Public Assessment Report

Decentralised Procedure

Transimune 25mg, soft capsules
Transimune 50mg, soft capsules
Transimune 100mg, soft capsules

UK/H/0982/001-3/DC
UK licence no: PL 20117/0039-41

Morningside Healthcare Ltd
LAY SUMMARY

On 13 February 2008, the MHRA granted Morningside Healthcare Ltd Marketing Authorisations (licences) for the medicinal products Transimune 25mg, soft capsules (PL 20117/0039), Transimune 50mg, soft capsules (PL 20117/0040) and Transimune 100mg, soft capsules (PL 20117/0041). These are prescription only medicines (POM) for the prevention of rejection of newly transplanted organs or bone marrow transplants. They may also be used for the treatment of severe psoriasis, kidney disease, severe arthritis and severe eczema.

The active ingredient, ciclosporin, is an immunosuppressant which suppresses the immune system and reduces inflammation.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Transimune 25mg, 50mg and 100mg soft capsules outweigh the risks; hence Marketing Authorisations have been granted.
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Module 1

Information About Initial Procedure

| Product Name       | Transimune 25mg, soft capsules  
                      | Transimune 50mg, soft capsules  
                      | Transimune 100mg, soft capsules |
|--------------------|--------------------------------|
| Type of Application | Article 10.1, Generic Application |
| Active Substance   | Ciclosporin                      |
| Form               | Soft capsule                     |
| Strength           | 25mg, 50mg and 100mg             |
| MA Holder          | Morningside Healthcare Ltd       
                      | 115 Narborough Road               
                      | Leicester                         
                      | LE3 0PA                          |
| Reference Member State | United Kingdom                  |
| Concerned Member States | Czech Republic, Germany, Greece, Slovakia |
| Procedure Number   | UK/H/0982/001-3/DC              |
| Timetable          | Day 210 – 08 November 2007      |
Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Transimune 25 mg, soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Transimune 25 mg, soft capsules
1 soft capsule contains 25 mg of ciclosporin
1 soft capsule 25mg contains 25.00mg ethanol and 95.00 mg macrogolglycerol hydroxystearate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Soft capsules.
25 mg: Grey gelatin capsules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
In combination with other immunosuppressant substances for the prevention of acute and chronic transplant rejection following allogenic transplantation of kidneys, liver, heart, heart-lung, lung or pancreas.
Treatment of transplant rejection in patients who have previously received other immunosuppressants.
Prevention and treatment of graft-versus-host-disease (GVHD) following allogenic bone marrow transplantation.
Treatment of severe forms of psoriasis, particularly of the plaque type, which are not sufficiently treatable with conventional systemic therapy.
Treatment of severe atopic dermatitis in patients in whom conventional therapy is inappropriate or ineffective.
Treatment of steroid-dependent and steroid-resistant nephrotic syndrome due to glomerular disorders such as glomerular minimum changes, focal segmental glomerulosclerosis or membranous glomerulonephritis in adults and children whose glucocorticoids or alkylating agents are either insufficiently effective or involve unacceptable risks.
Transimune can be administered to achieve remission or maintenance of this condition. It can also be used to maintain steroid-induced remission and thus allow for reduction of corticosteroids.
Treatment of severe, active rheumatoid arthritis in adults when conventional therapy including at least one highly effective disease modifying antirheumatic medicinal product (DMARD) (e.g. low-dose methotrexate) has proved inadequate.
4.2 Posology and method of administration

Oral administration

The daily dose of Transimune should always be divided in 2 doses.

The capsules should be swallowed whole.

In transplant patients routine monitoring of the ciclosporin blood levels should be performed in order to avoid the risk of adverse reactions (if blood levels are too high) and organ rejection (if blood levels are too low).

Due to possible differences in bioavailability patients should not be transferred to or from other oral formulations of ciclosporin without appropriate close monitoring of ciclosporin blood concentrations, serum creatinine levels and blood pressure. For this reason it may be appropriate to prescribe by brand.

For drug level monitoring, whole blood is preferred, measured by a specific analytical method. A number of methods that measure unaltered ciclosporin (HPLC, specific monoclonal specific radioimmunoassays) as well as unspecific methods that also measure some metabolites have been developed for determining ciclosporin levels: The results of the various determination methods are not interchangeable. Determination of ciclosporin levels by means of specific monoclonal antibodies or by HPLC is to be given preference. Target concentration ranges depend on organ type, time after transplantation and immunosuppressive regimen.

It should be noted that other factors besides ciclosporin blood level can affect the clinical condition of the patient. The results are therefore intended only as a guide for dosing and should be used together with other clinical and laboratory parameters.

A higher oral dose of ciclosporin or an intravenous dose may be necessary if absorption is impaired by gastrointestinal disturbances.

Organ transplantation:

Treatment with Transimune is initiated within 12 hours prior to surgery with a dose of 10-15 mg/kg given in two divided doses. This daily dose is continued 1-2 weeks following surgery, whereupon the daily dose is gradually reduced in agreement with the blood concentration to a maintenance dose of approximately 2-6 mg/kg given in two divided doses.

When Transimune is used with other immunosuppressants (e.g. with corticosteroids or in poly-therapy), a lower dose is administered (e.g. initially 3-6 mg/kg given in two divided doses).

Bone marrow transplantation:

For the prevention of graft-versus-dost-disease (GVHD), ciclosporin is commonly used initially, short-term, in combination with methotrexate. The optimum dose should be adjusted individually. In general, treatment should be initiated 1 to 2 days before bone marrow transplantation with intravenous ciclosporin (dosage 2.5 to 5 mg/kg/day). This is replaced by oral administration as soon as patients are able to tolerate oral medication (generally at 12.5 mg/kg/day). Oral treatment should be continued for at least 3–6 months, before gradual dose reduction and eventual discontinuation.

Alternative treatment regimes are intravenous ciclosporin as mono therapy at 5 mg/kg/day (day -1 to day 3) and 3 mg/kg/day (day 4 to day 14) or combination therapy with intravenous Ciclosporin at 3 - 5 mg/kg/day and corticosteroids. In these cases, treatment should also be changed to the oral route as soon as possible and continued over a longer period.

If Transimune is used to initiate therapy, the recommended dose is 12.5 to 15mg/kg/day, given in two divided doses, starting on the day before transplantation.

Some patients may experience GVHD after discontinuation of ciclosporin treatment, but usually respond positively to repeated treatment. A low dose of Transimune can be used for mild, chronic GVHD.
Nephrotic syndrome:
For induction of remission the recommended oral dose is 5 mg/kg/day given in two divided doses for adults and 6 mg/kg/day for children, if renal function is normal. In patients with reduced renal function, the initial dose should not exceed 2.5 mg/kg/day.
Appropriate monitoring of the ciclosporin level pre-dose to avoid overdose in children is recommended.
In focal segmental glomerulosclerosis, a combination of ciclosporin and corticosteroids may be of benefit.
In the absence of efficacy after 3 months treatment for minimal change and focal segmental glomerulosclerosis or 6 months treatment for membranous glomerulonephritis, ciclosporin therapy should be discontinued.
The dose should be individually adjusted according to effect (proteinuria) and safety (mainly serum creatinine), but should not exceed 5 mg/kg/day for adults and 6 mg/kg/day for children.
In maintenance treatment the dose is slowly reduced to the lowest therapeutically effective level.

Rheumatoid arthritis:
For the first six weeks of therapy, the recommended dose is 2.5 mg/kg/day, given in two divided doses. The dose may be decreased depending on tolerance. The daily dose may be increased gradually, if the clinical effect is considered insufficient. Normally, the daily dose may not exceed 4 mg/kg/day. In individual cases, the dose may be increased up to 5 mg/kg/day. If the dose is increased too soon, there is a risk of overdosage.
In patients weighing less than 80 kg capsules of 100mg strength may be not appropriate for a precise dose titration.
For maintenance, the dosage should be adjusted individually to the lowest effective dose.
Low-dose corticosteroids and/or NSAIDs can be used in combination with Transimune (see also “4.5 Interaction with other medicinal products and other forms of interaction”).

Psoriasis:
Treatment of this condition is individually adjusted, since the disease varies greatly. For induction of remission the recommended initial dose is 2.5 mg/kg/day orally given in two divided doses. If no improvement is seen after 1 month, the daily dose can gradually be increased to maximum 5 mg/kg. The treatment should be discontinued in patients with psoriasis lesions which do not show a sufficient response within 6 weeks at 5 mg/kg/day or where the clinically effective dose is not compatible with the established safety guidelines.
An initial dose of 5 mg/kg/day is justified in patients whose condition requires rapid improvement. When a satisfactory response is achieved, treatment with Transimune can be discontinued and a possible relapse can be treated with Transimune at the previous clinically effective dose. Some patients may require continuous maintenance treatment.
In maintenance treatment the dose is individually titrated to the lowest clinically effective level and the dose should not exceed 5 mg/kg/day given in two divided doses.

Atopic dermatitis:
Treatment of this condition is individually adjusted, since the disease varies greatly. The recommended dose is 2.5-5 mg/kg/day orally given in two divided doses, for a maximum of 8 weeks. If an initial dose of 2.5 mg/kg/day does not give a satisfactory result within 2 weeks, the daily dose can be increased to maximum of 5 mg/kg. In very severe cases, the disease can be controlled with an initial dose of 5 mg/kg/day. When a satisfactory response is achieved, the dose should be gradually reduced and treatment discontinued.
Administration method:
The dose range is intended only as a guide. Routine monitoring of ciclosporin blood level is required in order to achieve the optimal therapeutic concentration for individual patients. Monitoring can be done by means of a RIA method based on monoclonal antibodies.

The total daily dose should always be administered in two divided doses. The divided doses should always be administered at the same time of day and the times between single doses should be approximately equivalent. Therefore, it is recommended to take the two divided doses in the morning and in the evening.

Transimune can be administered with food or alone.

Transimune should be taken with liquid and swallowed whole.

Switching from other oral ciclosporin preparations to Transimune:
In order to switch patients from other oral ciclosporin preparations to Transimune, ciclosporin trough blood levels, serum creatinine levels, and blood pressure should be checked prior to the switch (i.e., while using other oral ciclosporin preparations). The patient should be switched to the same daily dose of Transimune that was used for the prior ciclosporin preparation (mg per mg conversion). It is recommended that ciclosporin trough levels, serum creatinine, and blood pressure be checked after 4 - 7 days. If necessary, the dose of Transimune should be adjusted accordingly. Additional check-ups may be necessary in the first two months following the switch (e.g., weeks 2, 4, and 8) and the dose adjusted accordingly.

Dosage in renal insufficiency:
Specific investigations have not been performed on the pharmacokinetics of ciclosporin in transplant patients with impaired renal function. Special caution is required if a rapid rise in serum creatinine occurs (even within the normal range) after starting treatment with Transimune. A rise in serum creatinine or fall in creatinine clearance may also be the expression of an acute rejection reaction, particularly after renal transplantation. Initiation of treatment with Transimune in existing renal dysfunction and subsequent dose adjustment should only be undertaken after careful consideration of the benefits and risks, taking into account the overall clinical picture and ciclosporin blood levels.

For patients with nephrotoxic syndrome and moderately impaired renal function (baseline values of serum creatinine in adults <200 µmol/L, in children <140 µmol/L), an initial dose of 2.5 mg ciclosporin/kg body weight per day should not be exceeded. Patients must be monitored closely.

Dosage in impaired hepatic function:
Impaired liver function may considerably modify the pharmacokinetics of ciclosporin in some cases. Blood concentrations of ciclosporin (c_min) must be monitored closely in patients with impaired hepatic function and the dose adjusted accordingly.

In psoriasis, administration of Transimune should be terminated if liver enzymes and bilirubin levels are twice the baseline values.

In nephrotic syndrome patients with severe liver function disturbances, the initial dose should be decreased by 25% to 50%.

Elderly:
There is limited experience with the use of ciclosporin in the elderly, but no special problems have been seen at the recommended dose. However, factors associated with ageing, such as impaired renal function, necessitate careful supervision and possible dosage adjustment.

Children:
Experience in children is limited. However, ciclosporin has been used at the recommended dose for children from 1 year without special problems. In several studies children needed a higher dose of ciclosporin per kg body weight than adults and they tolerated the higher dose
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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Ciclosporin is contra-indicated 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 (see section 4.4 precautions).
- Ciclosporin is contra-indicated in rheumatoid arthritis patients with abnormal renal function, uncontrolled hypertension, uncontrolled infections or any kind of malignancy.
- Renal function disorders except in patients with nephrotic syndrome and mild-moderate renal insufficiency.
- Ciclosporin is contra-indicated in psoriasis patients receiving PUVA, UVB, coal tar, radiation therapy and other immunosuppressants.
- Ciclosporin is contra-indicated in nephrotic syndrome patients with uncontrolled hypertension, uncontrolled infections, or any kind of malignancy.
- Ciclosporin should not be used to treat rheumatoid arthritis in children and adolescents due to limited experiences in this population.
- Concomitant use of tacrolimus is specifically contra-indicated.
- Concomitant use of Hypericum perforatum (St. John’s Wort) drastically reduces the plasma concentration of ciclosporin. This may result in a loss of therapeutic effect (see section 4.5 Interactions)

4.4 Special warnings and precautions for use

Transimune should only be prescribed by physicians specialising in organ transplantation, dermatology, nephrology or rheumatology. Patients should be monitored in facilities with sufficient laboratory capacity and supporting medical resources. The responsible physician should have all the available information in preparation for the follow-up patients.

Ciclosporin should not be given in combination with other calcineurin inhibitors such as tacrolimus, since this can be expected to lead to an increase in adverse effects (see also 4.5 Interactions with other medicinal products and other forms of interactions) without an improvement in efficacy.

In patients being given Transimune, the use of potassium-sparing diuretics, medicinal products containing potassium, ACE inhibitors, angiotensin-II-receptor antagonists and a high intake of potassium with food should be avoided.

Grapefruit juice may elevate the blood levels of ciclosporin by interacting with the cytochrome-P450 system. The extent of these changes of ciclosporin levels in the blood, however, differs in individual cases and is not predictable. Therefore, grapefruit juice should not be taken in conjunction with Transimune.

The use of medicinal products that can cause gingival hyperplasia (e.g. nifedipine) should be avoided in patients who develop gingival proliferation under Transimune (see “4.8 Undesirable effects”).

When using inactivated vaccines or toxoid vaccines, the immune response should always be controlled by means of titer determination (see “4.5 Interaction with other medicinal products and other forms of interaction”).
Caution should be exercised in patients with hyperuricaemia since ciclosporin may further elevate uric acid levels.

Ciclosporin may impair renal function. For this reason, a reliable creatinine baseline value must be established prior to therapy with Transimune. In the first three months of treatment, the serum creatinine and serum urea values must be checked every two weeks.

In the event that kidney transplant patients who have very high ciclosporin levels in the blood present with continuously worsening renal function values and if the latter do not respond to a corresponding dose reduction, more extensive diagnostic tests should be conducted, e.g. a kidney biopsy.

Ciclosporin may also impair liver function. For this reason the parameters for liver function should be checked on a routine basis.

Since ciclosporin may on occasion precipitate hyperkalaemia or hypomagnesaemia or exacerbate existing electrolytic disturbances of this kind, it is recommended serum potassium and magnesium levels be monitored, particularly in patients with marked renal dysfunction.

During treatment with ciclosporin, a routine blood pressure check is required (see “4.8 Undesirable effects”). Treatment with Transimune should be discontinued if hypertension cannot be controlled with appropriate antihypertensive treatment.

When taking ciclosporin, a reversible elevation of blood lipids may occur. For this reason it is recommended that blood lipid values be determined prior to initiating treatment and following the first month of treatment. Should blood lipids become elevated, the intake of fats with food should be restricted and/or the ciclosporin dose should be reduced.

Routine dental check-ups (e.g. every three months) are recommended. In order to preclude or reduce gingival hyperplasia, teeth should be cleaned professionally and the patient should be instructed about measures necessary for personal dental hygiene.

Under ciclosporin treatment, there is an increased frequency of skin tumours. For this reason, patients should be warned against unnecessary radiation from the sun. A routine examination of the skin as well as histological examination of suspicious alterations is recommended.

Particular caution is advised in patients with untreated acute infections.

The routine determination of the minimum ciclosporin concentration in whole blood is an important safety measure within the scope of therapy monitoring in transplant patients (see “4.2 Posology and method of administration” under “Organ transplantation”).

It should be taken into account that the determination of the ciclosporin levels in whole blood, plasma, or serum is only one of the factors contributing to the clinical assessment of the patient's status. Therefore, blood ciclosporin levels should only serve as a reference for treatment and are to be supplemented by additional clinical and laboratory parameters.

Ciclosporin 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, ciclosporin should be withdrawn due to the possible risk of permanent visual loss.

**Further precautions in nephrotic syndrome**

Since Transimune may reduce the renal function, frequent monitoring is necessary and if the serum creatinine levels are more than 30% above baseline in more than one measurement, the dose of Transimune should be reduced by 25-50%. Patients with an abnormal baseline for renal function should be treated initially with 2.5 mg/kg/day and monitored carefully.

It should be noted that in some nephrotic syndrome itself can cause alterations in renal function. Thus, structural kidney alterations have been observed in association with Ciclosporin treatment, without an increase in serum creatinine levels. Renal biopsy is indicated in patients treated with ciclosporin for more than one year to assess the progression of renal disease and the extent of any ciclosporin-associated changes in renal morphology that may co-exist.
In patients with nephrotic syndrome treated with immunosuppressants (including ciclosporin), there have been reports of malignant growths (including Hodgkin’s lymphoma). Long-term data on ciclosporin 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.

