclosporine are justified in patients whose condition requires rapid improvement.

For maintenance treatment, Cyclosporine dosage must be individually titrated to the lowest effective level, and the dosage should not exceed 5mg/kg per day, given orally in two divided doses.

Some clinical data provide evidence that once satisfactory response is achieved, Cyclosporine may be discontinued and subsequent relapse managed with re-introduction of Cyclosporine at the previous effective dose. In some patients continuous maintenance therapy may be necessary.

Atopic dermatitis

The recommended dose range for Cyclosporine is 2.5-5mg/kg per day given orally in two divided doses for a maximum of 8 weeks. If a starting dose of 2.5mg/kg/day does not achieve a good initial response within 2 weeks the dose may be rapidly increased to a maximum of 5mg/kg per day. In very severe cases rapid and adequate control of disease is more likely with a starting dose of 5mg/kg per day, given orally in two divided doses.

Rheumatoid arthritis

It is recommended that initiation of Cyclosporine therapy should take place over a period of 12 weeks. For the first 6 weeks of treatment, the recommended dose is 2.5mg/kg per day, given orally in two divided doses. If the clinical effect is considered insufficient, the daily dose may be increased gradually as tolerability permits, but should not exceed 4mg/kg per day.

If, after 3 months of treatment at the maximum permitted or tolerable dose the response is considered inadequate, treatment should be discontinued.

For maintenance treatment the dose has to be titrated individually according to tolerability.

Cyclosporine can be given in combination with low-dose corticosteroids. Pharmacodynamics interactions can occur between Cyclosporine and NSAIDs and therefore this combination should be used with care.

Long-term data on the use of Cyclosporine in the treatment of rheumatoid arthritis are still limited. Therefore, it is recommended that patients are re-evaluated after 6 months of maintenance treatment and therapy only continued if the benefits of treatment outweigh the risks.

Nephrotic syndrome

To induce remission, the recommended dose is 5mg/kg per day given orally in two divided doses for adults and 6mg/kg per day given orally in two divided doses for children if, with the exception of proteinuria, renal function is normal. In patients with impaired renal function, the initial dose should not exceed 2.5mg/kg per day orally.

In focal segmental glomerulosclerosis, the combination of Cyclosporine and low dose corticosteroids may be of benefit.

In the absence of efficacy after 3 months treatment for minimal change glomerulonephritis and focal segmental glomerulosclerosis or 6 months treatment for membranous glomerulonephritis, Cyclosporine therapy should be discontinued.

For maintenance treatment the maximum recommended dose is 5mg/kg per day orally in adults or 6mg/kg per day orally in children. The doses need to be slowly reduced individually according to efficacy (proteinuria) and safety (primarily serum creatinine), to the lowest effective level.

Long-term data of Cyclosporine in the treatment of nephrotic syndrome are limited. However, in clinical trials patients have received treatment for 1 to 2 years. Long-term treatment may be considered if there has been a significant reduction in proteinuria with preservation of creatinine clearance and provided adequate precautions are taken.

USE IN SPECIAL POPULATIONS

Use in the Elderly

Experience with Cyclosporine in the elderly is limited. However, no particular problems have been reported following the use of Cyclosporine at the recommended dose. Factors sometimes associated with ageing, in particular impaired renal function, make careful supervision essential and may necessitate dosage adjustment.

In rheumatoid arthritis clinical trials with Cyclosporine, 17.5% of patients were aged 65 or older. These patients were more likely to develop systolic hypertension on therapy, and more likely to show serum creatinine rises ≥ 50% above the baseline after 3-4 months of therapy.

Clinical studies of Cyclosporine in transplant and psoriasis patients did not include a sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experiences have not identified differences in response between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Use in Children

There is currently no experience with Cyclosporine in young children. However, transplant recipients from three months of age have received Cyclosporine at the recommended dosage with no particular problems although at dosages above the upper end of the recommended range children seem to be more susceptible to fluid retention, convulsions and hypertension. This responds to dosage reduction.

The safety and efficacy of Cyclosporine treatment in children with juvenile rheumatoid arthritis or psoriasis below the age of 18 have not been established.

Pregnancy

Animal studies have shown reproductive toxicity in rats and rabbits.

Experience with Cyclosporine in pregnant women is limited. Pregnant women receiving immunosuppressive therapies after transplantation, including Cyclosporine and Cyclosporine containing regimens, are at risk of premature delivery (<37 weeks).

A limited number of observations in children exposed to Cyclosporine in utero are available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal.

