SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LYMUNIR 100 mg Soft Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains:

Active substance:
Cyclosporine..... 100 mg

Excipients:
Macrogol glycerol hydroxystearate. … 410 mg
Anhydrous ethanol..... 125 mg
See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Soft capsule.
Oblong, grayish-colored, opaque soft capsule.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

• Transplantation indications

Organ transplantation
Allogeneic transplantation of kidney, liver, heart, lung, combined heart-lung, or pancreas to prevent graft rejection.

Treatment of organ rejection in patients previously treated with other immunosuppressive drugs.

Bone marrow transplantation
Prevention of graft rejection following bone marrow transplantation.

Prevention or treatment of graft-versus-host disease (GVHD).

• Non-transplantation indications

Endogenous uveitis

Non-infectious, active intermediate or posterior uveitis threatening visual function, where conventional treatment has failed or caused undesirable side effects.
Behçet's uveitis with recurrent inflammatory attacks involving the retina in patients without neurological involvement.

Nephrotic syndrome
Steroid-dependent and steroid-resistant nephrotic syndrome cases in adults and children associated with glomerular diseases such as minimal change nephropathy, focal and segmental glomerulosclerosis, or membranous glomerulonephritis.

LYMUNIR can be used to achieve and maintain remission. It can also be used to allow discontinuation of steroids in the maintenance of steroid-induced remissions.

Rheumatoid arthritis
Treatment of severe, active rheumatoid arthritis.

Psoriasis
LYMUNIR is indicated for severe psoriasis patients in whom conventional therapy is inadequate or inappropriate.

Atopic dermatitis
LYMUNIR is indicated for the treatment of patients with severe atopic dermatitis requiring systemic therapy.

4.2. Posology and method of administration

The dosage ranges provided for oral administration are for guidance only.
The daily doses of LYMUNIR must be divided into two equal doses.
It is recommended that LYMUNIR be administered according to a consistent schedule in terms of the time of day and relation to meals.

LYMUNIR should only be prescribed by a physician experienced in immunosuppressive therapy and/or organ transplantation, or in close collaboration with such a physician.

Due to the possibility of inter-individual variability in absorption and excretion and pharmacokinetic drug interactions (see Section 4.5 "Interaction with other medicinal products and other forms of interaction"), doses should be titrated on an individual basis according to clinical response and tolerability. In these transplant patients, routine monitoring of trough serum levels of cyclosporine is necessary to avoid adverse effects associated with high levels and to prevent organ rejection associated with low levels (see Section 4.4 Special warnings and precautions for use).

In patients treated for indications other than transplantation, monitoring of cyclosporine blood levels is of limited value except in cases of unexpected treatment failure or relapse; monitoring may be appropriate in cases of treatment failure or relapse to detect the possibility of very low levels of , which may be due to non-compliance with treatment, impaired gastrointestinal absorption, or pharmacokinetic interactions (see Section 4.4 Special warnings and precautions for use).

Following initiation of treatment with LYMUNIR, patients should not be switched to another oral cyclosporine formulation without appropriate monitoring of cyclosporine blood concentrations, serum creatinine levels, and blood pressure, due to the different bioavailability of different oral cyclosporine formulations.

Due to differences in bioavailability between different oral cyclosporine formulations, it is important that prescribing physicians, pharmacists, and patients understand that switching to another oral cyclosporine formulation is not recommended, as this may lead to changes in cyclosporine blood levels.

Posology / Frequency and duration of administration:
General target population:

• Transplantation

Organ transplantation
LYMUNIR should initially be administered in a divided dose of 10-15 mg/kg within 12 hours prior to surgery. This dose is continued for 1-2 weeks in the post-operative period. The dose is then gradually reduced according to blood levels, reaching a maintenance dose of 2-6 mg/kg/day administered in divided doses. Serum trough levels of cyclosporine should be monitored and the dose adjusted according to renal function.