**Further precautions in rheumatoid arthritis**

Since Transimune may reduce renal function, a reliable baseline for serum creatinine in at least two measurements should be established before treatment. Afterwards, serum creatinine levels should be monitored weekly for one month. Thereafter serum creatinine should be monitored every two weeks in the first 3 months of treatment and thereafter once a month. More frequent control is required when the dose of Transimune dose is increased, if concomitant treatment with a non-steroidal anti-inflammatory substance is initiated or increased.

If serum creatinine levels are more than 30% above baseline in several measurements, the dose of Transimune should be reduced. If serum creatinine levels increase by more than 50%, the dose should be reduced by 50%. These recommendations apply even if values are within the normal laboratory range. If serum creatinine levels do not decrease within 1 month, treatment with Transimune should be discontinued.

Treatment should also be discontinued if treatment-emergent hypertension cannot be controlled with appropriate antihypertensive treatment.

As with other long immunosuppressive treatments there is an increased risk of lymphoproliferative disturbances. Caution is advised if Transimune is used concomitantly with methotrexate.

When treating rheumatoid arthritis, and taking into consideration the safety of the patient, additional controls should be carried out in accordance with the following time frame:

- haematology profile (red blood count, leucocyte and thrombocyte counts): primary and thereafter every 4 weeks
- liver enzymes: primary and thereafter every 4 weeks
- urine status: primary and thereafter every 4 weeks
- blood pressure: primary and thereafter every 2 weeks for 3 months. Afterwards, every 4 weeks.
- potassium, lipids: primary and thereafter every 4 weeks.

Experience is available from clinical studies for a period of up to 12 months. There is currently insufficient experience for longer treatment periods. If there is no perceptible effect after 3 months of treatment, administration with Transimune should be discontinued.

**Further precautions in psoriasis**

Since Transimune may reduce the renal function, a reliable baseline for serum creatinine in at least two measurements should be established before the treatment, and serum creatinine should be monitored every two weeks in the first 3 months of the treatment and thereafter once a month. If serum creatinine levels increase to more than 30% above baseline and are continually increased in more than one measurement, the dose of Transimune dose should be reduced by 25-50%. If serum creatinine level increases by more than 50%, the dose should be reduced by 50%. These recommendations apply even if values are within the normal laboratory range. If serum creatinine levels do not decrease within 1 month, treatment with Transimune should be discontinued.

The treatment should also be discontinued if treatment-emergent hypertension cannot be controlled with appropriate antihypertensive treatment.
Elderly patients should only be treated if their psoriasis is debilitating, and their renal function should be monitored carefully.

The duration of use is normally 12 weeks. Insufficient experience exists with treatment regimens longer than 24 weeks in duration. Termination of the treatment is recommended if high blood pressure which cannot be adequately controlled occurs during treatment with Transimune.

Development of malignant growths (especially of the skin) has been reported in psoriasis patients receiving treatment with ciclosporin as well as those treated with traditional immunosuppressants. A scan for all forms of pre-existing tumours, including those of the skin and cervix, should be carried out. A biopsy should be performed before starting Ciclosporin treatment on skin lesions which are not typical for psoriasis to exclude skin cancers, mycosis fungoides or other premalignant disorders. Patients with malignant or premalignant skin alterations should only be treated with Transimune after appropriate treatment of these lesions and only if there is no alternative treatment.

A small number of psoriasis patients on ciclosporin treatment have developed lymphoproliferative disturbances which were reversible by immediate discontinuation of treatment. Patients treated with Transimune should not receive concomitant irradiation treatment with UV-B-radiation or PUVA-photochemotherapy.

In view of the potential risk of skin malignancy, patients on Transimune should be warned to avoid excessive unprotected sun exposure

**Further precautions in atopic dermatitis**

Since Transimune may reduce the renal function, a reliable baseline for serum creatinine in at least two measurements should be established before the treatment, and serum creatinine should be monitored every two weeks in the first 3 months of the treatment and thereafter once a month. If serum creatinine levels increase to more than 30% above baseline and are continuously increased in more than one measurement, the dose of Transimune should be reduced by 25-50%. These recommendations apply even if values are within the normal laboratory range. If serum creatinine levels do not decrease within 1 month, treatment with Transimune should be discontinued.

Treatment should also be discontinued if treatment-emergent hypertension cannot be controlled with appropriate antihypertensive treatment.

Since experience with ciclosporin in children with atopic dermatitis is limited, Transimune is not recommended for use in children.

Elderly patients should only be treated if their atopic dermatitis is debilitating, and their renal function should be monitored carefully.

Benign lymphadenopathy is often connected with flare-up of atopic dermatitis and disappears spontaneously or with improvement in the disease. Lymphadenopathy observed in association with ciclosporin treatment should be monitored carefully. If lymphadenopathy continues despite improvement, a preventive biopsy should be made to exclude the possibility of lymphoma.

Active herpes simplex-infections should be eliminated before treatment with Transimune is initiated, but discontinuation of ciclosporin treatment is only warranted if severe infection develops during treatment.

Skin infections with *Staphylococcus aureus* are not an absolute contraindication for treatment with Transimune, but should be treated with appropriate antibacterial drugs. Oral erythromycin may increase the blood concentration of ciclosporin (see “4.5 Interaction with other medicinal products and other forms of interaction) and should therefore be avoided. If there is no alternative available, blood concentrations of ciclosporin, renal function and possible adverse reactions to Ciclosporin should be monitored closely.
Since there is a potential risk of malignant skin growths, patients treated with Transimune should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant radiotherapy with UV-B-radiation or PUVA-photochemotherapy.

**Excipients of Transimune**

This medicine contains macrogolglycerol hydroxystearate which may cause stomach upset and diarrhoea.

This medicinal product contains ethanol:

A Transimune 25 mg soft capsule contains 25.00mg pure ethanol.

This medicinal product contains 12.7 vol% ethanol (alcohol), i.e. up to 525mg per dose, equivalent to 13ml beer, 6ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding woman, children and high-risk groups such as patients with liver disease, or epilepsy

4.5 Interaction with other medicinal products and other forms of interaction

**Interaction with foods**

Concomitant administration of grapefruit juice has been shown to increase the bioavailability of ciclosporin.

**Interaction with other medicines**

The section below list the medicines for which an interaction with Ciclosporin has been sufficiently proven and is considered to be clinically relevant.

Different medicines either increase or decrease the plasma or whole blood concentration of ciclosporin, usually by inhibition or induction of enzymes involved in the metabolism of ciclosporin (particularly cytochrome P450).

The product contains ethanol (see section 4.4). Ethanol may interact with other medical products.

**Medicines which reduce ciclosporin concentrations:**

Barbiturates, carbamazepine, phenytoin, phenobarbital; primidone; griseofulvin; metamizole; nafcillin, sulfadimidine and trimethoprim i.v.; rifampicin; octreotide; probucol; sulphadiazine; orlistat; troglitazone; *Hypericum perforatum* (St. John’s Wort); ticlopidine.

Patients on ciclosporin treatment should not use products/herbal medicines, which contain *Hypericum perforatum*, since this may cause a marked reduction in plasma concentrations of ciclosporin by induction of CYP3A4, and thus a diminution of therapeutic efficacy (see 4.3.Contraindications).

**Medicines which increase ciclosporin concentrations:**

Macrolide antibiotics (mainly erythromycin, clarithromycin, josamycin, roxithromycin, and pristinamycin); ketoconazole, fluconazole, itraconazole; calcium antagonists (such as diltiazem, nicardipine, verapamil); metoclopramide; oral contraceptives; propafenone; danazol; methylprednisolone (high dose); allopurinol; anti-H2 (cimetidine, ranitidine); chloroquine; amiodarone; bromocriptine; protease inhibitors; doxycycline.

**Other relevant forms of interaction with other medicines**

Caution is advised when the concomitant use of other medicines with ciclosporin results in nephrotoxic synergy: aminoglycosides (including gentamicin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+sulfamethoxazole); non-steroidal antiinflammatory substances (including diclofenac, naproxen, sulindac); melphalan tacrolimus and sirolimus.
During treatment with ciclosporin vaccinations may be less effective, so the use of live weakened vaccine should be avoided.

Concomitant administration of nifedipine and ciclosporin may exacerbate the gingival hyperplasia that is seen when ciclosporin is used alone.

When combining Transimune with corticosteroids, methylprednisolone, prednisone, or prednisolone, an increased risk of brain seizures has been reported. This is especially true for high doses of corticosteroids.

Concomitant use of diclofenac and ciclosporin has shown to cause a pronounced increase in the bioavailability of diclofenac, which may cause reversible reduced renal function. The increase in the bioavailability of diclofenac is probably due to a reduction in the high first-pass effect of diclofenac. If non-steroidal anti-inflammatory substances with a low first-pass effect (e.g. acetylsalicylic acid) are used concomitantly with ciclosporin, no increase in bioavailability is expected.

Ciclosporin may also reduce the excretion of digoxin, colchicine, lovastatin, pravastatin, simvastatin, atorvastatin and prednisolone and may therefore lead to digoxin toxicity or increase the risk of muscle toxicity (including muscle pain and weakening, myositis and occasionally rhabdomyolysis) due to colchicin, lovastatin, pravastatin, simvastatin and atorvastatin.

**Recommendations**

If concomitant use of medicines which have an interaction with ciclosporin is unavoidable, the following basic recommendations should be followed:

During concomitant use of medicines which cause nephrotoxic synergy, renal function (especially serum creatinine) should be monitored carefully. If renal function is considerably reduced, the dose of the concomitant medicine should be decreased or an alternative treatment should be considered.

**Medicines, which are known to reduce or increase the bioavailability of ciclosporin:**

In transplant patients frequent measurement of ciclosporin concentrations is required with possible dose adjustment, especially during initiation of treatment or at discontinuation of the concomitant medicine. In non-transplant patients, the value of monitoring blood concentrations of ciclosporin is doubtful, since the relationship between blood concentration and clinical effect is not well established. If medicines which increase the ciclosporin concentrations are used concomitantly, it may be more useful to measure renal function frequently and to monitor the patient carefully with regards to ciclosporin related adverse reactions.

Concomitant use of nifedipine should be avoided in patients with gingival hyperplasia.

Non-steroidal anti-inflammatory substances, which are known to have a marked first-pass metabolism (e.g. diclofenac), should be given at a lower dose than that normally recommended for patients not receiving ciclosporin.

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

If digoxin, colchicine, lovastatin, pravastatin or simvastatin are used concomitantly with ciclosporin, carefully clinical monitoring is required.

### 4.6 Pregnancy and lactation

**Pregnancy:**

Experience with ciclosporin in pregnant women is limited.
Ciclosporin does not demonstrate teratogenicity in experimental animals. Limited experience regarding the safety of administration of ciclosporin to pregnant women has shown no indications of teratogenicity. Ciclosporin does pass into the placenta. Initial experience with transplantation patients, however, did indicate that ciclosporin, as with other immunosuppressive agents, increases the probability of specific complications during pregnancy, such as pre-eclampsia and premature births with decreased birth weights. Transimune should be given during pregnancy only when the benefits outweigh the risks. Pregnant women who are being treated with Transimune should be observed carefully.

**Lactation:**
Ciclosporin is excreted in the breast milk. Women receiving Transimune treatment should not breastfeed.

### 4.7 Effects on ability to drive and use machines

No data exist on the effects of ciclosporin on ability to drive and use machines. The product contains ethanol (see section 4.4). Ethanol may have an influence on the ability to drive and use machines.

### 4.8 Undesirable effects

Many of the adverse reactions to ciclosporin are dose dependent and can be avoided by dose reduction. The adverse reactions are generally the same in the different indications, but occur at differing frequencies. Since a higher initial dose and longer maintenance treatment is required after transplantation, adverse reactions are seen more frequently and are usually more severe in transplant patients than in patients treated for other indications.

Frequency estimates:
- **Very common** (≥1/10)
- **Common** (≥1/100 to <1/10)
- **Uncommon** (≥1/1,000 to <1/100)
- **Rare** (≥1/10,000 to <1/1,000)
- **Very rare** (<1/10,000), not known (cannot be estimated from the available data)

**Blood and lymphatic system disorders**
- Uncommon: Anaemia, thrombocytopenia.
- Rare: Microangiopathic haemolytic anaemia, haemolytic uraemic syndrome.

**Endocrine disorders**
- Uncommon: Malignant neoplasia or lymphoproliferative diseases have been reported, with incidence and distribution similar to those in patients receiving traditional immunosuppressive therapy.
- Rare: Menstrual disturbances, gynecomastia.

**Metabolism and nutrition disorders**
- Very common: Hyperlipidaemia.
- Common: Hyperuricaemia, hyperkalaemia, hypomagnesaemia.
- Rare: Hyperglycaemia.

**Nervous system disorders**
- Very common: Tremor, headache.
Common: Paresthesia.
Uncommon: Signs of encephalopathy, e.g. convulsion, confusion, disorientation, decreased responsiveness, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis, cerebellar ataxia.
Rare: Motor polyneuropathy.
Very rare: Oedema in the visual pupil, including disk oedema with possible visual weakening following benign intracranial hypertension.
Vascular disorders
Very common: Hypertension.
Gastrointestinal disorders
Common: Anorexia, nausea, vomiting, abdominal pain, diarrhoea, gingival hyperplasia.
Hepatobiliary disorders
Common: Hepatic dysfunction.
Rare: Pancreatitis.
Skin and subcutaneous tissue disorders
Common: Hypertrichosis.
Uncommon: Allergic rash.
Musculoskeletal and connective tissue disorders
Common: Muscle cramps, myalgia.
Rare: Muscle weakness, myopathy.
Renal and urinary disorders
Very common: Renal dysfunction (see 4.4 Special warnings and precautions for use).
General disorders and administration site conditions
Common: Fatigue.
Uncommon: Oedema, weight gain.

4.9 Overdose
a) Symptoms of intoxication
Little experience exists with overdose. After ingestion of doses up to 10 g ciclosporin (approximately 150 mg/kg), vomiting, somnolence, headache, tachycardia and in some patients a moderately severe, reversible kidney dysfunction was observed. There have been reports of severe intoxication symptoms with preterm infants after inadvertent parenteral overdose.

b) Therapy of intoxication
Possible signs of nephrotoxicity are reversible in most cases after discontinuation of administration of Transimune. In case of an overdose, symptomatic treatment and general supportive measures should be applied. Ciclosporin is not dialyzable nor is it eliminated by activated charcoal-haemoperfusion therapy.
Therefore, elimination is limited to non-specific treatment, e.g. gastrolavage. However, activated charcoal eliminates small amounts of ciclosporin from the enterohepatic circulation. Within the first few hours after overdose, it may be beneficial for the patient to induce vomiting.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Immunosuppressants, ATC code: L 04 AA 01
Ciclosporin (also called cyclosporin A) is a cyclic poly peptide, which consists of 11 amino acids. It is a strong immunosuppressive substance, which in animals increases the survival of allogenic transplantations of skin, heart, kidneys, pancreas, bone marrow, small intestine and lungs. Studies show that ciclosporin inhibits the development of cell-mediated reactions, including allotransplantation immunity, delayed skin hypersensitivity, experimental allergic encephalomyelitis, Freund’s adjuvant arthritis, graft-versus-host disease (GVHD) and the production of T-cell dependent antibodies. At the cellular level ciclosporin inhibits the production and release of lymphokines, including interleukin 2 (T-cell growth factor, TCGF). Ciclosporin apparently blocks the resting lymphocytes in phase G0 or G1 in the cell cycle and inhibits the antigen triggered release of lymphokines from activated T-cells.

The existing evidence indicates that ciclosporin acts specifically and reversibly on lymphocytes. Contrary to cytostatic agents, ciclosporin does not suppress haemopoiesis and has no effect on phagocytic cell function. Patients treated with ciclosporin are less susceptible to infections than those treated with other immunosuppressants.

Successful organ and bone marrow transplantations have been carried out in humans, where ciclosporin has been used to prevent and treat rejection and GVHD.

Treatment with ciclosporin has also shown to be advantageous in a series of other conditions with a known autoimmune origin or considered to be of autoimmune origin.

5.2 Pharmacokinetic properties
The maximal blood concentration (Cmax) is achieved within 1-2 hours (Tmax). The absolute bioavailability is 30-60%. The inter- and intra-individual pharmacokinetic variability is 10-20% for AUC and Cmax in healthy volunteers. Transimune can be administered with food or alone.

The results of several studies have shown that monitoring of the ciclosporin area under the time-concentration curve for the first 4 hours after administration of dose (AUC0-4) gives a more precise prediction of the ciclosporin exposure than at base (C0) monitoring.

The results from further studies indicate that a single test point 2 hours after the dose (C2) correlate well with the AUC0-4 in transplantation patients.

In medical practice either trough level monitoring or C2 monitoring of ciclosporin can be used for pharmacotherapeutic surveillance.

Ciclosporin is mainly distributed outside the blood volume. In the blood there is 33-47% ciclosporin in plasma, 4-9% in the lymphocytes, 5-12% in the granulocytes and 41-58% in the erythrocytes. In plasma approximately 90% is bound to proteins, mainly lipoproteins.

Ciclosporin is biotransformed by several metabolic routes into approximately 15 metabolites. The elimination is mainly biliary, where only 6% of an oral dose is eliminated with the urine. Only 0.1% is eliminated unchanged in the urine.

There is a great variation in the available data regarding the terminal half life of ciclosporin depending on the analysis and the target population. The terminal half life varied from 6.3 hours in healthy volunteers to 20.4 hours in patients with severe hepatic disease.