However there are no adequate and well controlled studies in pregnant women and, therefore Cyclosporine should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus.

Lactation

Cyclosporine passes into breast milk. Mothers receiving treatment with Cyclosporine should not breast-feed.

CONTRAINDICATIONS

Hypersensitivity to Cyclosporine or to any of the other ingredients of Cyclosporine.

Cyclosporine is contraindicated in, psoriatic and atopic dermatitis patients with abnormal renal function, uncontrolled hypertension, uncontrolled infections or any kind of malignancy (other than that of the skin).

Cyclosporine is contraindicated in rheumatoid arthritis patients with abnormal renal function, uncontrolled hypertension, uncontrolled infections or any kind of malignancy.

Cyclosporine should not be used to treat rheumatoid arthritis in patients under the age of 18 years.

Cyclosporine is contraindicated in nephrotic syndrome patients with uncontrolled hypertension, uncontrolled infections, or any kind of malignancy.

Psoriasis patients who are treated with Cyclosporine should not receive concomitant PUVA or UVB therapy, methotrexate or other immunosuppressive agents, coal tar or radiation therapy.

Concomitant use of Tacrolimus is specifically contraindicated.

Concomitant use of Rosuvastatin is specifically contraindicated.

WARNINGS

Cyclosporine should be prescribed only by physicians who are experienced in immunosuppressive therapy, and can provide adequate follow-up, including regular full physical examination, measurement of blood pressure, and control of laboratory safety parameters. Transplantation patients receiving the drug should be managed in facilities with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should receive complete information for the follow-up of the patient.

Like other immunosuppressant's, Cyclosporine increases the risk of developing lymphomas and other malignancies, particularly those of the skin. The increased risk appears to be related to the degree and duration of immunosuppression rather than to the use of specific agents.

Hence a treatment regimen containing multiple immunosuppressant's (including Cyclosporine) should be used with caution as this could lead to lymphoproliferative disorders and solid organ tumours, some with reported fatalities.

In view of the potential risk of skin malignancy, patients on Cyclosporine, in particular those treated for psoriasis or atopic dermatitis should be warned to avoid excess unprotected sun exposure and should not receive concomitant ultraviolet B irradiation or PUVA photo chemotherapy.

Like other immunosuppressant's, Cyclosporine predisposes patients to the development of a variety of bacterial, fungal, parasitic and viral infections often with opportunistic pathogens.

Activation of latent Polyomavirus infections that may lead to Polyomavirus associated nephropathy (PVAN), especially to BK virus nephropathy (BKVN), or to JC virus associated progressive multifocal leukoencephalopathy (PML) have been observed in patients receiving Cyclosporine. These conditions are often related to a high total immunosuppressive burden and should be considered in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Serious and/or fatal outcomes have been reported. Effective pre-emptive and therapeutic strategies should be employed particularly in patients on multiple long-term immunosuppressive therapy.

A frequent and potentially serious complication, an increase in serum creatinine and urea may occur during the first few weeks of Cyclosporine therapy. These functional changes are dose-dependent and reversible, usually responding to dose reduction. During long-term treatment, some patients may develop structural changes in the kidney (e.g. interstitial fibrosis) which, in renal transplant patients, must be differentiated from changes due to chronic rejection. Cyclosporine may also cause dose-dependent, reversible increases in serum bilirubin and, occasionally, in liver enzymes. There have been solicited and spontaneous reports of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure in patients treated with Cyclosporine. Most reports included patients with significant co-morbidities, underlying conditions and other confounding factors including infectious complications and co-medications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported.

Close monitoring of parameters that assess renal and hepatic function is required. Abnormal values may necessitate dose reduction.

In elderly patients, renal function should be monitored with particular care.

For monitoring Cyclosporine levels in whole blood, a specific monoclonal antibody (measurement of parent drug) is preferred; a HPLC method, which also measures the parent drug, can be used as well. If plasma or serum is used, a standard separation protocol (time and temperature) should be followed. For the initial monitoring of liver transplant patients, either the specific monoclonal antibody should be used, or parallel measurements using both the specific monoclonal antibody and the nonspecific monoclonal antibody should be performed, to ensure a dosage that provides adequate immunosuppression.

It must be remembered that the Cyclosporine concentration in blood, plasma, or serum is only one of many factors contributing to the clinical status of the patient. Results should therefore serve only as a guide to dosage in relationship to other clinical and laboratory parameters.

Regular monitoring of blood pressure is required during Cyclosporine therapy; if hypertension develops, appropriate antihypertensive treatment must be instituted.

