Panimun Bioral Solution
(Cyclosporine Oral Solution USP-100 mg/ml)

Description
Pale yellow coloured, clear liquid.

Composition
Each ml of solution contains:
Cyclosporine USP........100 mg.

Panimun Bioral 25 mg
(Cyclosporine Capsules USP-25 mg)

Description
Reddish brown coloured, oval shaped, soft gelatin capsules containing pale yellow coloured, clear liquid.

Composition
Each soft gelatin capsule contains:
cyclosporine USP....... 25 mg
Approved colours used in capsule shells

Panimun Bioral 50 mg
(Cyclosporine Capsules USP-50 mg)

Description
Coffee brown coloured, oblong shaped, soft gelatin capsules containing pale yellow coloured, clear liquid.

Composition
Each soft gelatin capsule contains:
cyclosporine USP....... 50 mg
Approved colours used in capsule shells

Panimun Bioral 100 mg
(Cyclosporine Capsules USP-100 mg)

Description
Reddish brown coloured, oblong shaped, soft gelatin capsules containing pale yellow coloured, clear liquid.
Composition
Each soft gelatin capsule contains:
cyclosporine USP........ 100 mg
Approved colours used in capsule shells

PROPERTIES
The cyclosporine (also known as cyclosporine A) is a lipophillic cyclic polypeptide composed of 11 amino acids. It is a potential immunosupressor which has shown to be able to prolong in animals, the survival of transplants such as skin, heart, kidneys, pancreas, bone marrow, small intestine and lungs.
Various studies on animals have proved that cyclosporine inhibits the development of cell mediated immunity including allograft immunity, delayed cutaneous hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, reaction from transplantation towards host (graft versus host disease, GVHD) and the production of T cell dependent antibodies.
Cyclosporine inhibits the production as well as the release of lymphokines such as interleukin 2 (T cell growth factor, TCGF). From experimental data it can be noticed that cyclosporine blocks the quiescent lymphocytes in phase G or at the beginning of phase G1 of the cellular cycle.
All the available data indicates that cyclosporine acts on the lymphocytes in a specific and reversible manner. Cyclosporine does not depress hemopoiesis and does not alter the function of phagocytes. Patients treated with cyclosporine are less susceptible to infections as compared to those that receive another immunosuppressive treatment.

PHARMACOKINETICS
After oral administration (oral solution and capsules) the peak plasma blood concentration is reached between the first and third hour. Absolute bio-availability of oral preparation in stationery state is 20-50% (average 34%).
The $C_{\text{max}}$, $T_{\text{max}}$ and AUC$_{0-24\text{hrs}}$ of Panimun Bioral solution was $858.06 \pm 54.22$ ng/ml, $1.42 \pm 0.11$ hrs and $2995.78 \pm 139.32$ ng hr ml$^{-1}$ respectively, after a single dose of 1.8 ml solution equivalent to 180 mg cyclosporine. The $C_{\text{max}}$, $T_{\text{max}}$ and AUC$_{0-12\text{hrs}}$ of Panimun Bioral Capsule was $792.94 \pm 54.07$ ng/ml, $2.09 \pm 0.08$ hrs and $3266.71 \pm 197.12$ ng hr ml$^{-1}$ respectively, after single oral dose of 175 mg capsule. Assay employed was Radio Immuno Assay. The mean elimination half life ($t_{1/2}$) of single oral dose of solution and capsule was $4.87 \pm 1.73$ hrs and $4.80 \pm 1.58$ hrs respectively.

In human beings cyclosporine has given positive results in kidney transplants, bone marrow transplants to prevent and treat rejection and GVHD, and in a series of diseases of autoimmune origin.