5.3 Preclinical safety data
Ciclosporin showed no mutagenic or teratogenic effects in appropriate test systems.
Reproduction studies in rats showed only negative effects at doses, which were toxic for the
females. At toxic doses (rats 30 mg/kg and rabbits 100 mg/kg/day orally), ciclosporin was embryo- and foeto-toxic, which was indicated by increased prenatal and postnatal mortality and reduced foetal weight and bone formation.

Within the well tolerated dose range (in rats up to 17 mg/kg/day and in rabbits up to 30 mg/kg/day orally) ciclosporin showed no embryo-lethal or teratogenic effects.

Carcinogenicity studies were carried out on male and female rats and mice. In the mouse study, which lasted 78 weeks, there was a statistically significantly greater incidence of lymphocytic lymphomas in female mice at a dose of 1, 4 and 16 mg/kg/day and a considerably higher occurrence of hepatocellular carcinomas in male mice, compared to control animals. In the rat study, which lasted 24 months and involved a dose of 0.5, 2 and 8 mg/kg/day, the incidence of island cell adenomas in the pancreas considerably exceeded the control value at the low dose. Hepatocellular carcinomas and island cell adenomas in the pancreas were not dose related.

Studies in male and female rats showed no reduction in fertility.

Ciclosporin was not found to be mutagenic/genotoxic in the Ames-test, the v79-hgppt-test or the micronucleus test in mice and Chinese hamsters or the chromosome aberration test of the bone marrow of Chinese hamsters, the dominating mortality analysis in mice and the DNA-repair test in semen from treated mice. An in-vitro analysis of sister chromatid exchange (SCE) in human lymphocytes showed a positive effect of ciclosporin at high doses in this system.

An increased occurrence of malignant growths is a recognised complication in connection with immunosuppression in organ transplant patients. The most common forms of neoplasms are non-Hodgkin’s related lymphomas and skin carcinomas. The risk of malignant growths during treatment with ciclosporin is higher than in a normal healthy population, but is similar to the risk for patients treated with other immunosuppressants. Reports that reduction or discontinuation of immunosuppressants may cause regression of lesions are available.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Content of the soft capsules**

- Ethanol anhydrous,
- Tocopherol acetate
- Diethylene glycol monoethyl ether
- Oleoyl macrogolglycerides
- Macrogolglycerol Hydroxystearate

**Capsule shell**

- Gelatin, Glycerol
- Propylene glycol
- Titanium dioxide (E171),
- Iron oxide black (E172)
- Purified water.

#### 6.2 Incompatibilities

Not applicable.
6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.
Store in the original package.

6.5 Nature and contents of container
The soft capsules are available in aluminium-aluminium blister of:
10, 20, 30, 50 & 60 capsules
Not all pack sizes may be marketed

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Morningside Healthcare Ltd
115 Narborough Road
Leicester
LE3 0PA
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 20117/0039

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
13/02/2008

10 DATE OF REVISION OF THE TEXT
13/02/2008

11 DOSIMETRY (IF APPLICABLE)
12  INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Transimune 50 mg, soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Transimune 50 mg, soft capsules
1 soft capsule contains 50 mg of ciclosporin
1 soft capsule 50mg contains 50.00mg ethanol and 190.00 mg macrogolglycerol hydroxystearate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Soft capsules.
50 mg: White gelatin capsules

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
In combination with other immunosuppressant substances for the prevention of acute and chronic transplant rejection following allogenic transplantation of kidneys, liver, heart, heart-lung, lung or pancreas.
Treatment of transplant rejection in patients who have previously received other immunosuppressants.
Prevention and treatment of graft-versus-host-disease (GVHD) following allogenic bone marrow transplantation.
Treatment of severe forms of psoriasis, particularly of the plaque type, which are not sufficiently treatable with conventional systemic therapy.
Treatment of severe atopic dermatitis in patients in whom conventional therapy is inappropriate or ineffective.
Treatment of steroid-dependent and steroid-resistant nephrotic syndrome due to glomerular disorders such as glomerular minimum changes, focal segmental glomerulosclerosis or membranous glomerulonephritis in adults and children whose glucocorticoids or alkylating agents are either insufficiently effective or involve unacceptable risks.
Transimune can be administered to achieve remission or maintenance of this condition. It can also be used to maintain steroid-induced remission and thus allow for reduction of corticosteroids.
Treatment of severe, active rheumatoid arthritis in adults when conventional therapy including at least one highly effective disease modifying antirheumatic medicinal product (DMARD) (e.g. low-dose methotrexate) has proved inadequate.
4.2 Posology and method of administration

The daily dose of Transimune should always be divided in 2 doses.

The capsules should be swallowed whole.

In transplant patients routine monitoring of the ciclosporin blood levels should be performed in order to avoid the risk of adverse reactions (if blood levels are too high) and organ rejection (if blood levels are too low).

Due to possible differences in bioavailability patients should not be transferred to or from other oral formulations of ciclosporin without appropriate close monitoring of ciclosporin blood concentrations, serum creatinine levels and blood pressure. For this reason it may be appropriate to prescribe by brand.

For drug level monitoring, whole blood is preferred, measured by a specific analytical method. A number of methods that measure unaltered ciclosporin (HPLC, specific monoclonal specific radioimmunoassays) as well as unspecific methods that also measure some metabolites have been developed for determining ciclosporin levels: The results of the various determination methods are not interchangeable. Determination of ciclosporin levels by means of specific monoclonal antibodies or by HPLC is to be given preference. Target concentration ranges depend on organ type, time after transplantation and immunosuppressive regimen.

It should be noted that other factors besides ciclosporin blood level can affect the clinical condition of the patient. The results are therefore intended only as a guide for dosing and should be used together with other clinical and laboratory parameters.

A higher oral dose of ciclosporin or an intravenous dose may be necessary if absorption is impaired by gastrointestinal disturbances.

Organ transplantation:

Treatment with Transimune is initiated within 12 hours prior to surgery with a dose of 10-15 mg/kg given in two divided doses. This daily dose is continued 1-2 weeks following surgery, whereupon the daily dose is gradually reduced in agreement with the blood concentration to a maintenance dose of approximately 2-6 mg/kg given in two divided doses.

When Transimune is used with other immunosuppressants (e.g. with corticosteroids or in poly-therapy), a lower dose is administered (e.g. initially 3-6 mg/kg given in two divided doses).

Bone marrow transplantation:

For the prevention of graft-versus-dost-disease (GVHD), ciclosporin is commonly used initially, short-term, in combination with methotrexate. The optimum dose should be adjusted individually. In general, treatment should be initiated 1 to 2 days before bone marrow transplantation with intravenous ciclosporin (dosage 2.5 to 5 mg/kg/day). This is replaced by oral administration as soon as patients are able to tolerate oral medication (generally at 12.5 mg/kg/day). Oral treatment should be continued for at least 3–6 months, before gradual dose reduction and eventual discontinuation.

Alternative treatment regimes are intravenous ciclosporin as mono therapy at 5 mg/kg/day (day -1 to day 3) and 3 mg/kg/day (day 4 to day 14) or combination therapy with intravenous Ciclosporin at 3 - 5 mg/kg/day and corticosteroids. In these cases, treatment should also be changed to the oral route as soon as possible and continued over a longer period.

If Transimune is used to initiate therapy, the recommended dose is 12.5 to 15mg/kg/day, given in two divided doses, starting on the day before transplantation.

Some patients may experience GVHD after discontinuation of ciclosporin treatment, but usually respond positively to repeated treatment. A low dose of Transimune can be used for mild, chronic GVHD.
Nephrotic syndrome:

For induction of remission the recommended oral dose is 5 mg/kg/day given in two divided doses for adults and 6 mg/kg/day for children, if renal function is normal. In patients with reduced renal function, the initial dose should not exceed 2.5 mg/kg/day.

Appropriate monitoring of the ciclosporin level pre-dose to avoid overdose in children is recommended.

In focal segmental glomerulosclerosis, a combination of ciclosporin and corticosteroids may be of benefit.

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

The dose should be individually adjusted according to effect (proteinuria) and safety (mainly serum creatinine), but should not exceed 5 mg/kg/day for adults and 6 mg/kg/day for children.

In maintenance treatment the dose is slowly reduced to the lowest therapeutically effective level.

Rheumatoid arthritis:

For the first six weeks of therapy, the recommended dose is 2.5 mg/kg/day, given in two divided doses. The dose may be decreased depending on tolerance. The daily dose may be increased gradually, if the clinical effect is considered insufficient. Normally, the daily dose may not exceed 4 mg/kg/day. In individual cases, the dose may be increased up to 5 mg/kg/day. If the dose is increased too soon, there is a risk of overdosage.

In patients weighing less than 80 kg capsules of 100mg strength may be not appropriate for a precise dose titration.

For maintenance, the dosage should be adjusted individually to the lowest effective dose.

Low-dose corticosteroids and/or NSAIDs can be used in combination with Transimune (see also “4.5 Interaction with other medicinal products and other forms of interaction”).

Psoriasis:

Treatment of this condition is individually adjusted, since the disease varies greatly. For induction of remission the recommended initial dose is 2.5 mg/kg/day orally given in two divided doses. If no improvement is seen after 1 month, the daily dose can gradually be increased to maximum 5 mg/kg. The treatment should be discontinued in patients with psoriasis lesions which do not show a sufficient response within 6 weeks at 5 mg/kg/day or where the clinically effective dose is not compatible with the established safety guidelines.

An initial dose of 5 mg/kg/day is justified in patients whose condition requires rapid improvement. When a satisfactory response is achieved, treatment with Transimune can be discontinued and a possible relapse can be treated with Transimune at the previous clinically effective dose. Some patients may require continuous maintenance treatment.

In maintenance treatment the dose is individually titrated to the lowest clinically effective level and the dose should not exceed 5 mg/kg/day given in two divided doses.

Atopic dermatitis:

Treatment of this condition is individually adjusted, since the disease varies greatly. The recommended dose is 2.5-5 mg/kg/day orally given in two divided doses, for a maximum of 8 weeks. If an initial dose of 2.5 mg/kg/day does not give a satisfactory result within 2 weeks, the daily dose can be increased to maximum of 5 mg/kg. In very severe cases, the disease can be controlled with an initial dose of 5 mg/kg/day. When a satisfactory response is achieved, the dose should be gradually reduced and treatment discontinued.
Administration method:
The dose range is intended only as a guide. Routine monitoring of ciclosporin blood level is required in order to achieve the optimal therapeutic concentration for individual patients. Monitoring can be done by means of a RIA method based on monoclonal antibodies.
The total daily dose should always be administered in two divided doses. The divided doses should always be administered at the same time of day and the times between single doses should be approximately equivalent. Therefore, it is recommended to take the two divided doses in the morning and in the evening.
Transimune can be administered with food or alone.
Transimune should be taken with liquid and swallowed whole.
Switching from other oral ciclosporin preparations to Transimune:
In order to switch patients from other oral ciclosporin preparations to Transimune, ciclosporin trough blood levels, serum creatinine levels, and blood pressure should be checked prior to the switch (i.e., while using other oral ciclosporin preparations). The patient should be switched to the same daily dose of Transimune that was used for the prior ciclosporin preparation (mg per mg conversion). It is recommended that ciclosporin trough levels, serum creatinine, and blood pressure be checked after 4 - 7 days. If necessary, the dose of Transimune should be adjusted accordingly. Additional check-ups may be necessary in the first two months following the switch (e.g., weeks 2, 4, and 8) and the dose adjusted accordingly.
Dosage in renal insufficiency:
Specific investigations have not been performed on the pharmacokinetics of ciclosporin in transplant patients with impaired renal function. Special caution is required if a rapid rise in serum creatinine occurs (even within the normal range) after starting treatment with Transimune. A rise in serum creatinine or fall in creatinine clearance may also be the expression of an acute rejection reaction, particularly after renal transplantation. Initiation of treatment with Transimune in existing renal dysfunction and subsequent dose adjustment should only be undertaken after careful consideration of the benefits and risks, taking into account the overall clinical picture and ciclosporin blood levels.
For patients with nephrototoxic syndrome and moderately impaired renal function (baseline values of serum creatinine in adults <200 µmol/L, in children <140 µmol/L), an initial dose of 2.5 mg ciclosporin/kg body weight per day should not be exceeded. Patients must be monitored closely.
Dosage in impaired hepatic function:
Impaired liver function may considerably modify the pharmacokinetics of ciclosporin in some cases. Blood concentrations of ciclosporin (cmin) must be monitored closely in patients with impaired hepatic function and the dose adjusted accordingly.
In psoriasis, administration of Transimune should be terminated if liver enzymes and bilirubin levels are twice the baseline values.
In nephrotic syndrome patients with severe liver function disturbances, the initial dose should be decreased by 25% to 50%.
Elderly:
There is limited experience with the use of ciclosporin in the elderly, but no special problems have been seen at the recommended dose. However, factors associated with ageing, such as impaired renal function, necessitate careful supervision and possible dosage adjustment.
Children:
Experience in children is limited. However, ciclosporin has been used at the recommended dose for children from 1 year without special problems. In several studies children needed a higher dose of ciclosporin per kg body weight than adults and they tolerated the higher dose
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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Ciclosporin is contra-indicated 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 (see section 4.4 precautions).
- Ciclosporin is contra-indicated in rheumatoid arthritis patients with abnormal renal function, uncontrolled hypertension, uncontrolled infections or any kind of malignancy.
- Renal function disorders except in patients with nephrotic syndrome and mild-moderate renal insufficiency.
- Ciclosporin is contra-indicated in psoriasis patients receiving PUVA, UVB, coal tar, radiation therapy and other immunosuppressants.
- Ciclosporin is contra-indicated in nephrotic syndrome patients with uncontrolled hypertension, uncontrolled infections, or any kind of malignancy.
- Ciclosporin should not be used to treat rheumatoid arthritis in children and adolescents due to limited experiences in this population.
- Concomitant use of tacrolimus is specifically contraindicated.
- Concomitant use of *Hypericum perforatum* (St. John’s Wort) drastically reduces the plasma concentration of ciclosporin. This may result in a loss of therapeutic effect (see section 4.5 Interactions).

4.4 Special warnings and precautions for use

Transimune should only be prescribed by physicians specialising in organ transplantation, dermatology, nephrology or rheumatology. Patients should be monitored in facilities with sufficient laboratory capacity and supporting medical resources. The responsible physician should have all the available information in preparation for the follow-up patients.

Ciclosporin should not be given in combination with other calcineurin inhibitors such as tacrolimus, since this can be expected to lead to an increase in adverse effects (see also 4.5 Interactions with other medicinal products and other forms of interactions) without an improvement in efficacy.

In patients being given Transimune, the use of potassium-sparing diuretics, medicinal products containing potassium, ACE inhibitors, angiotensin-II-receptor antagonists and a high intake of potassium with food should be avoided.

Grapefruit juice may elevate the blood levels of ciclosporin by interacting with the cytochrome-P450 system. The extent of these changes of ciclosporin levels in the blood, however, differs in individual cases and is not predictable. Therefore, grapefruit juice should not be taken in conjunction with Transimune.

The use of medicinal products that can cause gingival hyperplasia (e.g. nifedipine) should be avoided in patients who develop gingival proliferation under Transimune (see “4.8 Undesirable effects”).

When using inactivated vaccines or toxoid vaccines, the immune response should always be controlled by means of titer determination (see “4.5 Interaction with other medicinal products and other forms of interaction”).
Caution should be exercised in patients with hyperuricaemia since ciclosporin may further elevate uric acid levels.

Ciclosporin may impair renal function. For this reason, a reliable creatinine baseline value must be established prior to therapy with Transimune. In the first three months of treatment, the serum creatinine and serum urea values must be checked every two weeks.

In the event that kidney transplant patients who have very high ciclosporin levels in the blood present with continuously worsening renal function values and if the latter do not respond to a corresponding dose reduction, more extensive diagnostic tests should be conducted, e. g. a kidney biopsy.

Ciclosporin may also impair liver function. For this reason the parameters for liver function should be checked on a routine basis.

Since ciclosporin may on occasion precipitate hyperkalaemia or hypomagnesaemia or exacerbate existing electrolytic disturbances of this kind, it is recommended serum potassium and magnesium levels be monitored, particularly in patients with marked renal dysfunction.

During treatment with ciclosporin, a routine blood pressure check is required (see “4.8 Undesirable effects”). Treatment with Transimune should be discontinued if hypertension cannot be controlled with appropriate antihypertensive treatment.

When taking ciclosporin, a reversible elevation of blood lipids may occur. For this reason it is recommended that blood lipid values be determined prior to initiating treatment and following the first month of treatment. Should blood lipids become elevated, the intake of fats with food should be restricted and/or the ciclosporin dose should be reduced.

Routine dental check-ups (e.g. every three months) are recommended. In order to preclude or reduce gingival hyperplasia, teeth should be cleaned professionally and the patient should be instructed about measures necessary for personal dental hygiene.

Under ciclosporin treatment, there is an increased frequency of skin tumours. For this reason, patients should be warned against unnecessary radiation from the sun. A routine examination of the skin as well as histological examination of suspicious alterations is recommended.

Particular caution is advised in patients with untreated acute infections.

The routine determination of the minimum ciclosporin concentration in whole blood is an important safety measure within the scope of therapy monitoring in transplant patients (see “4.2 Posology and method of administration” under “Organ transplantation”).