Since, on rare occasions, Cyclosporine has been reported to induce a reversible slight increase in blood lipids, it is advisable to perform lipid determinations before treatment and after the first month of therapy. In the event of increased lipids being found, restriction of dietary fat and, if appropriate, a dose reduction, should be considered.

Cyclosporine enhances the risk of hyperkalemia, especially in patients with renal dysfunction. Caution is also required when Cyclosporine is co-administered with potassium sparing drugs (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists) and potassium containing drugs as well as in patients on a potassium rich diet. Control of potassium levels in these situations is advisable.

Cyclosporine enhances the clearance of magnesium. This can lead to symptomatic hypomagnesaemia, especially in the peri-transplant period. Control of serum magnesium levels is therefore recommended in the peri-transplant period, particularly in the presence of neurological symptom/signs. If considered necessary, magnesium supplementation should be given.

Caution is required in treating patients with hyperuricaemia.

Caution should be observed while co-administering lercanidipine with Cyclosporine.

Cyclosporine may increase blood levels of concomitant medications that are substrates of P-glycoprotein (Pgp) such as aliskiren.

Cyclosporine may increase the risk of Benign Intracranial Hypertension. Patients presenting with signs of raised intracranial pressure should be investigated and if Benign Intracranial Hypertension is diagnosed, Cyclosporine should be withdrawn due to the possible risk of permanent visual loss.

Cyclosporine contains Polyoxyl 40 hydrogenated castor oil which may cause stomach upsets and diarrhoea.

Thrombotic Microangiopathy

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure. The vasculopathy can occur in the absence of rejection and is accompanied by avid platelet consumption within the graft as demonstrated by Indium 111 labeled platelet studies. Neither the pathogenesis nor the management of this syndrome is clear. Though resolution has occurred after reduction or discontinuation of Cyclosporine and 1) administration of streptokinase and heparin or 2) plasmapheresis, this appears to depend upon early detection with Indium 111 labeled platelet scans.

Neurotoxicity

There have been reports of convulsions in adult and pediatric patients receiving cyclosporine, particularly in combination with high dose methylprednisolone.

Encephalopathy has been described. Manifestations include impaired consciousness, convulsions, visual disturbances (including blindness), loss of motor function, movement disorders and psychiatric disturbances. In many cases, changes in the white matter have been detected using imaging techniques and pathologic specimens. Predisposing factors such as hypertension, hypomagnesemia, hypocholesterolemia, high-dose corticosteroids, high cyclosporine blood concentrations, and graft-versus-host disease have been noted in many but not all of the reported cases. The changes in most cases have been reversible upon discontinuation of cyclosporine, and in some cases improvement was noted after reduction of dose. It appears that patients receiving liver transplant are more susceptible to encephalopathy than those receiving kidney transplant. Another rare manifestation of Cyclosporine-induced neurotoxicity, occurring in transplant a patient more frequently than in other indications, is optic disc edema including papilloedema, with possible visual impairment, secondary to benign intracranial hypertension.

PRECAUTIONS

During treatment with Cyclosporine, vaccination may be less effective; the use of live attenuated vaccines should be avoided.

Precautions in non-transplant indications

Patients with impaired renal function (except in nephrotic syndrome patients with a permissible degree of renal impairment), uncontrolled hypertension, uncontrolled infections, or any kind of malignancy should not receive Cyclosporine.

Precautions in nephrotic syndrome:

Since Cyclosporine can impair renal function, it is necessary to assess renal function frequently and if the serum creatinine remains increased by more than 30% above baseline at more than one measurement, to reduce the dosage of Cyclosporine by 25 to 50%.

Patients with abnormal baseline renal function should initially be treated with 2.5mg/kg per day and must be monitored very carefully.

In some patients it may be difficult to detect Cyclosporine-induced renal dysfunction because of changes in renal function related to the nephrotic syndrome itself. This explains why, in rare cases, Cyclosporine -associated structural kidney alterations have been observed without increases in serum creatinine. Renal biopsy should be considered for patients with steroid-dependent minimal-change nephropathy, in whom Cyclosporine therapy has been maintained for more than 1 year.

In patients with nephrotic syndrome treated with immunosuppressants (including Cyclosporine), the occurrence of malignancies (including Hodgkin's lymphoma) has occasionally been reported.

The use of Cyclosporine therapy for the treatment of patients with nephrotic syndrome requires careful monitoring and follow-up. Cyclosporine should only be used provided that the necessary expertise and adequate equipment, laboratory and supporting medical resources are available.