THERAPEUTIC INDICATIONS
a) Organ transplantation
Cyclosporine is indicated as immunosuppressor for the prevention of refusal (or rejection) of allogenic transplantation of kidney, liver, heart, lung and pancreas. It may be used alone or in association with other immunosuppressants with low doses of corticosteroids. Cyclosporine may also be used in the treatment for rejection of transplantation in patients who have received previously other immunosuppressants.

b) Bone-marrow transplantation & Aplastic Anaemia
Cyclosporine is indicated as immunosuppressor in the prevention of rejection of bone marrow transplantation and or in the prevention and in the therapy of the graft versus host disease (GVHD) alone or in combination with other drugs.
c) **Endogenous uveitis**
Cyclosporine is indicated for treatment of posterior or intermediate uveitis of non infectious origin in active phase, with grave risk of loss of visual function, when the other conventional therapies have not proven to be effective or when they provoke unacceptable side effects. Cyclosporine is also indicated for treatment of uveitis in the Behcet's Syndrome, with repeated inflammatory attacks of the retina.

d) **Psoriasis**
Cyclosporine is indicated for patients with serious psoriasis, in whom the conventional therapies have proved to be ineffective or inappropriate.

e) **Rheumatoid arthritis**
Cyclosporine is indicated for the treatment of severe rheumatoid arthritis in active phase, in whom the classic antirheumatic medicines are inefficient and inappropriate.

f) **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.

g) **Unlabelled indications**
Other conditions where cyclosporine can be used are primary biliary cirrhosis, atopic dermatitis, lichen planus, pyoderma gangrenosum, alopecia areata, bullous disorders, psoriasis vulgaris, ulcerative colitis, crohn's disease, chronic viral active hepatitis, auto immune chronic active hepatitis, nephrotic syndrome, type I (Insulin dependent) diabetes mellitus and to a limited extent in myasthenia gravis and multiple sclerosis.

**CONTRAINDICATIONS**
Hypersensitivity is known for cyclosporine.

**PRECAUTIONS**
Cyclosporine must be used only by medical specialists who have experience of immunosuppressive therapy and/or of treatment of organ transplantation or transplantation of bone marrow. Patients receiving cyclosporine must be followed by centres equipped with appropriate laboratory facilities and adequate support of medical personnel.

Patients with malabsorption syndrome may have difficulty in achieving therapeutic levels.

Hypertension is a common side effect of cyclosporine therapy. Generally mild to moderate hypertension is seen. However, on continuous administration incidence decreases with time. Antihypertensives are generally recommended for this. Since hyperkalaemia may be seen with cyclosporine therapy, potassium sparing diuretics are not recommended for treating this condition. In such patients calcium antagonists can be effective agents for treating such hypertension. Due to alterations in metabolism of cyclosporine by some calcium antagonists, dosage adjustments of cyclosporine may be required.

During treatment with cyclosporine, vaccination may be less effective. Use of live attenuated vaccines should be avoided

Repeated laboratory tests for renal, liver functions should be done to know the status of kidney and liver. Since cyclosporine has tendency to alter lipid profile, it is advisable to evaluate the lipid profile before and after treatment and after first month of therapy. In case of significant increase, it is advisable to restrict dietary fats and if necessary reduce cyclosporine dosage.

Use cautiously in the treatment of patients with hyperuricemia. The dosage must be inspected rigorously. Laboratory checks should be done periodically.

In case of infections, even trivial ones (cold, influenza etc.) the doctor must be immediately informed.

For monitoring of the serum level of cyclosporine in whole blood, use of methods based on specific monoclonal antibodies (RIA methods) or by HPLC are preferred. A standard separation protocol (time and temperature) should be followed. It is necessary to keep in mind that the concentration of cyclosporine in the blood, is only one of the many factors that contribute to the clinical state of the patient. The repeated serum levels must therefore, be utilised as a guideline for determining the dosage in the context of the other clinical or laboratory parameters.
SPECIAL WARNINGS
Cyclosporine has not been shown to be teratogenic in animals. Experience with cyclosporine in pregnant females is still limited. Data relative to women subjected to organ transplantation indicate that, in comparison with the traditional immunosuppressive therapy, cyclosporine does not provoke any additional risk on the course and outcome of pregnancy. However, there are no adequate well controlled studies in pregnancy and hence cyclosporine should be used during pregnancy only if potential benefits outweigh the risk to foetus.