It should be taken into account that the determination of the ciclosporin levels in whole blood, plasma, or serum is only one of the factors contributing to the clinical assessment of the patient's status. Therefore, blood ciclosporin levels should only serve as a reference for treatment and are to be supplemented by additional clinical and laboratory parameters.

Ciclosporin 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, ciclosporin should be withdrawn due to the possible risk of permanent visual loss.

Further precautions in nephrotic syndrome

Since Transimune may reduce the renal function, frequent monitoring is necessary and if the serum creatinine levels are more than 30% above baseline in more than one measurement, the dose of Transimune should be reduced by 25-50%. Patients with an abnormal baseline for renal function should be treated initially with 2.5 mg/kg/day and monitored carefully.

It should be noted that in some nephrotic syndrome itself can cause alterations in renal function. Thus, structural kidney alterations have been observed in association with Ciclosporin treatment, without an increase in serum creatinine levels. Renal biopsy is indicated in patients treated with ciclosporin for more than one year to assess the progression of renal disease and the extent of any ciclosporin-associated changes in renal morphology that may co-exist.
In patients with nephrotic syndrome treated with immunosuppressants (including ciclosporin), there have been reports of malignant growths (including Hodgkin’s lymphoma).

Long-term data on ciclosporin 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.

**Further precautions in rheumatoid arthritis**

Since Transimune may reduce renal function, a reliable baseline for serum creatinine in at least two measurements should be established before treatment. Afterwards, serum creatinine levels should be monitored weekly for one month. Thereafter serum creatinine should be monitored every two weeks in the first 3 months of treatment and thereafter once a month. More frequent control is required when the dose of Transimune dose is increased, if concomitant treatment with a non-steroidal anti-inflammatory substance is initiated or increased.

If serum creatinine levels are more than 30% above baseline in several measurements, the dose of Transimune should be reduced. If serum creatinine levels increase by more than 50%, the dose should be reduced by 50%. These recommendations apply even if values are within the normal laboratory range. If serum creatinine levels do not decrease within 1 month, treatment with Transimune should be discontinued.

Treatment should also be discontinued if treatment-emergent hypertension cannot be controlled with appropriate antihypertensive treatment.

As with other long immunosuppressive treatments there is an increased risk of lympho-proliferative disturbances. Caution is advised if Transimune is used concomitantly with methotrexate.

When treating rheumatoid arthritis, and taking into consideration the safety of the patient, additional controls should be carried out in accordance with the following time frame:

- haematology profile (red blood count, leucocyte and thrombocyte counts): primary and thereafter every 4 weeks
- liver enzymes: primary and thereafter every 4 weeks
- urine status: primary and thereafter every 4 weeks
- blood pressure: primary and thereafter every 2 weeks for 3 months. Afterwards, every 4 weeks.
- potassium, lipids: primary and thereafter every 4 weeks.

Experience is available from clinical studies for a period of up to 12 months. There is currently insufficient experience for longer treatment periods. If there is no perceptible effect after 3 months of treatment, administration with Transimune should be discontinued.

**Further precautions in psoriasis**

Since Transimune may reduce the renal function, a reliable baseline for serum creatinine in at least two measurements should be established before the treatment, and serum creatinine should be monitored every two weeks in the first 3 months of the treatment and thereafter once a month. If serum creatinine levels increases to more than 30% above baseline and are continually increased in more than one measurement, the dose of Transimune dose should be reduced by 25-50%. If serum creatinine level increases by more than 50%, the dose should be reduced by 50%. These recommendations apply even if values are within the normal laboratory range. If serum creatinine levels do not decrease within 1 month, treatment with Transimune should be discontinued.

The treatment should also be discontinued if treatment-emergent hypertension cannot be controlled with appropriate antihypertensive treatment.
Elderly patients should only be treated if their psoriasis is debilitating, and their renal function should be monitored carefully.

The duration of use is normally 12 weeks. Insufficient experience exists with treatment regimens longer than 24 weeks in duration. Termination of the treatment is recommended if high blood pressure which cannot be adequately controlled occurs during treatment with Transimune.

Development of malignant growths (especially of the skin) has been reported in psoriasis patients receiving treatment with ciclosporin as well as those treated with traditional immunosuppressants. A scan for all forms of pre-existing tumours, including those of the skin and cervix, should be carried out. A biopsy should be performed before starting Ciclosporin treatment on skin lesions which are not typical for psoriasis to exclude skin cancers, mycosis fungoides or other premalignant disorders. Patients with malignant or premalignant skin alterations should only be treated with Transimune after appropriate treatment of these lesions and only if there is no alternative treatment.

A small number of psoriasis patients on ciclosporin treatment have developed lymphoproliferative disturbances which were reversible by immediate discontinuation of treatment. Patients treated with Transimune should not receive concomitant irradiation treatment with UV-B-radiation or PUVA-photochemotherapy.

In view of the potential risk of skin malignancy, patients on Transimune should be warned to avoid excessive unprotected sun exposure

**Further precautions in atopic dermatitis**

Since Transimune may reduce the renal function, a reliable baseline for serum creatinine in at least two measurements should be established before the treatment, and serum creatinine should be monitored every two weeks in the first 3 months of the treatment and thereafter once a month. If serum creatinine levels increase to more than 30% above baseline and are continuously increased in more than one measurement, the dose of Transimune should be reduced by 25-50%. These recommendations apply even if values are within the normal laboratory range. If serum creatinine levels do not decrease within 1 month, treatment with Transimune should be discontinued.

Treatment should also be discontinued if treatment-emergent hypertension cannot be controlled with appropriate antihypertensive treatment.

Since experience with ciclosporin in children with atopic dermatitis is limited, Transimune is not recommended for use in children.

Elderly patients should only be treated if their atopic dermatitis is debilitating, and their renal function should be monitored carefully.

Benign lymphadenopathy is often connected with flare-up of atopic dermatitis and disappears spontaneously or with improvement in the disease. Lymphadenopathy observed in association with ciclosporin treatment should be monitored carefully. If lymphadenopathy continues despite improvement, a preventive biopsy should be made to exclude the possibility of lymphoma.

Active herpes simplex-infections should be eliminated before treatment with Transimune is initiated, but discontinuation of ciclosporin treatment is only warranted if severe infection develops during treatment.

Skin infections with *Staphylococcus aureus* are not an absolute contraindication for treatment with Transimune, but should be treated with appropriate antibacterial drugs. Oral erythromycin may increase the blood concentration of ciclosporin (see “4.5 Interaction with other medicinal products and other forms of interaction”) and should therefore be avoided. If there is no alternative available, blood concentrations of ciclosporin, renal function and possible adverse reactions to Ciclosporin should be monitored closely.
Since there is a potential risk of malignant skin growths, patients treated with Transimune should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant radiotherapy with UV-B-radiation or PUVA-photochemotherapy.

**Excipients of Transimune**

This medicine contains macrogolglycerol hydroxystearate which may cause stomach upset and diarrhoea.

This medicinal product contains ethanol:

A Transimune 50 mg soft capsule contains 50.00mg pure ethanol.

This medicinal product contains 12.7 vol% ethanol (alcohol), i.e. up to 525mg per dose, equivalent to 13ml beer, 6ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding woman, children and high-risk groups such as patients with liver disease, or epilepsy

4.5 Interaction with other medicinal products and other forms of interaction

**Interaction with foods**

Concomitant administration of grapefruit juice has been shown to increase the bioavailability of ciclosporin.

**Interaction with other medicines**

The section below list the medicines for which an interaction with Ciclosporin has been sufficiently proven and is considered to be clinically relevant.

Different medicines either increase or decrease the plasma or whole blood concentration of ciclosporin, usually by inhibition or induction of enzymes involved in the metabolism of ciclosporin (particularly cytochrome P450).

The product contains ethanol (see section 4.4). Ethanol may interact with other medical products.

**Medicines which reduce ciclosporin concentrations:**

Barbiturates, carbamazepine, phenytoin, phenobarbital; primidone; griseofulvin; metamizole; nafcillin, sulfadimidine and trimethoprim i.v.; rifampicin; octreotide; probucol; sulphadiazine; orlistat; troglitazone; *Hypericum perforatum* (St. John’s Wort); ticlopidine.

Patients on ciclosporin treatment should not use products/herbal medicines, which contain *Hypericum perforatum*, since this may cause a marked reduction in plasma concentrations of ciclosporin by induction of CYP3A4, and thus a diminution of therapeutic efficacy (see 4.3.Contraindications).

**Medicines which increase ciclosporin concentrations:**

Macrolide antibiotics (mainly erythromycin, clarithromycin, josamycin, roxithromycin, and pristinamycin); ketoconazole, fluconazole, itraconazole; calcium antagonists (such as diltiazem, nicardipine, verapamil); metoclopramide; oral contraceptives; propafenone; danazol; methylprednisolone (high dose); allopurinol; anti-H2 (cimetidine, ranitidine); chloroquine; amiodarone; bromocriptine; protease inhibitors; doxycycline.

**Other relevant forms of interaction with other medicines**

Caution is advised when the concomitant use of other medicines with ciclosporin results in nephrotoxic synergy: aminoglycosides (including gentamicin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+sulfamethoxazole); non-steroidal antiinflammatory substances (including diclofenac, naproxen, sulindac); melphalan tacrolimus and sirolimus.
During treatment with ciclosporin vaccinations may be less effective, so the use of live weakened vaccine should be avoided.

Concomitant administration of nifedipine and ciclosporin may exacerbate the gingival hyperplasia that is seen when ciclosporin is used alone.

When combining Transimune with corticosteroids, methylprednisolone, prednisone, or prednisolone, an increased risk of brain seizures has been reported. This is especially true for high doses of corticosteroids.

Concomitant use of diclofenac and ciclosporin has shown to cause a pronounced increase in the bioavailability of diclofenac, which may cause reversible reduced renal function. The increase in the bioavailability of diclofenac is probably due to a reduction in the high first-pass effect of diclofenac. If non-steroidal anti-inflammatory substances with a low first-pass effect (e.g. acetylsalicylic acid) are used concomitantly with ciclosporin, no increase in bioavailability is expected.

Ciclosporin may also reduce the excretion of digoxin, colchicine, lovastatin, pravastatin, simvastatin, atorvastatin and prednisolone and may therefore lead to digoxin toxicity or increase the risk of muscle toxicity (including muscle pain and weakening, myositis and occasionally rhabdomyolysis) due to colchicin, lovastatin, pravastatin, simvastatin and atorvastatin.

**Recommendations**

If concomitant use of medicines which have an interaction with ciclosporin is unavoidable, the following basic recommendations should be followed:

During concomitant use of medicines which cause nephrotoxic synergy, renal function (especially serum creatinine) should be monitored carefully. If renal function is considerably reduced, the dose of the concomitant medicine should be decreased or an alternative treatment should be considered.

**Medicines, which are known to reduce or increase the bioavailability of ciclosporin:**

In transplant patients frequent measurement of ciclosporin concentrations is required with possible dose adjustment, especially during initiation of treatment or at discontinuation of the concomitant medicine. In non-transplant patients, the value of monitoring blood concentrations of ciclosporin is doubtful, since the relationship between blood concentration and clinical effect is not well established. If medicines which increase the ciclosporin concentrations are used concomitantly, it may be more useful to measure renal function frequently and to monitor the patient carefully with regards to ciclosporin related adverse reactions.

Concomitant use of nifedipine should be avoided in patients with gingival hyperplasia.

Non-steroidal anti-inflammatory substances, which are known to have a marked first-pass metabolism (e.g. diclofenac), should be given at a lower dose than that normally recommended for patients not receiving ciclosporin.

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

If digoxin, colchicine, lovastatin, pravastatin or simvastatin are used concomitantly with ciclosporin, carefully clinical monitoring is required.

**4.6 Pregnancy and lactation**

**Pregnancy:**

Experience with ciclosporin in pregnant women is limited.
Ciclosporin does not demonstrate teratogenicity in experimental animals. Limited experience regarding the safety of administration of ciclosporin to pregnant women has shown no indications of teratogenicity. Ciclosporin does pass into the placenta. Initial experience with transplantation patients, however, did indicate that ciclosporin, as with other immunosuppressive agents, increases the probability of specific complications during pregnancy, such as pre-eclampsia and premature births with decreased birth weights. Transimune should be given during pregnancy only when the benefits outweigh the risks. Pregnant women who are being treated with Transimune should be observed carefully.

**Lactation:**

Ciclosporin is excreted in the breast milk. Women receiving Transimune treatment should not breastfeed.

### 4.7 Effects on ability to drive and use machines

No data exist on the effects of ciclosporin on ability to drive and use machines. The product contains ethanol (see section 4.4). Ethanol may have an influence on the ability to drive and use machines.

### 4.8 Undesirable effects

Many of the adverse reactions to ciclosporin are dose dependent and can be avoided by dose reduction. The adverse reactions are generally the same in the different indications, but occur at differing frequencies. Since a higher initial dose and longer maintenance treatment is required after transplantation, adverse reactions are seen more frequently and are usually more severe in transplant patients than in patients treated for other indications.

**Frequency estimates:**

- **Very common** (≥1/10)
- **Common** (≥1/100 to <1/10)
- **Uncommon** (≥1/1,000 to <1/100)
- **Rare** (≥1/10,000 to <1/1,000)
- **Very rare** (<1/10,000), not known (cannot be estimated from the available data)

**Blood and lymphatic system disorders**

- Uncommon: Anaemia, thrombocytopenia.
- Rare: Microangiopathic haemolytic anaemia, haemolytic uraemic syndrome.

**Endocrine disorders**

- Uncommon: In some patients malignant neoplasia or lymphoproliferative diseases have been reported, with incidence and distribution similar to those in patients receiving traditional immunosuppressive therapy.
- Rare: Menstrual disturbances, gynecomastia.

**Metabolism and nutrition disorders**

- Very common: Hyperlipidaemia.
- Common: Hyperuricaemia, hyperkalaemia, hypomagnesaemia.
- Rare: Hyperglycaemia.

**Nervous system disorders**

- Very common: Tremor, headache.
Common: Paresthesia.

Uncommon: Signs of encephalopathy, e.g. convulsion, confusion, disorientation, decreased responsiveness, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis, cerebellar ataxia.

Rare: Motor polyneuropathy.

Very rare: Oedema in the visual pupil, including disk oedema with possible visual weakening following benign intracranial hypertension.

Vascular disorders

Very common: Hypertension.

Gastrointestinal disorders

Common: Anorexia, nausea, vomiting, abdominal pain, diarrhoea, gingival hyperplasia.

Hepatobiliary disorders

Common: Hepatic dysfunction.

Rare: Pancreatitis.

Skin and subcutaneous tissue disorders

Common: Hypertrichosis.

Uncommon: Allergic rash.

Musculoskeletal and connective tissue disorders

Common: Muscle cramps, myalgia.

Rare: Muscle weakness, myopathy.

Renal and urinary disorders

Very common: Renal dysfunction (see 4.4 Special warnings and precautions for use).

General disorders and administration site conditions

Common: Fatigue.

Uncommon: Oedema, weight gain.

4.9 Overdose

a) Symptoms of intoxication

Little experience exists with overdose. After ingestion of doses up to 10 g ciclosporin (approximately 150 mg/kg), vomiting, somnolence, headache, tachycardia and in some patients a moderately severe, reversible kidney dysfunction was observed. There have been reports of severe intoxication symptoms with preterm infants after inadvertent parenteral overdose.

b) Therapy of intoxication

Possible signs of nephrotoxicity are reversible in most cases after discontinuation of administration of Transimune. In case of an overdose, symptomatic treatment and general supportive measures should be applied. Ciclosporin is not dialyzable nor is it eliminated by activated charcoal-haemoperfusion therapy.

Therefore, elimination is limited to non-specific treatment, e.g. gastrolavage. However, activated charcoal eliminates small amounts of ciclosporin from the enterohepatic circulation. Within the first few hours after overdose, it may be beneficial for the patient to induce vomiting.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Immunosuppressants, ATC code: L 04 AA 01

Ciclosporin (also called cyclosporin A) is a cyclic poly peptide, which consists of 11 amino acids. It is a strong immunosuppressive substance, which in animals increases the survival of allogenic transplantations of skin, heart, kidneys, pancreas, bone marrow, small intestine and lungs. Studies show that ciclosporin inhibits the development of cell-mediated reactions, including allotransplantation immunity, delayed skin hypersensitivity, experimental allergic encephalomyelitis, Freund’s adjuvant arthritis, graft-versus-host disease (GVHD) and the production of T-cell dependent antibodies. At the cellular level ciclosporin inhibits the production and release of lymphokines, including interleukin 2 (T-cell growth factor, TCGF). Ciclosporin apparently blocks the resting lymphocytes in phase G0 or G1 in the cell cycle and inhibits the antigen triggered release of lymphokines from activated T-cells.

The existing evidence indicates that ciclosporin acts specifically and reversibly on lymphocytes. Contrary to cytostatic agents, ciclosporin does not suppress haemopoiesis and has no effect on phagocytic cell function. Patients treated with ciclosporin are less susceptible to infections than those treated with other immunosuppressants.

Successful organ and bone marrow transplantations have been carried out in humans, where ciclosporin has been used to prevent and treat rejection and GVHD.

Treatment with ciclosporin has also shown to be advantageous in a series of other conditions with a known autoimmune origin or considered to be of autoimmune origin.

5.2 Pharmacokinetic properties
The maximal blood concentration (Cmax) is achieved within 1-2 hours (Tmax). The absolute bioavailability is 30-60%. The inter- and intra-individual pharmacokinetic variability is 10-20% for AUC and Cmax in healthy volunteers. Transimune can be administered with food or alone.