Precautions in rheumatoid arthritis

Since Cyclosporine can impair renal function, a reliable baseline level of serum creatinine should be established by at least two measurements prior to treatment, and serum creatinine should be monitored at 2-weekly intervals during the first 3 months of therapy and thereafter once a month. After 6 months of therapy, serum creatinine needs to be measured every 4 to 8 weeks depending on the stability of the disease, its co-medication, and concomitant diseases. More frequent checks are necessary when the Cyclosporine dose is increased, or concomitant treatment with a non-steroidal anti-inflammatory drug is initiated or its dosage increased. Because the pharmacodynamics interaction between Cyclosporine and NSAIDs may adversely affect renal function, caution should be exercised if NSAID therapy is to be continued.

If the serum creatinine remains increased by more than 30% above baseline at more than one measurement, the dosage of Cyclosporine should be reduced. If the serum creatinine increases by more than 50%, a dosage reduction by 50% is mandatory. These recommendations apply even if the patient's values still lie within the laboratory normal range. If dose reduction is not successful in reducing levels within one month, Cyclosporine treatment should be discontinued.

Discontinuation of the drug may also become necessary if hypertension developing during Cyclosporine therapy cannot be controlled by appropriate antihypertensive therapy.

As hepatotoxicity is a potential side effect of non-steroidal anti-inflammatory drugs, regular monitoring of hepatic function is advised when Cyclosporine is co-administered with these drugs in rheumatoid arthritis patients.

Size 360 x 240 mm (Back)

The use of Cyclosporine therapy for the treatment of patients with rheumatoid arthritis requires careful monitoring and follow-up. Cyclosporine should only be used provided that the necessary expertise and adequate equipment, laboratory and supportive medical resources are available.
Patients with rheumatoid arthritis have an increased incidence of malignancies compared to the general population. Use of disease modifying drugs increases the risk of malignancy further. The use of Cyclosporine in the treatment of rheumatoid arthritis has not been shown to increase the incidence of malignancies more than other disease-modifying drugs.
As with other long-term immunosuppressive treatments (including Cyclosporine), an increased risk of lymphoproliferative disorders must be borne in mind.
If Cyclosporine is used in combination with methotrexate, CBC and LFT are recommended to be monitored monthly.
Precautions in psoriasis
Careful dermatological and physical examinations, including measurements of blood pressure and renal function on at least two occasions prior to starting therapy should be performed to establish an accurate baseline status.
Since Cyclosporine can impair renal function, a reliable baseline level of serum creatinine should be established by at least two measurements prior to treatment, and serum creatinine should be monitored at 2-weekly intervals for the first 3 months of therapy.
Thereafter, if creatinine remains stable, measurements should be made at monthly intervals. If serum creatinine increases and remains increased to more than 30% above baseline at more than one measurement, the dosage of Cyclosporine must be reduced by 25 to 50%. These recommendations apply even if the patient's values still lie within the laboratory's normal range. If dose reduction is not successful in reducing levels within one month, Cyclosporine treatment should be discontinued.
Discontinuation of Cyclosporine therapy is also recommended if hypertension developing during Cyclosporine treatment cannot be controlled with appropriate therapy.
Elderly patients should be treated only in the presence of disabling psoriasis, and renal function should be monitored with particular care.
There is only limited experience with the use of Cyclosporine in children with psoriasis.
In psoriatic patients on Cyclosporine, as in those on conventional immunosuppressive therapy, development of malignancies (in particular of the skin) has been reported. Skin lesions not typical for psoriasis, but suspected to be malignant or pre-malignant should be biopsied before Cyclosporine treatment is started. Patients with malignant or pre-malignant alterations of the skin should be treated with Cyclosporine only after appropriate treatment of such lesions, and if no other option for successful therapy exists.
In a few psoriatic patients treated with Cyclosporine, lymphoproliferative disorders have occurred. These were responsive to prompt drug discontinuation.
Patients on Cyclosporine should not receive concomitant ultraviolet B irradiation or PUVA photo chemotherapy.
Cyclosporine treatment and its monitoring should be carried out under the supervision of a dermatologist experienced in the management of severe skin diseases.
Precautions in atopic dermatitis
Careful dermatological and physical examinations, including measurements of blood pressure and renal function on at least two occasions prior to starting therapy should be performed to establish an accurate baseline status.
Since Cyclosporine can impair renal function, a reliable baseline level of serum creatinine should be established by at least two measurements prior to treatment, and serum creatinine should be monitored at 2-weekly intervals for the first 3 months of therapy.
Thereafter, if creatinine remains stable, measurements should be made at monthly intervals. If serum creatinine increases and remains increased to more than 30% above baseline at more than one measurement, the dosage of Cyclosporine must be reduced by 25 to 50%. These recommendations apply even if the patient's values still lie within the laboratory's normal range. If dose reduction is not successful in reducing levels within one month, Cyclosporine treatment should be discontinued.
Discontinuation of Cyclosporine therapy is also recommended if hypertension developing during Cyclosporine treatment cannot be controlled with appropriate therapy.
The experience with Cyclosporine in children with atopic dermatitis is limited.
Elderly patients should be treated only in the presence of disabling atopic dermatitis and renal function should be monitored with particular care.
Benign lymphadenopathy is commonly associated with flares in atopic dermatitis, and invariably disappears spontaneously or with general improvement in the disease.
Lymphadenopathy observed on treatment with Cyclosporine should be regularly monitored.
Lymphadenopathy which persists despite improvement in disease activity should be examined by biopsy as a precautionary measure to ensure the absence of lymphoma.
Active Herpes simplex infections should be allowed to clear before treatment with Cyclosporine is initiated, but is not necessarily a reason for drug withdrawal if they occur during treatment unless infection is severe.
Skin infections with *Staphylococcus aureus* are not an absolute contraindication for Cyclosporine therapy but should be controlled with appropriate antibacterial agents. Oral erythromycin, known to have the potential to increase the blood concentration of Cyclosporine should be avoided or, if there is no alternative, it is recommended to closely monitor blood levels of Cyclosporine, renal function, and for side effects of Cyclosporine.
Patients on Cyclosporine should not receive concomitant ultraviolet B irradiation or PUVA photo chemotherapy.
Cyclosporine treatment and its monitoring should be carried out under the supervision of a dermatologist experienced in the management of severe skin diseases.
Pediatric use in non-transplant indications
Except for the treatment of nephrotic syndrome, there is no adequate experience available with Cyclosporine; its use in children under 16 years of age for nontransplant indications other than nephrotic syndrome cannot be recommended.