Safety during lactation:
Infants of women receiving cyclosporine should not be breast-fed as the drug passes into breast milk.

Cyclosporine in children:
Experience with cyclosporine in children is still limited. However, children of the age of 1 year and above have received cyclosporine in standard dose with no particular problems. In many studies pediatric patients have required and tolerated higher doses of cyclosporine per kg of body weight, in comparison with those used in adults.

INTERACTIONS
Particular attention must be paid in administering cyclosporine in association with medicines with noted nephrotoxic effects, for example aminoglycosides, amphotericin B, ciprofloxacin, digoxin, melfalan, colchicine and trimethoprim.
Since nonsteroidal antiinflammatory drugs (NSAIDs) may alter the renal function, association of these with cyclosporine or an increase of their dosage, must be accompanied in the initial phase by an attentive monitoring of the renal function.
Cyclosporine can increase the risk of muscular toxicity, including pain and weakness of muscles which may be noticed in the course of treatment with lovastatin. Hence, use of such medicines along with cyclosporine must be attentively and carefully considered. It is known that various medicines are capable of increasing or decreasing serum concentration of cyclosporine acting through competitive inhibition or induction of hepatic enzymes (in particular cytochrome P450) involved in the metabolism and excretion of cyclosporine. The following medicines can increase the serum levels of cyclosporine, e.g. ketoconazole, some macrolide antibiotics including erythromycin and josamycin, methyl prednisolone, metoclopramide, ranitidine, amiodarone, itraconazole, danazol, metronidazole, norfloxacin, and some calcium channel antagonists such as diltiazem, nicardipine and verapamil. Avoid taking nifedipine for patients who have developed gingival hypertrophy. Among the medicines that decrease the concentration of cyclosporine in plasma or in the whole blood, following have been indicated; barbiturates, carbamazepine, phenytoin and rifampicin. Hence, it is recommended that administration of cyclosporine along with these medicines must be avoided. If the concomitant administration of cyclosporine and one of these medicines is inevitable, blood concentration of cyclosporine must be monitored and appropriate modifications of dosage of cyclosporine must be brought about.

SIDE EFFECTS
The side effects are dose dependent and regress with the reduction of the dose. Those observed more frequently include hypertrichosis, tremors, renal dysfunction, hypertension, hepatic dysfunction, fatigue, gingival hypertrophy, gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhoea) and sensation of burning of the hands and feet (usually during the first week of the treatment). Occasionally headache and rashes, possibly of allergic origin are observed, besides slight anaemia, hyperkalemia, hyperuricemia, hypomagnesemia, increase in weight, oedema, pancreatitis, paresthesia and convulsions. In rare cases muscular cramps, muscular weakness and myopathy have been observed.

Especially in patients who have undergone liver transplantation, signs of encephalopathy, disturbances of vision and movement and altered consciousness have been observed. It has not yet been established if such alterations are caused by cyclosporine, by the underlying pathology itself, or by other conditions. Rarely a syndrome of thrombocytopenia and microangiopathic hemolytic anaemia and renal failure (hemolytic uremic syndrome) has been observed. In some patients neoplasms or lymphoproliferative disorders have been observed but their incidence and
distribution is similar to those in patients who have undergone conventional immunosuppressive therapy.

**POSOLOGY AND FREQUENCY OF ADMINISTRATION**

The intervals of dosage specified successively must be understood as per indications and references. Regular monitoring of the cyclosporine blood levels is advised.