The results of several studies have shown that monitoring of the ciclosporin area under the time-concentration curve for the first 4 hours after administration of dose (AUC0-4) gives a more precise prediction of the ciclosporin exposure than at base (C0) monitoring.

The results from further studies indicate that a single test point 2 hours after the dose (C2) correlate well with the AUC0-4 in transplantation patients.

In medical practice either trough level monitoring or C2 monitoring of ciclosporin can be used for pharmacotherapeutic surveillance.

Ciclosporin is mainly distributed outside the blood volume. In the blood there is 33-47% ciclosporin in plasma, 4-9% in the lymphocytes, 5-12% in the granulocytes and 41-58% in the erythrocytes. In plasma approximately 90% is bound to proteins, mainly lipoproteins.

Ciclosporin is biotransformed by several metabolic routes into approximately 15 metabolites. The elimination is mainly biliary, where only 6% of an oral dose is eliminated with the urine. Only 0.1% is eliminated unchanged in the urine.

There is a great variation in the available data regarding the terminal half life of ciclosporin depending on the analysis and the target population. The terminal half life varied from 6.3 hours in healthy volunteers to 20.4 hours in patients with severe hepatic disease.

5.3 Preclinical safety data
Ciclosporin showed no mutagenic or teratogenic effects in appropriate test systems.
Reproduction studies in rats showed only negative effects at doses, which were toxic for the
females. At toxic doses (rats 30 mg/kg and rabbits 100 mg/kg/day orally), ciclosporin was embryo- and foeto-toxic, which was indicated by increased prenatal and postnatal mortality and reduced foetal weight and bone formation.

Within the well tolerated dose range (in rats up to 17 mg/kg/day and in rabbits up to 30 mg/kg/day orally) ciclosporin showed no embryo-lethal or teratogenic effects.

Carcinogenicity studies were carried out on male and female rats and mice. In the mouse study, which lasted 78 weeks, there was a statistically significantly greater incidence of lymphocytic lymphomas in female mice at a dose of 1, 4 and 16 mg/kg/day and a considerably higher occurrence of hepatocellular carcinomas in male mice, compared to control animals. In the rat study, which lasted 24 months and involved a dose of 0.5, 2 and 8 mg/kg/day, the incidence of island cell adenomas in the pancreas considerably exceeded the control value at the low dose. Hepatocellular carcinomas and island cell adenomas in the pancreas were not dose related.

Studies in male and female rats showed no reduction in fertility.

Ciclosporin was not found to be mutagenic/genotoxic in the Ames-test, the v79-hgpnt-test or the micronucleus test in mice and Chinese hamsters or the chromosome aberration test of the bone marrow of Chinese hamsters, the dominating mortality analysis in mice and the DNA-repair test in semen from treated mice. An in-vitro analysis of sister chromatid exchange (SCE) in human lymphocytes showed a positive effect of ciclosporin at high doses in this system.

An increased occurrence of malignant growths is a recognised complication in connection with immunosuppression in organ transplant patients. The most common forms of neoplasms are non-Hodgkin’s related lymphomas and skin carcinomas. The risk of malignant growths during treatment with ciclosporin is higher than in a normal healthy population, but is similar to the risk for patients treated with other immunosuppressants. Reports that reduction or discontinuation of immunosuppressants may cause regression of lesions are available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Content of the soft capsules

Ethanol anhydrous,
Tocopherol acetate
Diethylene glycol monoethyl ether
Oleoyl macrogolglycerides
Macrogolglycerol Hydroxystearate

Capsule shell

Gelatin, Glycerol
Propylene glycol
Titanium dioxide (E171),
Purified water.

6.2 Incompatibilities

Not applicable.
6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions. Store in the original package.

6.5 Nature and contents of container
The soft capsules are available in aluminium-aluminium blister of:
10, 20, 30, 50 & 60 capsules
Not all pack sizes may be marketed

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORITY
Morningside Healthcare Ltd
115 Narborough Road
Leicester.
LE3 0PA
UK

8 MARKETING AUTHORIZATION NUMBER(S)
PL 20117/0040

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
13/02/2008

10 DATE OF REVISION OF THE TEXT
13/02/2008

11 DOSIMETRY (IF APPLICABLE)
12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Transimune 100 mg, soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Transimune 100 mg, soft capsules
1 soft capsule contains 100 mg of ciclosporin
1 soft capsule 100mg contains 100.00mg ethanol and 380.00 mg macrogolglycerol hydroxystearate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Soft capsules.
100 mg: Grey gelatin capsules

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
In combination with other immunosuppressant substances for the prevention of acute and chronic transplant rejection following allogenic transplantation of kidneys, liver, heart, heart-lung, lung or pancreas.

Treatment of transplant rejection in patients who have previously received other immunosuppressants.

Prevention and treatment of graft-versus-host-disease (GVHD) following allogenic bone marrow transplantation.

Treatment of severe forms of psoriasis, particularly of the plaque type, which are not sufficiently treatable with conventional systemic therapy.

Treatment of severe atopic dermatitis in patients in whom conventional therapy is inappropriate or ineffective.

Treatment of steroid-dependent and steroid-resistant nephrotic syndrome due to glomerular disorders such as glomerular minimum changes, focal segmental glomerulosclerosis or membranous glomerulonephritis in adults and children whose glucocorticoids or alkylating agents are either insufficiently effective or involve unacceptable risks.

Transimune can be administered to achieve remission or maintenance of this condition. It can also be used to maintain steroid-induced remission and thus allow for reduction of corticosteroids.

Treatment of severe, active rheumatoid arthritis in adults when conventional therapy including at least one highly effective disease modifying antirheumatic medicinal product (DMARD) (e. g. low-dose methotrexate) has proved inadequate.
4.2 Posology and method of administration

Oral administration

The daily dose of Transimune should always be divided in 2 doses. The capsules should be swallowed whole.

In transplant patients routine monitoring of the ciclosporin blood levels should be performed in order to avoid the risk of adverse reactions (if blood levels are too high) and organ rejection (if blood levels are too low).

Due to possible differences in bioavailability patients should not be transferred to or from other oral formulations of ciclosporin without appropriate close monitoring of ciclosporin blood concentrations, serum creatinine levels and blood pressure. For this reason it may be appropriate to prescribe by brand.

For drug level monitoring, whole blood is preferred, measured by a specific analytical method. A number of methods that measure unaltered ciclosporin (HPLC, specific monoclonal specific radioimmunoassays) as well as unspecific methods that also measure some metabolites have been developed for determining ciclosporin levels: The results of the various determination methods are not interchangeable. Determination of ciclosporin levels by means of specific monoclonal antibodies or by HPLC is to be given preference. Target concentration ranges depend on organ type, time after transplantation and immunosuppressive regimen.

It should be noted that other factors besides ciclosporin blood level can affect the clinical condition of the patient. The results are therefore intended only as a guide for dosing and should be used together with other clinical and laboratory parameters.

A higher oral dose of ciclosporin or an intravenous dose may be necessary if absorption is impaired by gastrointestinal disturbances.

Organ transplantation:

Treatment with Transimune is initiated within 12 hours prior to surgery with a dose of 10-15 mg/kg given in two divided doses. This daily dose is continued 1-2 weeks following surgery, whereupon the daily dose is gradually reduced in agreement with the blood concentration to a maintenance dose of approximately 2-6 mg/kg given in two divided doses.

When Transimune is used with other immunosuppressants (e.g. with corticosteroids or in poly-therapy), a lower dose is administered (e.g. initially 3-6 mg/kg given in two divided doses).

Bone marrow transplantation:

For the prevention of graft-versus-host-disease (GVHD), ciclosporin is commonly used initially, short-term, in combination with methotrexate. The optimum dose should be adjusted individually. In general, treatment should be initiated 1 to 2 days before bone marrow transplantation with intravenous ciclosporin (dosage 2.5 to 5 mg/kg/day). This is replaced by oral administration as soon as patients are able to tolerate oral medication (generally at 12.5 mg/kg/day). Oral treatment should be continued for at least 3–6 months, before gradual dose reduction and eventual discontinuation.

Alternative treatment regimes are intravenous ciclosporin as mono therapy at 5 mg/kg/day (day -1 to day 3) and 3 mg/kg/day (day 4 to day 14) or combination therapy with intravenous Ciclosporin at 3 - 5 mg/kg/day and corticosteroids. In these cases, treatment should also be changed to the oral route as soon as possible and continued over a longer period.

If Transimune is used to initiate therapy, the recommended dose is 12.5 to 15mg/kg/day, given in two divided doses, starting on the day before transplantation.

Some patients may experience GVHD after discontinuation of ciclosporin treatment, but usually respond positively to repeated treatment. A low dose of Transimune can be used for mild, chronic GVHD.
Nephrotic syndrome:

For induction of remission the recommended oral dose is 5 mg/kg/day given in two divided doses for adults and 6 mg/kg/day for children, if renal function is normal. In patients with reduced renal function, the initial dose should not exceed 2.5 mg/kg/day.

Appropriate monitoring of the ciclosporin level pre-dose to avoid overdose in children is recommended.

In focal segmental glomerulosclerosis, a combination of ciclosporin and corticosteroids may be of benefit.

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

The dose should be individually adjusted according to effect (proteinuria) and safety (mainly serum creatinine), but should not exceed 5 mg/kg/day for adults and 6 mg/kg/day for children.

In maintenance treatment the dose is slowly reduced to the lowest therapeutically effective level.

Rheumatoid arthritis:

For the first six weeks of therapy, the recommended dose is 2.5 mg/kg/day, given in two divided doses. The dose may be decreased depending on tolerance. The daily dose may be increased gradually, if the clinical effect is considered insufficient. Normally, the daily dose may not exceed 4 mg/kg/day. In individual cases, the dose may be increased up to 5 mg/kg/day. If the dose is increased too soon, there is a risk of overdosage.

In patients weighing less than 80 kg capsules of 100mg strength may be not appropriate for a precise dose titration.

For maintenance, the dosage should be adjusted individually to the lowest effective dose.

Low-dose corticosteroids and/or NSAIDs can be used in combination with Transimune (see also “4.5 Interaction with other medicinal products and other forms of interaction”).

Psoriasis:

Treatment of this condition is individually adjusted, since the disease varies greatly. For induction of remission the recommended initial dose is 2.5 mg/kg/day orally given in two divided doses. If no improvement is seen after 1 month, the daily dose can gradually be increased to maximum 5 mg/kg. The treatment should be discontinued in patients with psoriasis lesions which do not show a sufficient response within 6 weeks at 5 mg/kg/day or where the clinically effective dose is not compatible with the established safety guidelines.

An initial dose of 5 mg/kg/day is justified in patients whose condition requires rapid improvement. When a satisfactory response is achieved, treatment with Transimune can be discontinued and a possible relapse can be treated with Transimune at the previous clinically effective dose. Some patients may require continuous maintenance treatment.

In maintenance treatment the dose is individually titrated to the lowest clinically effective level and the dose should not exceed 5 mg/kg/day given in two divided doses.

Atopic dermatitis:

Treatment of this condition is individually adjusted, since the disease varies greatly. The recommended dose is 2.5-5 mg/kg/day orally given in two divided doses, for a maximum of 8 weeks. If an initial dose of 2.5 mg/kg/day does not give a satisfactory result within 2 weeks, the daily dose can be increased to maximum of 5 mg/kg. In very severe cases, the disease can be controlled with an initial dose of 5 mg/kg/day. When a satisfactory response is achieved, the dose should be gradually reduced and treatment discontinued.
**Administration method:**

The dose range is intended only as a guide. Routine monitoring of ciclosporin blood level is required in order to achieve the optimal therapeutic concentration for individual patients. Monitoring can be done by means of a RIA method based on monoclonal antibodies.

The total daily dose should always be administered in two divided doses. The divided doses should always be administered at the same time of day and the times between single doses should be approximately equivalent. Therefore, it is recommended to take the two divided doses in the morning and in the evening.

Transimune can be administered with food or alone.

Transimune should be taken with liquid and swallowed whole.

Switching from other oral ciclosporin preparations to Transimune:

In order to switch patients from other oral ciclosporin preparations to Transimune, ciclosporin trough blood levels, serum creatinine levels, and blood pressure should be checked prior to the switch (i.e., while using other oral ciclosporin preparations). The patient should be switched to the same daily dose of Transimune that was used for the prior ciclosporin preparation (mg per mg conversion). It is recommended that ciclosporin trough levels, serum creatinine, and blood pressure be checked after 4 - 7 days. If necessary, the dose of Transimune should be adjusted accordingly. Additional check-ups may be necessary in the first two months following the switch (e.g., weeks 2, 4, and 8) and the dose adjusted accordingly.

**Dosage in renal insufficiency:**

Specific investigations have not been performed on the pharmacokinetics of ciclosporin in transplant patients with impaired renal function. Special caution is required if a rapid rise in serum creatinine occurs (even within the normal range) after starting treatment with Transimune. A rise in serum creatinine or fall in creatinine clearance may also be the expression of an acute rejection reaction, particularly after renal transplantation. Initiation of treatment with Transimune in existing renal dysfunction and subsequent dose adjustment should only be undertaken after careful consideration of the benefits and risks, taking into account the overall clinical picture and ciclosporin blood levels.

For patients with nephrotoxic syndrome and moderately impaired renal function (baseline values of serum creatinine in adults <200 µmol/L, in children <140 µmol/L), an initial dose of 2.5 mg ciclosporin/kg body weight per day should not be exceeded. Patients must be monitored closely.

**Dosage in impaired hepatic function:**

Impaired liver function may considerably modify the pharmacokinetics of ciclosporin in some cases. Blood concentrations of ciclosporin (c\text{min}) must be monitored closely in patients with impaired hepatic function and the dose adjusted accordingly.

In psoriasis, administration of Transimune should be terminated if liver enzymes and bilirubin levels are twice the baseline values.

In nephrotic syndrome patients with severe liver function disturbances, the initial dose should be decreased by 25% to 50%.

**Elderly:**

There is limited experience with the use of ciclosporin in the elderly, but no special problems have been seen at the recommended dose. However, factors associated with ageing, such as impaired renal function, necessitate careful supervision and possible dosage adjustment.

**Children:**

Experience in children is limited. However, ciclosporin has been used at the recommended dose for children from 1 year without special problems. In several studies children needed a higher dose of ciclosporin per kg body weight than adults and they tolerated the higher dose...
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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Ciclosporin is contra-indicated 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 (see section 4.4 precautions).
- Ciclosporin is contra-indicated in rheumatoid arthritis patients with abnormal renal function, uncontrolled hypertension, uncontrolled infections or any kind of malignancy.
- Renal function disorders except in patients with nephrotic syndrome and mild-moderate renal insufficiency.
- Ciclosporin is contra-indicated in psoriasis patients receiving PUVA, UVB, coal tar, radiation therapy and other immunosuppressants.
- Ciclosporin is contra-indicated in nephrotic syndrome patients with uncontrolled hypertension, uncontrolled infections, or any kind of malignancy.
- Ciclosporin should not be used to treat rheumatoid arthritis in children and adolescents due to limited experiences in this population.
- Concomitant use of tacrolimus is specifically contraindicated.
- Concomitant use of Hypericum perforatum (St. John’s Wort) drastically reduces the plasma concentration of ciclosporin. This may result in a loss of therapeutic effect (see section 4.5 Interactions)

4.4 Special warnings and precautions for use

Transimune should only be prescribed by physicians specialising in organ transplantation, dermatology, nephrology or rheumatology. Patients should be monitored in facilities with sufficient laboratory capacity and supporting medical resources. The responsible physician should have all the available information in preparation for the follow-up patients. Ciclosporin should not be given in combination with other calcineurin inhibitors such as tacrolimus, since this can be expected to lead to an increase in adverse effects (see also 4.5 Interactions with other medicinal products and other forms of interactions) without an improvement in efficacy.

In patients being given Transimune, the use of potassium-sparing diuretics, medicinal products containing potassium, ACE inhibitors, angiotensin-II-receptor antagonists and a high intake of potassium with food should be avoided.

Grapefruit juice may elevate the blood levels of ciclosporin by interacting with the cytochrome-P450 system. The extent of these changes of ciclosporin levels in the blood, however, differs in individual cases and is not predictable. Therefore, grapefruit juice should not be taken in conjunction with Transimune.

The use of medicinal products that can cause gingival hyperplasia (e. g. nifedipine) should be avoided in patients who develop gingival proliferation under Transimune (see “4.8 Undesirable effects”).

When using inactivated vaccines or toxoid vaccines, the immune response should always be controlled by means of titer determination (see “4.5 Interaction with other medicinal products and other forms of interaction”).
Caution should be exercised in patients with hyperuricaemia since ciclosporin may further elevate uric acid levels.

Ciclosporin may impair renal function. For this reason, a reliable creatinine baseline value must be established prior to therapy with Transimune. In the first three months of treatment, the serum creatinine and serum urea values must be checked every two weeks.

In the event that kidney transplant patients who have very high ciclosporin levels in the blood present with continuously worsening renal function values and if the latter do not respond to a corresponding dose reduction, more extensive diagnostic tests should be conducted, e.g. a kidney biopsy.

Ciclosporin may also impair liver function. For this reason the parameters for liver function should be checked on a routine basis.

Since ciclosporin may on occasion precipitate hyperkalaemia or hypomagnesaemia or exacerbate existing electrolytic disturbances of this kind, it is recommended serum potassium and magnesium levels be monitored, particularly in patients with marked renal dysfunction.

During treatment with ciclosporin, a routine blood pressure check is required (see “4.8 Undesirable effects”). Treatment with Transimune should be discontinued if hypertension cannot be controlled with appropriate antihypertensive treatment.