DRUG INTERACTIONS

Of the many drugs reported to interact with Cyclosporine, those for which the interactions are adequately substantiated and considered to have clinical implications are listed below.
Various agents are known to either increase or decrease plasma or whole blood Cyclosporine levels usually by inhibition or induction of enzymes involved in the metabolism of Cyclosporine, in particular CYP3A4. Cyclosporine is also an inhibitor of CYP3A4 and of the multidrug efflux transporter P-glycoprotein and may increase plasma levels of co-medications that are substrates of this enzyme and/or transporter.
Drugs that decrease Cyclosporine levels:
Barbiturates, Carbamazepine, Oxcarbazepine, Phenytoin, Nafcillin, Sulfadimidine i.v.; Rifampicin, Octreotide, Probucol, Orlistat, Hypericum perforatum (St John's Wort), Ticlopidine, Sulfinpyrazone, Terbinafine, Bosentan.
Drugs that increase Cyclosporine levels:
Macrolide Antibiotics (e.g. Erythromycin, Azithromycin and Clarithromycin); Ketoconazole, Fluconazole, Itraconazole, Voriconazole; Diltiazem, Nicardipine, Verapamil, Metoclopramide; oral contraceptives; danazol; methylprednisolone (high dose); allopurinol; amiodarone; cholic acid and derivatives; Protease Inhibitors, Imatinib, Colchicines, Nefazodone.
Other relevant drug interactions
Care should be taken when using Cyclosporine together with other drugs that exhibit nephrotoxic synergy such as: aminoglycosides (including gentamicin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); non-steroidal anti-inflammatory drugs (including diclofenac, naproxen, sulindac); melphalan, histamine H2-receptor antagonists (e.g. cimetidine, ranitidine); methotrexate.
Concomitant use with Tacrolimus should be avoided due to increased potential for nephrotoxicity.
The concurrent administration of Nifedipine with Cyclosporine may result in an increased rate of gingival hyperplasia compared with that observed when Cyclosporine is given alone.
Following concomitant administration of Cyclosporine and lercanidipine, the AUC of lercanidipine was increased threefold and the AUC of Cyclosporine was increased 21%. Therefore caution is recommended when co-administering Cyclosporine together with lercanidipine.
Cyclosporine is a highly potent Pgp inhibitor and may increase blood levels of concomitant medications that are substrates of Pgp such as aliskiren. Following concomitant administration of Cyclosporine and aliskiren, the Cmax of aliskiren was increased by approximately 2.5 fold and the AUC by approximately 5 fold. However, the pharmacokinetic profile of Cyclosporine was not significantly altered. Caution is recommended when co-administering Cyclosporine together with aliskiren.
The concomitant use of Diclofenac and Cyclosporine has been found to result in a significant increase in the bioavailability of Diclofenac, with the possible consequence of reversible renal function impairment. The increase in the bioavailability of Diclofenac is most probably caused by a reduction of its first-pass effect. If non-steroidal anti-inflammatory drugs with a low first-pass effect (e.g. acetylsalicylic acid) are given together with Cyclosporine, no increase in their bioavailability is to be expected.
Cyclosporine may reduce the clearance of digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins) and etoposide.
Severe digitalis toxicity has been seen within days of starting Cyclosporine in several patients taking digoxin. There are also reports on the potential of Cyclosporine to enhance the toxic effects of colchicine such as myopathy and neuropathy, especially in patients with renal dysfunction. If digoxin or colchicine is used concurrently with Cyclosporine, close clinical observation is required in order to enable early detection of toxic manifestations of digoxin or colchicine, followed by reduction of dosage or its withdrawal.
Myotoxicity, including muscle pain and weakness, myositis, and rhabdomyolysis, have been reported with concomitant administration of Cyclosporine with lovastatin, simvastatin, atorvastatin, pravastatin, and rarely, Fluvastatin. When concurrently administered with Cyclosporine, the dosage of these statins should be reduced according to label recommendations. Statin therapy needs to be temporarily withheld or discontinued in patients with signs and symptoms of myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis.
Rosuvastatin is specifically contraindicated with Cyclosporine.
Elevations in serum creatinine were observed in the studies using Everolimus or Sirolimus in combination with full-dose Cyclosporine for microemulsion. This effect is often reversible with Cyclosporine dose reduction. Everolimus and Sirolimus had only a minor influence on Cyclosporine pharmacokinetics. Co-administration of Cyclosporine significantly increases blood levels of Everolimus and Sirolimus.
Caution is required for concomitant use of potassium sparing drugs (e.g. potassium sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists) or potassium containing drugs since they may lead to significant increases in serum potassium.
Cyclosporine may increase the plasma concentrations of Repaglinide and thereby increase the risk of hypoglycemia.