**a) Solid Organ Transplantation**

The initial dose of cyclosporine equal to 10-15 mg/kg of cyclosporine must be administered within 12 hours before the operation in one intake. As a general rule, the same daily dose must be administered even after the operation for one or two weeks; then reduce the daily dose by five percent per week in accordance with the blood levels, till a maintenance dose of 2-6 mg/kg/day in divided doses. Cyclosporine concentrate for intravenous infusion can be used in case of gastroenteric intolerance so as to compromise the absorption of the oral preparations of the medicine. It is advised to change to oral preparations as soon as possible.

If cyclosporine is utilised in association with other immunosuppressive medicines (e.g. with corticosteroids or when triple or quadruple immunosuppressive therapy is necessary), lesser doses may be used (e.g. 3 to 6 mg/Kg/day given in two divided doses for initial treatment).

**b) Bone Marrow Transplantation**

The initial dose of cyclosporine must be administered the day preceding that of transplantation. In majority of the cases one prefers to use the concentrate for intravenous infusion at a dose of 2.5-5 mg/kg/day as initial dose and in the period following immediately the transplantation for a duration of not more than 2 weeks to pass on to the maintenance therapy by oral method at a dose of 12.5 mg/kg/day. In case of gastrointestinal complications that may reduce the absorption of medicine, a higher oral or intravenous dosage may be necessary. Cyclosporine may be given to initiate the treatment. In this case the advised dose is of 12.5-15 mg/kg/day in two divided doses from the first day of transplantation.

The maintenance therapy must be prolonged for at least 3-6 months (preferably 6 months) before reducing gradually to zero after one year. In some patients, discontinuation of cyclosporine may result in GVHD. In this case generally a positive response is obtained with the resumption of administration of cyclosporine. Low dose cyclosporine should be used to treat mild chronic GVHD. Intravenous cyclosporine is advised to be used in the treatment at a dose of 3.5 mg/kg/day, till the time the medicine cannot be taken orally. If possible oral administration at a dose of 12.5-15 mg/kg/day may be utilised right from the beginning. Initial posology must be maintained for about 2 months, reducing then gradually the dose (5% every week) till reaching 2 mg/kg/day. At such dosage the treatment can be suspended.

**c) Aplastic Anaemia**

The exact cyclosporine dosage has not yet been formalised in patients of aplastic anaemia. However, cyclosporine in initial dosage should be given in range of 3 to 7 mg/kg/day adjusted according to the response and serum creatinine levels. Cyclosporine should be continued for at least 3 months and until peripheral blood count has stabilized for at least one month and then drug is tapered off slowly.

**d) Endogenous Uveitis (including Behcet’s syndrome)**

It is recommended to start with an oral dose of 5 mg/kg/day in two divided doses till remission of the active inflammation of the uvea and improvement of vision is achieved. In refractory cases, dose can be increased to 7 mg/kg/day for a limited period, on condition that cyclosporine is tolerated and that alterations of biochemical parameters (creatininemia) or of blood pressure are not present.

For obtaining the initial remission or for controlling repeated inflammatory ocular attacks, cyclosporine is administered in concomitance with systemic corticosteroids if cyclosporine alone provides insufficient control (0.2-0.6 mg/kg/day equivalent to prednisone or equivalent doses of other corticosteroids).

In the maintenance therapy, the posology must be decreased gradually to the minimum effective dose so that during the phase of remission it should not surpass 5 mg/kg/day.

**Warning**
Since cyclosporine may alter the renal function, only patients with normal renal function must be treated. It is necessary to frequently evaluate the renal function and reduce the dose by 25-50% if the serum creatinine increases beyond 30% of the value recorded before starting the therapy even if such value is in the normal range. If an improvement of the intraocular inflammation is not obtained after 3 months of treatment with cyclosporine at adequate doses and in association with steroids, the possibility of adopting alternative therapies must be looked into.

e) Psoriasis
For inducing remission, it is recommended to start with 2.5 mg/kg/day orally in two divided doses. If no improvement is noted within a month gradually increase the posology without surpassing 5mg/kg/day. In patients who do not show adequate response after 6 months of the therapy at a dose of 5 mg/kg/day, it is better to discontinue the administration; it is also better to discontinue it in patients in whom the minimum effective dose is not compatible with the norms given later (see warnings) for ensuring the treatment. It is possible to begin the therapy with 5 mg/kg/day in patients in whom rapid improvement is required due to seriousness of the disease. For every patient the minimum effective dose of maintenance must be established, such dose should not exceed 5 mg/kg/day.