When taking ciclosporin, a reversible elevation of blood lipids may occur. For this reason it is recommended that blood lipid values be determined prior to initiating treatment and following the first month of treatment. Should blood lipids become elevated, the intake of fats with food should be restricted and/or the ciclosporin dose should be reduced.

Routine dental check-ups (e.g. every three months) are recommended. In order to preclude or reduce gingival hyperplasia, teeth should be cleaned professionally and the patient should be instructed about measures necessary for personal dental hygiene.

Under ciclosporin treatment, there is an increased frequency of skin tumours. For this reason, patients should be warned against unnecessary radiation from the sun. A routine examination of the skin as well as histological examination of suspicious alterations is recommended.

Particular caution is advised in patients with untreated acute infections.

The routine determination of the minimum ciclosporin concentration in whole blood is an important safety measure within the scope of therapy monitoring in transplant patients (see “4.2 Posology and method of administration” under “Organ transplantation”).

It should be taken into account that the determination of the ciclosporin levels in whole blood, plasma, or serum is only one of the factors contributing to the clinical assessment of the patient's status. Therefore, blood ciclosporin levels should only serve as a reference for treatment and are to be supplemented by additional clinical and laboratory parameters.

Ciclosporin 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, ciclosporin should be withdrawn due to the possible risk of permanent visual loss.

Further precautions in nephrotic syndrome

Since Transimune may reduce the renal function, frequent monitoring is necessary and if the serum creatinine levels are more than 30% above baseline in more than one measurement, the dose of Transimune should be reduced by 25-50%. Patients with an abnormal baseline for renal function should be treated initially with 2.5 mg/kg/day and monitored carefully.

It should be noted that in some nephrotic syndrome itself can cause alterations in renal function. Thus, structural kidney alterations have been observed in association with Ciclosporin treatment, without an increase in serum creatinine levels. Renal biopsy is indicated in patients treated with ciclosporin for more than one year to assess the progression of renal disease and the extent of any ciclosporin-associated changes in renal morphology that may co-exist.
In patients with nephrotic syndrome treated with immunosuppressants (including ciclosporin), there have been reports of malignant growths (including Hodgkin's lymphoma).

Long-term data on ciclosporin 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.

**Further precautions in rheumatoid arthritis**

Since Transimune may reduce renal function, a reliable baseline for serum creatinine in at least two measurements should be established before treatment. Afterwards, serum creatinine levels should be monitored weekly for one month. Thereafter serum creatinine should be monitored every two weeks in the first 3 months of treatment and thereafter once a month. More frequent control is required when the dose of Transimune dose is increased, if concomitant treatment with a non-steroidal anti-inflammatory substance is initiated or increased.

If serum creatinine levels are more than 30% above baseline in several measurements, the dose of Transimune should be reduced. If serum creatinine levels increase by more than 50%, the dose should be reduced by 50%. These recommendations apply even if values are within the normal laboratory range. If serum creatinine levels do not decrease within 1 month, treatment with Transimune should be discontinued.

Treatment should also be discontinued if treatment-emergent hypertension cannot be controlled with appropriate antihypertensive treatment.

As with other long immunosuppressive treatments there is an increased risk of lymphoproliferative disturbances. Caution is advised if Transimune is used concomitantly with methotrexate.

When treating rheumatoid arthritis, and taking into consideration the safety of the patient, additional controls should be carried out in accordance with the following time frame:
- haematology profile (red blood count, leucocyte and thrombocyte counts): primary and thereafter every 4 weeks
- liver enzymes: primary and thereafter every 4 weeks
- urine status: primary and thereafter every 4 weeks
- blood pressure: primary and thereafter every 2 weeks for 3 months. Afterwards, every 4 weeks.
- potassium, lipids: primary and thereafter every 4 weeks.

Experience is available from clinical studies for a period of up to 12 months. There is currently insufficient experience for longer treatment periods. If there is no perceptible effect after 3 months of treatment, administration with Transimune should be discontinued.

**Further precautions in psoriasis**

Since Transimune may reduce the renal function, a reliable baseline for serum creatinine in at least two measurements should be established before the treatment, and serum creatinine should be monitored every two weeks in the first 3 months of the treatment and thereafter once a month. If serum creatinine levels increases to more than 30% above baseline and are continually increased in more than one measurement, the dose of Transimune dose should be reduced by 25-50%. If serum creatinine level increases by more than 50%, the dose should be reduced by 50%. These recommendations apply even if values are within the normal laboratory range. If serum creatinine levels do not decrease within 1 month, treatment with Transimune should be discontinued.

The treatment should also be discontinued if treatment-emergent hypertension cannot be controlled with appropriate antihypertensive treatment.
Elderly patients should only be treated if their psoriasis is debilitating, and their renal function should be monitored carefully.

The duration of use is normally 12 weeks. Insufficient experience exists with treatment regimens longer than 24 weeks in duration. Termination of the treatment is recommended if high blood pressure which cannot be adequately controlled occurs during treatment with Transimune.

Development of malignant growths (especially of the skin) has been reported in psoriasis patients receiving treatment with ciclosporin as well as those treated with traditional immunosuppressants. A scan for all forms of pre-existing tumours, including those of the skin and cervix, should be carried out. A biopsy should be performed before starting Ciclosporin treatment on skin lesions which are not typical for psoriasis to exclude skin cancers, mycosis fungoides or other premalignant disorders. Patients with malignant or premalignant skin alterations should only be treated with Transimune after appropriate treatment of these lesions and only if there is no alternative treatment.

A small number of psoriasis patients on ciclosporin treatment have developed lymphoproliferative disturbances which were reversible by immediate discontinuation of treatment. Patients treated with Transimune should not receive concomitant irradiation treatment with UV-B-radiation or PUVA-photochemotherapy.

In view of the potential risk of skin malignancy, patients on Transimune should be warned to avoid excessive unprotected sun exposure

**Further precautions in atopic dermatitis**

Since Transimune may reduce the renal function, a reliable baseline for serum creatinine in at least two measurements should be established before the treatment, and serum creatinine should be monitored every two weeks in the first 3 months of the treatment and thereafter once a month. If serum creatinine levels increase to more than 30% above baseline and are continuously increased in more than one measurement, the dose of Transimune should be reduced by 25-50%. These recommendations apply even if values are within the normal laboratory range. If serum creatinine levels do not decrease within 1 month, treatment with Transimune should be discontinued.

Treatment should also be discontinued if treatment-emergent hypertension cannot be controlled with appropriate antihypertensive treatment.

Since experience with ciclosporin in children with atopic dermatitis is limited, Transimune is not recommended for use in children.

Elderly patients should only be treated if their atopic dermatitis is debilitating, and their renal function should be monitored carefully.

Benign lymphadenopathy is often connected with flare-up of atopic dermatitis and disappears spontaneously or with improvement in the disease. Lymphadenopathy observed in association with ciclosporin treatment should be monitored carefully. If lymphadenopathy continues despite improvement, a preventive biopsy should be made to exclude the possibility of lymphoma.

Active herpes simplex-infections should be eliminated before treatment with Transimune is initiated, but discontinuation of ciclosporin treatment is only warranted if severe infection develops during treatment.

Skin infections with *Staphylococcus aureus* are not an absolute contraindication for treatment with Transimune, but should be treated with appropriate antibacterial drugs. Oral erythromycin may increase the blood concentration of ciclosporin (see “4.5 Interaction with other medicinal products and other forms of interaction) and should therefore be avoided. If there is no alternative available, blood concentrations of ciclosporin, renal function and possible adverse reactions to Ciclosporin should be monitored closely.
Since there is a potential risk of malignant skin growths, patients treated with Transimune should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant radiotherapy with UV-B-radiation or PUVA-photochemotherapy.

**Excipients of Transimune**

This medicine contains macrogolglycerol hydroxystearate which may cause stomach upset and diarrhoea.

This medicinal product contains ethanol:

- A Transimune 25 mg soft capsule contains 25.00mg pure ethanol.
- A Transimune 50 mg soft capsule contains 50.00mg pure ethanol.
- A Transimune 100 mg soft capsule contains 100.00mg pure ethanol.

This medicinal product contains 12.7 vol% ethanol (alcohol), i.e. up to 525mg per dose, equivalent to 13ml beer, 6ml wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding woman, children and high-risk groups such as patients with liver disease, or epilepsy

### 4.5 Interaction with other medicinal products and other forms of interaction

#### Interaction with foods

Concomitant administration of grapefruit juice has been shown to increase the bioavailability of ciclosporin.

#### Interaction with other medicines

The section below list the medicines for which an interaction with Ciclosporin has been sufficiently proven and is considered to be clinically relevant.

Different medicines either increase or decrease the plasma or whole blood concentration of ciclosporin, usually by inhibition or induction of enzymes involved in the metabolism of ciclosporin (particularly cytochrome P450).

The product contains ethanol (see section 4.4). Ethanol may interact with other medical products.

**Medicines which reduce ciclosporin concentrations:**

- Barbiturates, carbamazepine, phenytoin, phenobarbital; primidone; griseofulvin; metamizole; nafcillin, sulfadimidine and trimethoprim i.v.; rifampicin; octreotide; probucol; sulphadiazine; orlistat; troglitazone; *Hypericum perforatum* (St. John’s Wort); ticlopidine.

Patients on ciclosporin treatment should not use products/herbal medicines, which contain *Hypericum perforatum*, since this may cause a marked reduction in plasma concentrations of ciclosporin by induction of CYP3A4, and thus a diminution of therapeutic efficacy (see 4.3.Contraindications).

**Medicines which increase ciclosporin concentrations:**

- Macrolide antibiotics (mainly erythromycin, clarithromycin, josamycin, roxithromycin, and pristinamycin); ketoconazole, fluconazole, itraconazole; calcium antagonists (such as diltiazem, nicardipine, verapamil); metoclopramide; oral contraceptives; propafenone; danazol; methylprednisolone (high dose); allopurinol; anti-H2 (cimetidine, ranitidine); chloroquine; amiodarone; bromocriptine; protease inhibitors; doxycycline.

**Other relevant forms of interaction with other medicines**

Caution is advised when the concomitant use of other medicines with ciclosporin results in nephrotoxic synergy: aminoglycosides (including gentamicin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+sulfamethoxazole); non-steroidal
antiinflammatory substances (including diclofenac, naproxen, sulindac); melphalan
tacrolimus and sirolimus.

During treatment with ciclosporin vaccinations may be less effective, so the use of live
weakened vaccine should be avoided.

Concomitant administration of nifedipine and ciclosporin may exacerbate the gingival
hyperplasia that is seen when ciclosporin is used alone.

When combining Transimune with corticosteroids, methylprednisolone, prednisone, or
prednisolone, an increased risk of brain seizures has been reported. This is especially true for
high doses of corticosteroids.

Concomitant use of diclofenac and ciclosporin has shown to cause a pronounced increase in
the bioavailability of diclofenac, which may cause reversible reduced renal function. The
increase in the bioavailability of diclofenac is probably due to a reduction in the high first-
pass effect of diclofenac. If non-steroidal anti-inflammatory substances with a low first-pass
effect (e.g. acetylsalicylic acid) are used concomitantly with ciclosporin, no increase in
bioavailability is expected.

Ciclosporin may also reduce the excretion of digoxin, colchicine, lovastatin, pravastatin,
simvastatin, atorvastatin and prednisolone and may therefore lead to digoxin toxicity or
increase the risk of muscle toxicity (including muscle pain and weakening, myositis and
occasionally rhabdomyolysis) due to colchicin, lovastatin, pravastatin, simvastatin and
atorvastatin.

Recommendations

If concomitant use of medicines which have an interaction with ciclosporin is unavoidable,
the following basic recommendations should be followed:

During concomitant use of medicines which cause nephrotoxic synergy, renal function
(especialy serum creatinine) should be monitored carefully. If renal function is considerably
reduced, the dose of the concomitant medicine should be decreased or an alternative
treatment should be considered.

Medicines, which are known to reduce or increase the bioavailability of ciclosporin:

In transplant patients frequent measurement of ciclosporin concentrations is required with
possible dose adjustment, especially during initiation of treatment or at discontinuation of the
concomitant medicine. In non-transplant patients, the value of monitoring blood
concentrations of ciclosporin is doubtful, since the relationship between blood concentration
and clinical effect is not well established. If medicines which increase the ciclosporin
concentrations are used concomitantly, it may be more useful to measure renal function
frequently and to monitor the patient carefully with regards to ciclosporin related adverse
reactions.

Concomitant use of nifedipine should be avoided in patients with gingival hyperplasia.
Non-steroidal anti-inflammatory substances, which are known to have a marked first-pass
metabolism (e.g. diclofenac), should be given at a lower dose than that normally
recommended for patients not receiving ciclosporin.

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

If digoxin, colchicine, lovastatin, pravastatin or simvastatin are used concomitantly with
ciclosporin, carefully clinical monitoring is required.
4.6 Pregnancy and lactation

Pregnancy:
Experience with ciclosporin in pregnant women is limited. Ciclosporin does not demonstrate teratogenicity in experimental animals. Limited experience regarding the safety of administration of ciclosporin to pregnant women has shown no indications of teratogenicity. Ciclosporin does pass into the placenta. Initial experience with transplantation patients, however, did indicate that ciclosporin, as with other immunosuppressive agents, increases the probability of specific complications during pregnancy, such as pre-eclampsia and premature births with decreased birth weights. Transimune should be given during pregnancy only when the benefits outweigh the risks. Pregnant women who are being treated with Transimune should be observed carefully.

Lactation:
Ciclosporin is excreted in the breast milk. Women receiving Transimune treatment should not breastfeed.

4.7 Effects on ability to drive and use machines

No data exist on the effects of ciclosporin on ability to drive and use machines. The product contains ethanol (see section 4.4). Ethanol may have an influence on the ability to drive and use machines.

4.8 Undesirable effects

Many of the adverse reactions to ciclosporin are dose dependent and can be avoided by dose reduction. The adverse reactions are generally the same in the different indications, but occur at differing frequencies. Since a higher initial dose and longer maintenance treatment is required after transplantation, adverse reactions are seen more frequently and are usually more severe in transplant patients than in patients treated for other indications.

Frequency estimates:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000), not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Uncommon: Anaemia, thrombocytopenia.
Rare: Microangiopathic haemolytic anaemia, haemolytic uraemic syndrome.

Endocrine disorders
Uncommon: In some patients malignant neoplasia or lymphoproliferative diseases have been reported, with incidence and distribution similar to those in patients receiving traditional immunosuppressive therapy.
Rare: Menstrual disturbances, gynecomastia.

Metabolism and nutrition disorders
Very common: Hyperlipidaemia.
Common: Hyperuricaemia, hyperkalaemia, hypomagnesaemia.
Rare: Hyperglycaemia.

Nervous system disorders
Very common: Tremor, headache.
Common: Paresthesia.
Uncommon: Signs of encephalopathy, e.g. convulsion, confusion, disorientation, decreased responsiveness, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis, cerebellar ataxia.
Rare: Motor polyneuropathy.
Very rare: Oedema in the visual pupil, including disk oedema with possible visual weakening following benign intracranial hypertension.

Vascular disorders
Very common: Hypertension.

Gastrointestinal disorders
Common: Anorexia, nausea, vomiting, abdominal pain, diarrhoea, gingival hyperplasia.

Hepatobiliary disorders
Common: Hepatic dysfunction.
Rare: Pancreatitis.

Skin and subcutaneous tissue disorders
Common: Hypertrichosis.
Uncommon: Allergic rash.

Musculoskeletal and connective tissue disorders
Common: Muscle cramps, myalgia.
Rare: Muscle weakness, myopathy.

Renal and urinary disorders
Very common: Renal dysfunction (see 4.4 Special warnings and precautions for use).

General disorders and administration site conditions
Common: Fatigue.
Uncommon: Oedema, weight gain.

4.9 Overdose

a) Symptoms of intoxication
Little experience exists with overdose. After ingestion of doses up to 10 g ciclosporin (approximately 150 mg/kg), vomiting, somnolence, headache, tachycardia and in some patients a moderately severe, reversible kidney dysfunction was observed. There have been reports of severe intoxication symptoms with preterm infants after inadvertent parenteral overdose.

b) Therapy of intoxication
Possible signs of nephrotoxicity are reversible in most cases after discontinuation of administration of Transimune. In case of an overdose, symptomatic treatment and general
supportive measures should be applied. Ciclosporin is not dialyzable nor is it eliminated by activated charcoal-haemoperfusion therapy. Therefore, elimination is limited to non-specific treatment, e.g. gastrolavage. However, activated charcoal eliminates small amounts of ciclosporin from the enterohepatic circulation. Within the first few hours after overdose, it may be beneficial for the patient to induce vomiting.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Immunosuppressants, ATC code: L 04 AA 01
Ciclosporin (also called cyclosporin A) is a cyclic poly peptide, which consists of 11 amino acids. It is a strong immunosuppressive substance, which in animals increases the survival of allogenic transplantations of skin, heart, kidneys, pancreas, bone marrow, small intestine and lungs. Studies show that ciclosporin inhibits the development of cell-mediated reactions, including allotransplantation immunity, delayed skin hypersensitivity, experimental allergic encephalomyelitis, Freund’s adjuvant arthritis, graft-versus-host disease (GVHD) and the production of T-cell dependent antibodies. At the cellular level ciclosporin inhibits the production and release of lymphokines, including interleukin 2 (T-cell growth factor, TCGF). Ciclosporin apparently blocks the resting lymphocytes in phase G0 or G1 in the cell cycle and inhibits the antigen triggered release of lymphokines from activated T-cells.