Recommendations

If the concomitant use of drug known to interact with Cyclosporine cannot be avoided, the following basic recommendations should be observed.
During the concomitant use of a drug that may exhibit nephrotoxic synergy, close monitoring of renal function (in particular serum creatinine) should be performed. If a significant impairment of renal function occurs, the dosage of the co-administered drug should be reduced or alternative treatment considered.
In graft recipients there have been isolated reports of considerable but reversible impairment of kidney function (with corresponding increase in serum creatinine) following concomitant administration of fibric acid derivatives (e.g. bezafibrate, fenofibrate). Kidney function must therefore be closely monitored in these patients. In the event of significant impairment of kidney function the co-medication should be withdrawn.
Drugs known to reduce or increase the bioavailability of Cyclosporine:
In transplant patients frequent measurement of Cyclosporine levels and, if necessary, Cyclosporine dosage adjustment is required, particularly during the introduction or withdrawal of the co-administered drug. In non-transplant patients the value of Cyclosporine blood level monitoring is questionable, as in these patients the relationship between blood level and clinical effect is less well established. If drugs known to increase Cyclosporine levels are given concomitantly, frequent assessment of renal function and careful monitoring for Cyclosporine related side-effects may be more appropriate than blood level measurement.
The concomitant use of Nifedipine should be avoided in patients in whom gingival hyperplasia develops as a side effect of Cyclosporine.
Non-steroidal anti-inflammatory drugs known to undergo strong first-pass metabolism (e.g. Diclofenac) should be given at doses lower than those that would be used in patients not receiving Cyclosporine. When Diclofenac is given concomitantly with Cyclosporine the dose of Diclofenac should be reduced by approximately half.
If digoxin, colchicine or HMG-CoA reductase inhibitors (statins) are used concurrently with Cyclosporine, close clinical observation is required in order to enable early detection of toxic manifestations of the drugs, followed by reduction of its dosage or its withdrawal.
Food interactions
The concomitant intake of grapefruit juice has been reported to increase the bioavailability of Cyclosporine.