Warning
Patients with altered renal function, uncontrolled hypertension, clinically relevant infections or any type of malignancy (excluding the cutaneous ones, see later), should not be treated with cyclosporine. In patients with hyperuricemia or hyperkalemia, caution is necessary. Since cyclosporine may worsen the renal function, it is advisable to measure the serum creatinine levels every two weeks for the first three months of the therapy; subsequently in patients treated with 2.5 mg/kg/day, if serum creatinine remains stable, carry out a check every 2 months and monthly in those treated with higher doses. It is necessary to reduce the dose by 25-50% if the creatininemia increases beyond 30% with respect to base value, even if the values are in the normal range. If such reduction does not bring about the desired corrections of the parameter within one month, interrupt the treatment with cyclosporine. If in the course of the treatment an uncontrollable hypertension is set up even with an appropriate antihypertensive therapy, it is better to interrupt the treatment.

In patients with psoriasis, treated with cyclosporine or with other therapies, appearance of neoplasm, particularly of skin is reported. Cutaneous lesions, not typical of psoriasis which could make one think to be neoplastic or preneoplastic lesions, must be subjected to biopsy before initiating the treatment with cyclosporine. The patients who show cutaneous preneoplastic or neoplastic alterations can initiate the treatment with cyclosporine only after an adequate treatment of such lesions, and only if successful alternative therapy does not exist. Rarely appearance of lymphoproliferative disorders is observed in patients of psoriasis treated with cyclosporine which is readily reversible on suspension of the treatment.

f) Rheumatoid arthritis
The initial cyclosporine dose should range from 2.5 to 3.5 mg/kg/day with a maximum dosage of 5 mg/kg/day increased at 1-2 month interval by 0.5 mg/kg/day if clinical response is not seen. In responders cyclosporine dosage should be slowly reduced by 0.5 mg/kg/day, decrements every 1-2 months to lowest effective dosage.

In the subsequent maintenance therapy the dose must be adapted for individual patients in accordance with tolerability. Cyclosporine can be administered in combination with low doses of corticosteroids and/or non steroidal anti-inflammatory drugs.

Warning
Patients with reduced renal function, with uncontrollable hypertension or with malignant neoplasms of any type must not take cyclosporine. Since cyclosporine can alter renal function, it is necessary to determine the pretreatment value of serum creatinine carefully through at least two determinations. During the first three months of the therapy, it is advisable to monitor the levels of serum creatinine at intervals of two weeks, subsequently the determinations may be made every 4 week but a more frequent monitoring is necessary in case where the dose of cyclosporine is increased or concomitant treatment with a non steroidal anti-inflammatory drug is started. If serum creatinine reaches values exceeding 30% with respect to the base value in more than one measurement, it is necessary to reduce the dosage of cyclosporine. If the reduction of the dosage is not sufficient to decrease the values within a month, it is necessary to interrupt the
treatment with cyclosporine. Interruption of the therapy may also be necessary if during the course of the treatment, uncontrollable hypertension even with appropriate antihypertensive therapy has developed. As with other immunosuppressive medicines one must keep in mind the possibility of increase of the risk of occurrence of the lymphoproliferative disorders.

**g) Nephrotic syndrome**

For inducing remission, the recommended daily dose given in two divided oral doses is 5 mg/kg for adults and 6 mg/kg for children, if, except for proteinuria, renal function is normal. In patients with impaired renal function the initial dose should not exceed 2.5 mg/kg a day. The combination of cyclosporine with low doses of oral corticosteroids is recommended if the effect of cyclosporine alone is not satisfactory, especially in steroid resistant patients. If no improvement has been observed after 3 months treatment, cyclosporine therapy should be discontinued. The doses need to be adjusted individually according to efficacy (proteinuria) and safety (primarily serum creatinine) but should not exceed 5 mg/kg a day in adults and 6 mg/kg a day in children. For maintenance treatment the dose should be slowly reduced to the lowest effective level.