The existing evidence indicates that ciclosporin acts specifically and reversibly on lymphocytes. Contrary to cytostatic agents, ciclosporin does not suppress haemopoiesis and has no effect on phagocytic cell function. Patients treated with ciclosporin are less susceptible to infections than those treated with other immunosuppressants.

Successful organ and bone marrow transplantations have been carried out in humans, where ciclosporin has been used to prevent and treat rejection and GVHD.

Treatment with ciclosporin has also shown to be advantageous in a series of other conditions with a known autoimmune origin or considered to be of autoimmune origin.

5.2 Pharmacokinetic properties
The maximal blood concentration ($C_{max}$) is achieved within 1-2 hours ($T_{max}$). The absolute bioavailability is 30-60%. The inter- and intra-individual pharmacokinetic variability is 10-20% for AUC and $C_{max}$ in healthy volunteers. Transimune can be administered with food or alone.

The results of several studies have shown that monitoring of the ciclosporin area under the time-concentration curve for the first 4 hours after administration of dose ($AUC_{0-4}$) gives a more precise prediction of the ciclosporin exposure than at base ($C_0$) monitoring.

The results from further studies indicate that a single test point 2 hours after the dose ($C_2$) correlate well with the $AUC_{0-4}$ in transplantation patients.

In medical practice either trough level monitoring or $C_2$ monitoring of ciclosporin can be used for pharmacotherapeutic surveillance.

Ciclosporin is mainly distributed outside the blood volume. In the blood there is 33-47% ciclosporin in plasma, 4-9% in the lymphocytes, 5-12% in the granulocytes and 41-58% in the erythrocytes. In plasma approximately 90% is bound to proteins, mainly lipoproteins.

Ciclosporin is biotransformed by several metabolic routes into approximately 15 metabolites. The elimination is mainly biliary, where only 6% of an oral dose is eliminated with the urine. Only 0.1% is eliminated unchanged in the urine.
There is a great variation in the available data regarding the terminal half life of ciclosporin depending on the analysis and the target population. The terminal half life varied from 6.3 hours in healthy volunteers to 20.4 hours in patients with severe hepatic disease.

5.3 Preclinical safety data
Ciclosporin showed no mutagenic or teratogenic effects in appropriate test systems. Reproduction studies in rats showed only negative effects at doses, which were toxic for the females. At toxic doses (rats 30 mg/kg and rabbits 100 mg/kg/day orally), ciclosporin was embryo- and foeto-toxic, which was indicated by increased prenatal and postnatal mortality and reduced foetal weight and bone formation.

Within the well tolerated dose range (in rats up to 17 mg/kg/day and in rabbits up to 30 mg/kg/day orally) ciclosporin showed no embryo-lethal or teratogenic effects.

Carcinogenicity studies were carried out on male and female rats and mice. In the mouse study, which lasted 78 weeks, there was a statistically significantly greater incidence of lymphocytic lymphomas in female mice at a dose of 1, 4 and 16 mg/kg/day and a considerably higher occurrence of hepatocellular carcinomas in male mice, compared to control animals. In the rat study, which lasted 24 months and involved a dose of 0.5, 2 and 8 mg/kg/day, the incidence of island cell adenomas in the pancreas considerably exceeded the control value at the low dose. Hepatocellular carcinomas and island cell adenomas in the pancreas were not dose related.

Studies in male and female rats showed no reduction in fertility.

Ciclosporin was not found to be mutagenic/genotoxic in the Ames-test, the v79-hgprt-test or the micronucleus test in mice and Chinese hamsters or the chromosome aberration test of the bone marrow of Chinese hamsters, the dominating mortality analysis in mice and the DNA-repair test in semen from treated mice. An in-vitro analysis of sister chromatid exchange (SCE) in human lymphocytes showed a positive effect of ciclosporin at high doses in this system.

An increased occurrence of malignant growths is a recognised complication in connection with immunosuppression in organ transplant patients. The most common forms of neoplasms are non-Hodgkin’s related lymphomas and skin carcinomas. The risk of malignant growths during treatment with ciclosporin is higher than in a normal healthy population, but is similar to the risk for patients treated with other immunosuppressants. Reports that reduction or discontinuation of immunosuppressants may cause regression of lesions are available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Content of the soft capsules
Ethanol anhydrous,
Tocopherol acetate
Diethylene glycol monoethyl ether
Oleoyl macrogolglycerides
Macrogolglycerol Hydroxystearate
Capsule shell
Gelatin, Glycerol
Propylene glycol
Titanium dioxide (E171),
Iron oxide black (E172)
Purified water.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.
Store in the original package.

6.5 Nature and contents of container
The soft capsules are available in aluminium-aluminium blister of:
10, 20, 30, 50 & 60 capsules
Not all pack sizes may be marketed

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Morningside Healthcare Ltd
115 Narborough Road
Leicester
LE3 0PA

8 MARKETING AUTHORISATION NUMBER(S)
PL 20117/0041

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
13/02/2008
10 DATE OF REVISION OF THE TEXT

13/02/2008

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
Module 3
Patient Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR USER

Transimune 25, 50mg and 100mg mg soft capsules
Ciclosporin

Read all of this leaflet carefully, before you start taking the medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Transimune is and what it is used for
2. Before you take Transimune
3. How to take Transimune
4. Possible side effects
5. How to store Transimune
6. Further information

1. WHAT TRANSIMUNE IS AND WHAT IT IS USED FOR
Transimune is an immunosuppressant. It suppresses the immune system and reduces inflammation.

Transimune is used to prevent rejection of newly transplanted organs or bone marrow transplants.
Transimune also used for treatment of severe psoriasis, kidney disease (nephrotic syndrome), severe arthritis and severe eczema (atopic dermatitis).

2. BEFORE YOU TAKE TRANSIMUNE
Do not take Transimune:
- if you are allergic (hypersensitive) to ciclosporin, or any of the other ingredients of ciclosporin.
- if you are taking this medicine for psoriasis or other severe skin complaints, or for rheumatoid arthritis, and have any kidney problems. If you are taking this medicine for nephrotic syndrome you should continue with your treatment as your doctor will be monitoring your kidney function carefully
- if you have kidney disorders other than nephrotic syndrome
- if you have psoriasis and are receiving PUVA, UVB, coal tar, radiation therapy or other immunosuppressants
- if you have uncontrolled high blood pressure
- if you have any uncontrolled infections
- if you have been told that you have any kind of tumour
- if you are taking products/herbal medicines which contain Hypericum perforatum (St. John’s Wort).
- if you have rheumatoid arthritis and are under 18 years of age
- if you are taking tacrolimus
**Take special care with Transimune:**

Tell your doctor if any of the following applies to you:
- if you are treated with other immunosuppressants (e.g. methotrexate)
- if your diet contains a large amount of potassium or you receive medicine that contains potassium (ask your doctor)
- if you are suffering from a low amount of magnesium in the blood
- if you are suffering from an excess amount of uric acid in the blood (e.g. if you have a kidney disease or a certain kind of arthritis)
- if you are suffering from an excess amount of lipids in the blood
- if you have poor kidney and/or liver function
- if you have high blood pressure or are being treated for high blood pressure (with potassium sparing diuretics, ACE-inhibitors, angiotensin II receptor antagonists)

Transimune should only be prescribed by physicians specialising in organ transplantation, dermatology (skin diseases), nephrology (kidney diseases) or rheumatology.

Patients treated with Transimune should avoid excessive unprotected sun exposure.

Patients treated with Transimune should have their blood pressure and kidney function monitored regularly. Regular blood samples should be taken to monitor the concentration of ciclosporin and lipids in the blood and liver function.

Blood concentrations of Transimune should also be monitored if you are taking certain other drugs or when treatment with the other drug is discontinued.

Please inform your doctor if you suffer from an acute infection not treated with any medicine. Routine dental check-ups are recommended.

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

The following medicines reduce the effect of Transimune:

- Barbiturates, carbamazepine, phenytoin, phenobarbital, primidone (for treatment of epilepsy);
- nafcillin, rifampicin, griseofulvin, sulphadiazine, trimethoprim and sulfadimidine i.v. (antibiotic);
- octreotide (medicine that restricts the release of certain hormones); probucol (for treatment of high cholesterol); orlistat (for treatment of obesity); troglitazone (for treatment of type II-diabetes);
- ticlopidine (for inhibition of blood clotting), metamizole (analgesic), *Hypericum perforatum* (St. John’s Wort).

The following medicines increase the effect of Transimune:

- Macrolide antibiotics e.g. erythromycin, doxycycline, josamycin, roxithromycin, pristinamycin and clarithromycin (antibiotics); ketoconazole, fluconazole, itraconazole (anti-fungal); diltiazem, nicardipine, verapamil (for high blood pressure and heart disease); metoclopramide (for treatment of nausea); oral contraceptives; danazol (for a condition related to painful periods); bromocriptine (for treatment of infertility and Parkinson’s disease) methylprednisolone in high doses (anti-inflammatory); allopurinol (for treatment of arthritis); amiodarone, propafenone (for treatment of heart arrhythmia); cimetidine, ranitidine (reduces the amount of acid in the stomach); chloroquine (anti-malarial), protease inhibitors (used to treat HIV infection).
Transimune may **increase** the effect of the following medicines:
- Diclofenac (for rheumatic pain);
- digoxin (for treatment of heart arrhythmia);
- colchicines (for treatment of arthritis);
- lovastatin, pravastatin, simvastatin, atorvastatin (for treatment of high cholesterol);
- prednisolone; nifedipine (for high blood pressure and heart disease).

Other medicines that may interact with Transimune:
- aminoglycosides (such as gentamicin and tobramycin);
- ciprofloxacin, vancomycin (antibiotic);
- amphotericin B (anti-fungal);
- sulfamethoxazole (for urinary infection);
- non-steroidal anti-inflammatory drugs (for rheumatic pain);
- melphalan (cytostatic);
- tacrolimus and sirolimus (immunosuppressant).

Vaccines may be less effective during treatment with Transimune.

**Taking Ciclosporin with food and drink**
- Transimune can be taken with or without food.
- Grapefruit juice should be avoided because it may increase the effect of Transimune.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine.

**Pregnancy**
If you are pregnant, planning to become pregnant or get pregnant whilst taking Transimune you should inform your doctor immediately. Transimune should not be taken during pregnancy unless your doctor has discussed it with you.

**Breast-feeding**
Transimune should not be used when breast-feeding.

**Driving and using machines**
Transimune does not affect the ability to drive or use machines. However Transimune contains ethanol, if affected you should not drive or use machines.

**Important information about some of the ingredients of Transimune**
- This medicine contains macrogolglycerol hydroxystearate which may cause stomach upset and diarrhoea.
- This medicinal product contains small amount of ethanol i.e. upto 525mg ethanol per dose (maximum dose), e.g. 5 soft capsules Transimune 100mg or 11 soft capsules Transimune or 21 soft capsules Transimune are equivalent to approximately to 13ml beer, or approximately 6ml wine. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

### 3. HOW TO TAKE TRANSIMUNE

Always take Transimune exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
The daily dose of Transimune should always be divided in 2 doses and taken in the morning and in the evening.
The capsules should be swallowed whole.

**Organ transplantation:**
Individual dosage. It is important to follow the doctor’s prescription very carefully.

**Bone marrow transplantation:**
Individual dosage. It is important to follow the doctor’s prescription very carefully.

**Nephrotic syndrome (kidney disease):**
Initially the recommended oral dose is 5 mg per kg bodyweight daily divided in 2 doses for adults and 6 mg per kg bodyweight daily for children. The ciclosporin concentration should be monitored regularly. In patients with reduced kidney function the initial dose should not exceed 2.5 mg per kg bodyweight daily.

**Rheumatoid arthritis:**
Initially the recommended dose is 2.5-5 mg per kg bodyweight daily divided in 2 doses. To achieve full therapeutic effect it may be necessary to treat with Ciclosporin for up to 12 weeks.

**Psoriasis:**
The recommended oral initial dose is 2.5 mg per kg bodyweight daily divided in 2 doses. After 1 month, the daily dose can gradually be increased to a maximum of 5 mg per kg bodyweight. In *maintenance treatment* the dose is individually adjusted to the lowest clinically effective level.

**Atopic dermatitis:**
The treatment of this condition is individually adjusted, since the disease varies greatly. The recommended dose is 2.5-5 mg per kg bodyweight per day divided in 2 oral doses.

**Elderly:**
No special adjustment of the dose is necessary. Ask your doctor.

**Children:**
There is limited experience in children. However, ciclosporin has been used at the recommended dose for children from 1 year of age without special problems.

If you take more Transimune than you should
Contact your doctor or casualty department immediately.

If you forget to take Transimune
Take another one as soon as you remember, unless it is almost time for your next dose. Then go on as before. **Do not take a double dose to make up for a forgotten dose.**

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, Transimune can cause side effects, although not everybody gets them.
Very common (affecting more than 1 in 10 people)
Increased lipid in the blood, tremor, headache, high blood pressure, kidney problems.

Common (affecting between 1 in 100 and 1 in 10 people)
Increased uric acid in the blood, increased potassium in the blood, decreased magnesium in the blood, tingling, pricking, or numbness of the skin (paresthesia), loss of appetite, nausea, vomiting, stomach pain, diarrhoea, swollen gums, liver problems, increased hair growth, muscle cramps or pain, tiredness.

Uncommon (affecting between 1 in 1000 and 1 in 100 people)
Anaemia, reduced platelet count, signs of neurological disorder (e.g. convulsion, confusion, feeling disorientated, decreased reactivity, agitation, sleeplessness, blurred vision, blindness, partial muscle paralysis, muscle incoordination, coma), rash, water retention, weight gain, development of malignant tumours.

Rare (affecting between 1 in 10,000 and 1 in 1000 people)
Anaemia in the small blood vessels, haemolytic uraemic syndrome (acute kidney failure and anaemia), menstrual disturbances, enlargement of the male breast, increased blood glucose, progressive muscle weakness, pancreatitis, muscle weakness or stiffness or spasm.

Very rare (affecting less than 1 in 10,000 people)
Swelling of the optic nerve with possible visual impairment in cases of benign intracranial hypertension (increased pressure in the brain).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

5. HOW TO STORE TRANSIMUNE

Keep out of the reach and sight of children.

There are no special storage precautions for Transimune

Store in the original package.

Do not use Transimune after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION

What Transimune contains
The active substance is ciclosporin 25 mg, 50 mg or 100 mg.
The other ingredients are Ethanol anhydrous, Tocopherol acetate, Dyeethylene glycol monoethyl ether, Oleoyl macrogolglycerides, Macrogolglycerol Hydroxystearate, Gelatin, Glycerol, Propylene glycol, Titanium dioxide (E171), Iron oxide black (E172) (25mg and 100mg), Purified water.

What Transimune looks like and contents of the pack
Transimune is available in three strengths:
25mg which are grey in colour, 50mg which are white in colour and 100mg which are grey in colour

Pack size: The soft capsules are available in aluminium-aluminium blister of:
10, 20, 30, 50 & 60 capsules. Not all pack sizes may be marketed

Marketing Authorisation Holder
Morningside Healthcare Ltd
115 Narborough Road
Leicester,
LE3 0PA

Site responsible for batch relaease
Laboratório Medinfar – Morningside Pharmaceuticals Ltd
ProdutosFarmacêuticos S.A. 5 Pavilion Way,
Rua Henrique Paiva Couceiro, nº 29, Venda Loughborough.
Nova2700-451 Amadora, Leicestershire
Portugal U.K

This medical product is authorised in the Member States of the EEA under following names:

This leaflet was approved in November 2007
Module 4
Labelling

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

1. **NAME OF THE MEDICINAL PRODUCT**

   Transimune 25mg, soft capsules  
   Transimune 50mg, soft capsules  
   Transimune 100mg, soft capsules  
   Ciclosporin

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each soft capsule contains: Ciclosporin 25mg, 50mg, 100mg.

3. **LIST OF EXCPIIENTS**

   Ethanol and macrogolglycerol hydroxystearate.  
   See leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

   10 capsules  
   20 capsules  
   30 capsules  
   50 capsules  
   60 capsules

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   For oral administration  
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**
8. EXPIRY DATE

Expiry date: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

No special precautions for storage.

Store in the original package

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

N/A

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

To be completed nationally

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

13. MANUFACTURER'S BATCH NUMBER

Batch number:

14. GENERAL CLASSIFICATION FOR SUPPLY

[POM] Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

To be completed nationally.
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>Transimune 25mg, soft capsules</td>
</tr>
<tr>
<td>Transimune 50mg, soft capsules</td>
</tr>
<tr>
<td>Transimune 100mg, soft capsules</td>
</tr>
<tr>
<td>Ciclosporin</td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td>To be completed nationally</td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
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<tr>
<td>EXP: MM/YYYY</td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
</tr>
<tr>
<td>Batch number</td>
</tr>
<tr>
<td><strong>5. OTHER</strong></td>
</tr>
</tbody>
</table>
Module 5

Scientific Discussion During Initial Procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Transimune 25mg, soft capsules (PL 20117/0039), Transimune 50mg, soft capsules (PL 20117/0040) and Transimune 100mg, soft capsules (PL 20117/0041) on 13 February 2008. The products are prescription only medicines.

This application was made under Article 10.1 of 2001/83 EC, as amended, claiming that Transimune 25mg, 50mg and 100mg soft capsules are generic products of Sandimmune Optoral 25mg, 50mg and 100mg capsules (Novartis, Germany) which were authorised in May 1994. The UK reference products are Neoral Soft Gelatin Capsules 25mg, 50mg and 100mg (Novartis Pharmaceuticals UK Ltd, trading as Sandoz Pharmaceuticals) which were granted licenses in April 1995. The reference products have therefore been authorised in the EEA for at least 10 years.