UNDESIRABLE SIDE EFFECTS

Many side effects associated with Cyclosporine therapy are dose-dependent and responsive to dose reduction. In the various indications the overall spectrum of side effects is essentially the same; there are, however, differences in incidence and severity. As a consequence of the higher initial doses and longer maintenance therapy required after transplantation, side effects are more frequent and usually more severe in transplant patients than in patients treated for other indications.
Infections and infestations:
Patients receiving immunosuppressive therapies, including Cyclosporine and Cyclosporine-containing regimens are at increased risk of infections (viral, bacterial, fungal, parasitic). Both generalized and localized infections can occur. Pre-existing infections may also be aggravated and reactivation of Polyomavirus infections may lead to Polyomavirus associated nephropathy (PVAN) or to JC virus associated progressive multifocal leukoencephalopathy (PML). Serious and/or fatal outcomes have been reported. The most important infections observed during long-term post-marketing surveillance of solid-organ transplant patients were: Very common: Lower respiratory tract infection including cases of bronchiolitis, urinary tract infection, cytomegalovirus infection, upper respiratory tract infection. Common: Sepsis, herpes infections, Candidal infection.
Neoplasms benign, malignant and unspecified (including cysts and polyps):
Patients receiving immunosuppressive therapies, including Cyclosporine and Cyclosporine containing regimens, are at increased risk of developing lymphomas or lymphoproliferative disorders and other malignancies, particularly of the skin. The frequency of malignancies increases with the intensity and duration of therapy. Some malignancies may be fatal. The most frequently observed neoplasms were: Common:Skin Papilloma's, basal cell carcinoma, squamous cell carcinoma of skin, Bowen's disease, lymphoproliferative disorders. Uncommon:Seborrhoeic keratosis, melanoma, squamous cell carcinoma.
Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (< 1/10,000), including isolated reports.

Blood and lymphatic system disorders	
Uncommon	Anemia, Thrombocytopenia.
Rare	Microangiopathic haemolytic anemia, Haemolytic Uraemic syndrome.
Metabolism and nutrition disorders	
Very common	Hyperlipidemia, Hypercholesterolemia.
Common	Anorexia, Hyperuricaemia, Hyperkalemia, Hypomagnesaemia.
Rare	Hyperglycemia.
Nervous system disorders	
Very common	Tremor, Headache including migraine.
Common	Paraesthesia.
Uncommon	Signs of encephalopathy such as convulsions, Confusion, Disorientation, Decreased responsiveness, Agitation, Insomnia, Visual disturbances, Cortical blindness, Coma, Paresis, Cerebellar ataxia.
Rare	Motor polyneuropathy.
Very rare	Optic disc oedema including papilloedema, with possible visual impairment secondary to benign intracranial hypertension.
Vascular disorders	
Very common	Hypertension.
Gastrointestinal disorders	
Common	Nausea, vomiting, abdominal pain, Diarrhoea, gingival hyperplasia
Rare	Pancreatitis.
Hepatobiliary disorders	
Common	Hepatic function abnormal.
Skin and subcutaneous tissue disorders	
Common	Hypertrichosis.
Uncommon	Allergic rashes.
Musculoskeletal and connective tissue disorders	
Common	Muscle cramps, myalgia.
Rare	Muscle weakness, myopathy.
Renal and urinary disorders	
Very common	Renal impairment.
Reproductive system and breast disorders	
Rare	Menstrual disturbances, Gynecomastia.
General disorders and administration site conditions	
Common	Fatigue.
Uncommon	Oedema, weight increase.

Other adverse drug reactions
There have been reports of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure in patients treated with Cyclosporine. Most reports included patients with significant co-morbidities, underlying conditions and other confounding factors including infectious complications and co-medications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported.

OVERDOSE

There is a minimal experience with cyclosporine overdosage. Forced emesis and gastric lavage can be of value up to 2 hours after administration of Cyclosporine. Transient hepatotoxicity and nephrotoxicity may occur which should resolve following drug withdrawal. Oral doses of cyclosporine up to 10 g (about 150 mg/kg) have been tolerated with relatively minor clinical consequences, such as vomiting, drowsiness, headache, tachycardia and, in a few patients, moderately severe, reversible impairment of renal function. However, serious symptoms of intoxication have been reported following accidental parenteral overdosage with cyclosporine in premature neonates. General supportive measures and symptomatic treatment should be followed in all cases of overdosage. Cyclosporine is not dialyzable to any great extent, nor is it cleared well by charcoal hemoperfusion. The oral dosage at which half of experimental animals are estimated to die is 31 times, 39 times, and >54 times the human maintenance dose for transplant patients (6mg/kg; corrections based on body surface area) in mice, rats, and rabbits.