**Warning**

Since cyclosporine can impair renal function it is necessary to assess renal function frequently. If serum creatinine remains increased to more than 30% above creatinine levels recorded before starting cyclosporine therapy at more than one measurement, reduce the dosage of cyclosporine by 25 to 50%. Patients with abnormal baseline renal function should initially be treated with 2.5 mg/kg a 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 one year. In patients with nephrotic syndrome treated with immunosuppressants (including cyclosporine), the occurrence of malignancies (including Hodgkin’s lymphoma) has occasionally been reported.

**MODE OF ADMINISTRATION**

**Oral Solution**

For making the solution of the medicine, the syringe enclosed in the wrapping must be used.

**Procedure of making oral solution:**

1. Lift the plastic protection of the metallic cap
2. Remove completely the metallic cap
3. Remove the rubber plug and throw it away
4. Introduce the cannula in the bottle pushing the white cap till the mouth of the bottle.
5. Insert the syringe in the white cap of the cannula
6. Draw the required volume of solution
7. In case big air bubbles are formed inside the syringe, push the piston towards the base so that the bubbles escape from the cannula. Draw again the required volume of solution slowly. Presence of a few minute bubbles does not effect the quantity of the required dose.
8. After use, do not rinse the syringe, but clean only the external part with dry tissue paper and place it in the case. The cannula must remain in the bottle. Close the bottle with the black plastic cap provided separately.

Panimun Bioral should be diluted in a glass container (not of plastic), utilising preferably apple or orange juice (avoid grape juice). Soft drinks can be added according to individual taste. Prepare the solution immediately before taking. After having poured the medicine, mix well and drink immediately; subsequently rinse the glass with a small quantity of the same drink and drink it for ensuring that the full dose has been taken. The same drink should be continued for the entire duration of the treatment. The syringe for measuring the medicine must not get in contact with the drink. Cyclosporine solution should be used within 2 months of opening the bottle and be stored
between 25 and 35\(^{\circ}\)C - preferably not below 25\(^{\circ}\)C for prolonged periods as it contains oily components of natural origin which tend to solidify at low temperatures. A jelly like formation may occur below 25\(^{\circ}\)C, which is however reversible at temperature up to 35\(^{\circ}\)C. Minor flakes or a slight sediment may still be observed. These phenomena do not affect the efficacy and safety of the product, and the dosing by means of the syringe remains accurate. Do not utilise the solution if the aluminium seal is broken or has been removed before use.

**Capsules**

Panimun Bioral capsules should not be removed from the blister pack till required. On opening the blister pack one will notice a characteristic odour; it is normal and is not prejudicial to the utilisation of the medicine. The capsules must be swallowed whole and stored at temperature not exceeding 30\(^{\circ}\)C protected from moisture and should be administered in two divided doses.

**OVERDOSAGE**

Only minimal experience with overdose is available. However, because of slow absorption of cyclosporine (capsules and solution) forced emesis would be of value up to 2 hours of administration. Transient hepatotoxicity and nephrotoxicity may occur which resolve after drug withdrawal. General supportive measures and symptomatic treatment should be followed in such cases. Cyclosporine is not dialysable to large extent and neither is cleared by charcoal hemoperfusion.

The oral LD\(_{50}\) is 2329 mg/kg in mice, 1480 mg/kg in rats and more than 1000 mg/kg in rabbits while I.V. LD\(_{50}\) is 148 mg/kg in mice, 104 mg/kg in rats and 46 mg/kg in rabbits.

**CAUTION**

Do not utilise the medicine after the date of expiry as indicated.

**REFERENCES**