The products contain the active ingredient ciclosporin and are indicated in combination with other immunosuppressant substances for the prevention of acute and chronic transplant rejection following allogenic transplantation of kidneys, liver, heart, heart-lung, lung or pancreas. The products are also indicated for the prevention and treatment of graft-versus-host-disease (GVHD) following allogenic bone marrow transplantation as well as for the treatment of severe forms of psoriasis, atopic dermatitis and active rheumatoid arthritis.

Ciclosporin is a polypeptide which produces a specific and reversible inhibition of T lymphocytes in G0 and G1 cellular phase. Unlike cytostatics, ciclosporin does not suppress haematopoiesis and has no effects under phagocytic cells. As a result of this mechanism of action, ciclosporin has been widely used to prevent and treat the rejection of GVHD in bone marrow and solid organ transplants. Additionally, ciclosporin has beneficial effects in a wide range of autoimmune pathologies, such as rheumatoid arthritis, psoriasis and atopic dermatitis.

No new preclinical studies were conducted, which is acceptable given that the application referred to products that have been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application referred to products that have been licensed for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of the product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

The decentralised procedure was completed at Day 210 (08 November 2007), with the RMS and the CMS agreeing that the licences were approvable. The national phase of the decentralised procedure was completed in the UK on 13 February 2008.
## ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Transimune 25mg, soft capsules  
| Transimune 50mg, soft capsules  
| Transimune 100mg, soft capsules |
| Name(s) of the active substance(s) (INN) | Ciclosporin |
| Pharmacotherapeutic classification (ATC code) | Selective immunosuppressants (L04AA01) |
| Pharmaceutical form and strength(s) | 25mg, 50mg and 100mg soft capsules |
| Reference number for the Decentralised Procedure | UK/H/0982/001-3/DC |
| Reference Member State | United Kingdom |
| Concerned Member States | Czech Republic, Germany, Greece, Slovakia |
| Marketing Authorisation Number(s) | PL 20117/0039-41 |
| Name and address of the authorisation holder | Morningside Healthcare Ltd  
| 115 Narborough Road  
| Leicester  
| LE3 0PA |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

All aspects of the manufacture and control of ciclosporin are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of ciclosporin for inclusion in this medicinal product.

Appropriate stability data have been provided to support a retest period of 4 years when stored in the proposed packaging.

DRUG PRODUCT

Other Ingredients
The excipients present are ethanol anhydrous, tocopherol acetate, diethylene glycol monoethyl ether, oleoyl macrogolglycerides and macrogolglycerol hydroxystearate. Gelatin, glycerol, propylene glycol, titanium dioxide (E171), iron oxide black (E172) (25mg and 100mg capsules only) and purified water are also present in the capsule shell.

The excipients used comply with their respective European Pharmacopoiea monographs. Satisfactory certificates of analysis have been provided.

Gelatin is the only excipient that contains material of animal or human origin. A Transmissible Spongiform Encephalopathies (TSE) Certificate has been provided for gelatin confirming that the risk of transmitting TSE is sufficiently low.

Pharmaceutical Development
The applicant has provided suitable product development rationale and data.

Impurity Profile
Comparative impurity profiles for the German reference product and test product are provided. The test product has a lower total impurity content than the reference product.

Dissolution Profile
Comparative dissolution profiles were generated for the reference product (Neoral 100mg soft gelatine capsules, Novartis, Germany), reference biobatch (Neoral 100mg soft gelatine capsules, Novartis, France) and test biobatch (Transimune 100mg, soft capsules). The dissolution method used was chosen as it is the most discriminative.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. Suitable in-process controls are applied during the manufacturing process to ensure the quality of the product.

The manufacturing process has been validated and the results are satisfactory.
Control of Drug Product
The proposed finished product specification is acceptable and provides an assurance of the quality of the finished product. The analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed specification.

Reference Standards or Materials
Certificates of analysis for all reference standards used have been provided and are satisfactory.

Container Closure System
The finished product is packaged in aluminium-aluminium blisters in pack sizes of 10, 20, 30, 50 and 60 capsules. Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the Drug Product
The stability data provided support a shelf-life of 3 years, with storage conditions “Store in the original package.”

Bioequivalence/Bioavailability
Refer to the clinical assessment.

SPC, PIL, Labels
The SPC is pharmaceutically acceptable.

The Patient Information Leaflet (PIL) and labels are currently only available in text format as the Applicant intends to transfer ownership of the licenses.

CONCLUSION
It is recommended that Marketing Authorisations are granted for these applications.

III.2 NON-CLINICAL ASPECTS

Critical Evaluation of the Non-Clinical Overview and Summary
The pharmacodynamic, pharmacokinetic and toxicological properties of cyclosporine are well known. As cyclosporine is a widely used, well known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on a literature review is therefore appropriate.

The non-clinical overview has been written by an appropriately qualified pharmacist and is a concise summary of the literature reviewed. In view of the fact that cyclosporine is a well known compound it is adequate.

Section 5.3 of the SPC is identical to that of the reference medicinal product.

Conclusions
Cyclosporin is a well known active substance. The proposed indications are stated to be identical to the authorised indication for the reference product.

There are no objections to the approval of Transimune 25mg, 50mg and 100mg soft capsules.
III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

Pharmacokinetics
Ciclosporin is distributed largely outside the blood volume. In the blood, 33-47% is present in plasma, 4-9% in lymphocytes, 5-12% in granulocytes, and 41-58% in erythrocytes. In plasma, approximately 90% is bound to proteins, mostly lipoproteins.

Ciclosporin is extensively biotransformed to approximately 15 metabolites. There is no single major metabolic pathway. Elimination is primarily biliary, with only 6% of the oral dose excreted in the urine; only 0.1% is excreted in the urine as unchanged drug.

There is a high variability in the data reported on the terminal half-life of ciclosporin depending on the assay applied and the target population. The terminal half-life ranged from 6.3 hours in healthy volunteers to 20.4 hours in patients with severe liver disease.

To support the application, the applicant has submitted two bioequivalence studies (fasting and fed conditions) comparing the test product with the reference product.

The excipient ratio, manufacturing process/site and dissolution profile criteria support the use of single dose strength studies to confirm bioequivalence. With reference to the requirement for linear pharmacokinetics to support single dose strength studies, the pharmacokinetic linearity of the reference product has been demonstrated over a wide, clinically relevant range (approximately 200-800mg). Given the similarity of the test formulation to the reference product, linear PK can reasonably be expected for the Applicant’s product.

Study 1
This was a randomized, open-label, 2-way crossover, bioequivalence study of Transimune 100mg soft capsules and Neoral 100mg soft gelatine capsules from Novartis Pharma S.A.S., France (Reference) following a 200mg dose in healthy subjects under fasting conditions.

A single oral dose of cyclosporin as 2 x 100mg capsules was administered in each study period under fasting conditions. The treatment phases were separated by a washout period of 14 days. Blood samples were collected prior to study drug administration and 0.333, 0.667, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 12.0, 16.0, 24.0, 36.0, and 48.0 hours postdose in each period.

Analytical method:
Whole blood samples were analysed using Liquid Chromatography MS using a calibration curve range of 5.05 ng/ml to 1516.10 ng/ml.

The statistical methods used were:

Pharmacokinetics:
- Parametric ANOVA on $AUC_0-t$, $AUC_0-inf$, $C_{max}$, $T_{1/2,el}$ and $K_{el}$; geometric confidence intervals for $AUC_0-t$, $AUC_0-inf$ and $C_{max}$; and non-parametric test (Wilcoxon) for $T_{max}$;
- Covariates in the ANOVA model: sequence, subject within sequence, period and treatment;
- Ln-transformed parameters: $AUC_0-t$, $AUC_0-inf$ and $C_{max}$. 
Criteria for Bioequivalence:
For both potency corrected and uncorrected data: 90% geometric confidence intervals of the ratio (A/B) of least-squares means from the ANOVA of the ln-transformed AUC0-t and Cmax should be within 80% to 125%.

Results:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test (Cyclosporine (A))</th>
<th>Reference (Neoral (B))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>CV (%)</td>
</tr>
<tr>
<td></td>
<td>90% Geometric CI</td>
<td></td>
</tr>
<tr>
<td>AUC0-t</td>
<td>4124.94 ± 940.73</td>
<td>22.81</td>
</tr>
<tr>
<td>AUC0-∞</td>
<td>4257.27 ± 983.82</td>
<td>23.11</td>
</tr>
<tr>
<td>Cmax</td>
<td>1050.17 ± 217.96</td>
<td>20.75</td>
</tr>
<tr>
<td>Residual area</td>
<td>3.04 ± 0.88</td>
<td>29.08</td>
</tr>
<tr>
<td>T_{max}</td>
<td>1.43 ± 0.30</td>
<td>21.02</td>
</tr>
<tr>
<td>T_{max}</td>
<td>1.50 ± 0.50</td>
<td></td>
</tr>
<tr>
<td>Kd</td>
<td>0.0578 ± 0.0128</td>
<td>22.19</td>
</tr>
<tr>
<td>T_{1/2}</td>
<td>12.53 ± 2.58</td>
<td>20.61</td>
</tr>
</tbody>
</table>

* Median and interquartile ranges are presented.

A significant sequence effect was detected for the Test product. However, there was no detectable pre-dose concentration and there was no significant increase in PK parameters from period 1 to 2 indicating there is no evidence of carryover.

The residual area was calculated for each subject and treatment. The mean percentage of extrapolated area under the curve was lower than 20% for all treatments indicating that duration of blood sampling was adequate.

PK calculations were also performed on data corrected for measured content and the results are shown below.

<table>
<thead>
<tr>
<th>Statistical Analysis (Potency corrected)</th>
<th>Ratio (Test/Reference)</th>
<th>90% Geometric CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t</td>
<td>90.33%</td>
<td>95.95-102.83</td>
</tr>
<tr>
<td>AUC0-∞</td>
<td>99.18%</td>
<td>95.79-102.68</td>
</tr>
<tr>
<td>Cmax</td>
<td>99.19%</td>
<td>94.17-104.48</td>
</tr>
</tbody>
</table>

Safety

45 post-dose adverse events (AEs) occurred during the study, most of them rated as mild and few moderate. Of these, 31 were considered to be potentially related to the study medication: 12 (38.7%) following administration of test treatment and 18 (58.1%) following administration of reference treatment. The most commonly reported AEs were “Headache”, “Nausea”, and “Vasodilat”. No serious or significant adverse events were reported during this study.

Study 2
This was a randomized, open-label, 2-way crossover, bioequivalence study of Transimune 100mg soft capsules and Neoral 100mg soft gelatin capsules from Novartis Pharma S.A.S., France (Reference) following a 200 mg dose in healthy subjects under fed conditions.

A single oral dose of cyclosporin as 2 x 100mg capsules was administered in each study period under fed conditions. The treatment phases were separated by a washout period of 14 days. Blood samples were collected prior to study drug administration and 0.333, 0.667, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 12.0, 16.0, 24.0, 36.0, and 48.0 hours postdose in each period.

Analytical method:

Whole blood samples were analysed using Liquid Chromatography MS using a calibration curve range of 5.05 ng/ml to 1516.10 ng/ml.

The statistical methods used were:

Pharmacokinetics:
- Parametric ANOVA on AUC\(_{0-t}\), AUC\(_{0-\infty}\), C\(_{\text{max}}\), T\(_{1/2\text{el}}\) and K\(_{\text{el}}\); geometric confidence intervals for AUC\(_{0-t}\), AUC\(_{0-\infty}\) and C\(_{\text{max}}\); and non-parametric test (Wilcoxon) for T\(_{\text{max}}\);
- Covariates in the ANOVA model: sequence, subject within sequence, period and treatment;
- Ln-transformed parameters: AUC\(_{0-t}\), AUC\(_{0-\infty}\) and C\(_{\text{max}}\).

Criteria for Bioequivalence:
For both potency corrected and uncorrected data: 90% geometric confidence intervals of the ratio (A/B) of least-squares means from the ANOVA of the ln-transformed AUC\(_{0-t}\) and C\(_{\text{max}}\) should be within 80% to 125%.

Results:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test (Cyclosporine (A))</th>
<th>Reference (Neoral (B))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>CV (%)</td>
</tr>
<tr>
<td>AUC(_{0-t}) (ng h/mL)</td>
<td>3995.82 ± 1125.63</td>
<td>28.16</td>
</tr>
<tr>
<td>AUC(_{0-\infty}) (ng h/mL)</td>
<td>4109.72 ± 1159.39</td>
<td>28.21</td>
</tr>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>1069.72 ± 407.88</td>
<td>38.13</td>
</tr>
<tr>
<td>Residual area (%)</td>
<td>2.78 ± 0.76</td>
<td>27.31</td>
</tr>
<tr>
<td>T(_{\text{max}}) (h)</td>
<td>1.65 ± 0.80</td>
<td>48.34</td>
</tr>
<tr>
<td>T(_{\text{max}}) (h)</td>
<td>1.50 ± 0.38</td>
<td>-</td>
</tr>
<tr>
<td>K(_{\text{el}}) (h(^{-1}))</td>
<td>0.0611 ± 0.0229</td>
<td>37.47</td>
</tr>
<tr>
<td>T(_{0.5\text{el}}) (h)</td>
<td>12.25 ± 2.70</td>
<td>22.07</td>
</tr>
</tbody>
</table>

* Medians and interquartile ranges are presented.

The residual area was calculated for each subject and treatment. The mean percentage of extrapolated area under the curve was lower than 20% for all treatments indicating that the duration of blood sampling was sufficient.

PK calculations were performed on potency corrected (shown below) and uncorrected data. All PK calculations showed the 90% CI for AUC and C\(_{\text{max}}\) within the acceptance limits of 80%-125%.
**Statistical Analysis**

(Potency corrected)

<table>
<thead>
<tr>
<th></th>
<th>Ratio (Test/Reference)</th>
<th>90% Geometric CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0-t}$</td>
<td>97.46%</td>
<td>87.81-108.17</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$</td>
<td>97.53%</td>
<td>87.92-108.20</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>103.75%</td>
<td>87.79-122.61</td>
</tr>
</tbody>
</table>

**Safety**

68 post-dose adverse events (AEs) occurred during the study, 46 graded as mild and 14 as moderate. Of these, 50 were judged to be potentially related to the study medication: 24 (48.0%) following administration of test treatment and 19 adverse events (38.0 %) following administration of reference treatment. Of the potentially related AEs, the most commonly reported adverse events were “Headache”, “Pharyngitis” and “Vasodilat”. No serious adverse events were reported during this study.

**Conclusion**

Based on the submitted bioequivalence studies, Transimune 100 mg soft capsules are considered to be bioequivalent to the reference product. Performing the two studies (under fed and fasting conditions) has shown a good comparative in terms of bioequivalence between the test product and the reference product. The design and the method of the studies are satisfactory.

**Pharmacodynamics**

Ciclosporin is a potent immunosuppressive agent which prolongs survival of allogeneic transplants involving skin, heart, kidney, pancreas, bone marrow, small intestine and lung in animals. On a cellular level it inhibits the liberation of lymphocytes including interleukin 2 (T-cells growth factor, TCGF). As it appears, ciclosporin blocks the lymphocytes during phase G0 or G1 of the cellular cycle and inhibits the release of lymphokines unbound by antigens, by activated T-cells.

All of the evidence shows that ciclosporin acts specifically and in a reversible manner upon the lymphocytes. Contrary to cytostatic agents, ciclosporin does not depress the hematopoiesis and has no effect on the phagocytic cells.

Bone marrow transplants and solid organ transplants in humans have been accomplished with great success using ciclosporin for microemulsion to prevent and treat rejections and graft-versus-host-disease (GVHD). There have also been beneficial effects noted in ciclosporin therapy of various auto-immune diseases.

No new pharmacodynamic data have been submitted and none are required for this application.

**Efficacy**

No new efficacy data have been provided and none are required for applications of this type.

**Safety**

No new safety data have been provided and none are required for applications of this type.
EXPERT REPORT
A satisfactory clinical expert report has been submitted, which has been written by an appropriately qualified medical doctor.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
This is satisfactory and consistent with the SPC for the reference product.

PATIENT INFORMATION LEAFLET (PIL)
This is satisfactory and consistent with the SPC.

LABELLING
These are satisfactory.

CONCLUSION
The application contains an adequate review of published clinical data and bioequivalence has been shown. Approval is recommended from the clinical point of view. Conducting bioequivalence studies across the range of indications is accepted as difficult and therefore the results seen in healthy volunteers are considered sufficient for approval. However, an adequate post-marketing study addressing surveillance of acute graft rejection rates and renal function for a defined period following treatment with Transimune 25mg, 50mg and 100mg soft capsules is considered necessary.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Transimune 25mg, 50mg and 100mg soft capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Transimune 100mg soft capsules and Neoral 100mg soft gelatine capsules (Novartis Pharma S.A.S., France). Given that linear kinetics apply between the 25mg, 50mg and 100mg capsules, that proportional formulae for the capsules have been used, the method of manufacture is the same and that similar dissolution results have been shown for the three strengths, separate bioequivalence studies using the 25mg and 50mg capsules are not considered necessary.

No new or unexpected safety concerns arose from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s products and the reference products are interchangeable. Clinical experience with ciclosporin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
## Module 6

### Steps Taken After Initial Procedure - Summary

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
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