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Immunosuppressive agents, calcineurin inhibitors (ATC code L04A D01).
Cyclosporine (also known as Cyclosporine A) is a cyclic polypeptide consisting of 11 amino acids. It is a potent immunosuppressive agent which prolongs survival of allogeneic transplants involving skin, heart, kidney, pancreas, cornea, bone marrow, small intestine and lung in animals.
Successful solid organ and bone marrow allogeneic transplants have been performed in man, using Cyclosporine to prevent and treat rejection and GVHD. Cyclosporine has been used both in Hepatitis C Virus (HCV) positive and HCV negative liver transplants recipients. Marked beneficial effects of Cyclosporine therapy have also been shown in patients with severe psoriasis, atopic dermatitis, rheumatoid arthritis and nephrotic syndrome, conditions that may be considered to have an immunological mechanism.
Studies in animals suggest that Cyclosporine inhibits the development of cell mediated reactions. It appears to block the resting lymphocytes in the G_0 or early G_1 phase of the cell cycle, and also inhibits lymphokine production and release, including interleukin 2 (T cell growth factor, TCGF). The available evidence suggests that Cyclosporine acts specifically and reversibly on lymphocytes. It does not depress haemopoiesis and has no effect on the function of phagocytic cells.

PHARMACOKINETIC PROPERTIES

The immunosuppressive activity of cyclosporine is primarily due to parent drug. Following oral administration, absorption of cyclosporine is incomplete. The extent of absorption of cyclosporine is dependent on the individual patient, the patient population, and the formulation. Elimination of cyclosporine is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in urine. The disposition of cyclosporine from blood is generally biphasic, with a terminal half-life of approximately 8.4 hours (range 5-18 hours).
The relationship between administered dose and exposure (area under the concentration versus time curve, AUC) is linear within the therapeutic dose range. The inter subject variability (total, %CV) of cyclosporine exposure (AUC) when Cyclosporine is administered ranges from approximately 20% to 50% in renal transplant patients. This inter subject variability contributes to the need for individualization of the dosing regimen for optimal therapy.
Absorption
Following oral administration of Cyclosporine, the time to peak blood cyclosporine concentrations (Tmax) ranged from 1.5-2.0 hours. The administration of food with Cyclosporine decreases the cyclosporine AUC and Cmax. A high fat meal (669 kcal, 45 grams fat) consumed within one-half hour before Cyclosporine administration decreased the AUC by 13% and Cmax by 33%. The effects of a low fat meal (667 kcal, 15 grams fat) were similar.
Distribution
Cyclosporine is distributed largely outside the blood volume. The steady state volume of distribution during intravenous dosing has been reported as 3-5 L/kg in solid organ transplant recipients. In blood, the distribution is concentration dependent. Approximately 33%-47% is in plasma, 4%-9% in lymphocytes, 5%-12% in granulocytes, and 41%-58% in erythrocytes. At high concentrations, the binding capacity of leukocytes and erythrocytes becomes saturated. In plasma, approximately 90% is bound to proteins, primarily lipoproteins.
Metabolism
Cyclosporine is extensively metabolized by the cytochrome P-450 3A enzyme system in the liver, and to a lesser degree in the gastrointestinal tract, and the kidney. The metabolism of cyclosporine can be altered by the co-administration of a variety of agents.
At least 25 metabolites have been identified from human bile, feces, blood, and urine. The biological activity of the metabolites and their contributions to toxicity are considerably less than those of the parent compound. The major metabolites (M1, M9, and M4N) result from oxidation at the 1-beta, 9-gamma, and 4-N-demethylated positions, respectively.
Excretion
Only 0.1% of a cyclosporine dose is excreted unchanged in the urine. Elimination is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in the urine. Neither dialysis nor renal failure alter cyclosporine clearance significantly.

INCOMPATIBILITIES

Not applicable.

SHELF LIFE

36 months from the date of manufacturing.

PACKING INFORMATION

Panimun Bioral Solution
Bottle of 50 ml
Panimun Bioral Capsules 25 mg, 50 mg & 100 mg.
Boxes of 5 X 6's

STORAGE AND HANDLING INSTRUCTIONS

Panimun Bioral Solution
Store at a temperature between 25°C & 35°C, protect from light and moisture. Do not Refrigerate.
Panimun Bioral Capsules 25 mg, 50 mg & 100 mg.
Store protected from moisture, at a temperature not exceeding 30°C. Do not Refrigerate.

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