When LYMUNIR is administered with other immunosuppressants (e.g., with corticosteroids or as part of triple or quadruple drug therapy), lower doses (e.g., initial treatment of 3-6 mg/kg divided into two doses) may be administered.

Bone marrow transplantation
The initial dose should be administered the day before transplantation. For this purpose, IV infusion is preferred in most cases, and the recommended dose is 3-5 mg/kg daily. This dose is continued for approximately two weeks before transitioning to LYMUNIR maintenance therapy, which involves administering 12.5 mg/kg daily in divided doses during the early posttransplantation period. Maintenance therapy should continue for at least 3 months (preferably 6 months) before the dose is gradually reduced to zero within one year after transplantation. If LYMUNIR is to be used initially, the recommended dose is 12.5-15 mg/kg/day, administered in two divided doses starting the day before transplantation.

Higher doses of cyclosporine or IV therapy may be necessary in cases of gastrointestinal disorders that can reduce absorption.

In some patients, GVHD (graft-versus-host disease) occurs after discontinuation of cyclosporine, but this generally responds very well to reinitiation of therapy. In such cases of , an initial oral loading dose of 10 to 12.5 mg/kg should be given, followed by daily administration of the previously adequate oral maintenance dose. Low doses of LYMUNIR should be used in the treatment of mild, chronic GVHD.

• Non-transplantation indications
When using LYMUNIR for any of the specified non-transplantation indications, the following general rules must be followed:
• Baseline serum creatinine levels should be reliably determined with at least two measurements prior to initiating treatment. The estimated glomerular filtration rate (eGFR) calculated using the MDRD formula can be used to assess renal function in adults, and an appropriate formula should be used to assess eGFR in pediatric patients. Since LYMUNIR may impair renal function, renal function should be evaluated frequently. If the eGFR falls below 25% of the baseline value in multiple measurements, the LYMUNIR dose should be reduced by 25% to 50%. If the decrease in eGFR exceeds 35% from the baseline level, further reduction of the LYMUNIR dose should be considered. These recommendations apply even if the patient's values are still within the laboratory's normal range. If dose reduction does not improve eGFR within one month, LYMUNIR treatment should be discontinued (see Section 4.4 Special warnings and precautions for use).
• Regular monitoring of blood pressure is required.
• Measurement of bilirubin and parameters assessing hepatic function is required before starting treatment, and close monitoring is recommended during treatment. Regular measurement of serum lipids, potassium, magnesium, and uric acid is recommended before starting treatment and at regular intervals during treatment.
• In non-transplant indications, such as LYMUNIR, occasional monitoring of blood cyclosporine levels may be appropriate when administered concomitantly with substances that may affect the pharmacokinetic properties of cyclosporine or when unusual clinical responses occur (e.g., increased drug intolerance such as ineffectiveness or renal dysfunction).
• The normal route of administration is oral. If a concentrated infusion solution is used, careful consideration should be given to administering an adequate intravenous dose equivalent to the oral dose. Consultation with a physician experienced in the use of cyclosporine is recommended.
• Except for patients with vision-threatening endogenous uveitis and children with nephrotic syndrome, the total daily dose should not exceed 5 mg/kg.
• The lowest effective and well-tolerated dose should be determined on an individual basis for maintenance therapy.

LYMUNIR treatment should be discontinued in patients who do not achieve an adequate response within a specified period or whose effective dose is not consistent with established safety guidelines.

Endogenous uveitis
To achieve remission, an initial dose of 5 mg/kg per day, divided into two doses, is recommended until active uveal inflammation resolves and visual acuity improves. In refractory cases, the dose may be increased to 7 mg/kg per day for a limited period.

If adequate control cannot be achieved with LYMUNIR, systemic corticosteroid therapy at a dose of 0.2-0.6 mg/kg daily or equivalent may be added to achieve initial remission or to counter inflammatory ocular attacks. After three months, the dose of corticosteroids may be tapered down to the lowest effective dose.

For maintenance therapy, the dose should be gradually reduced to the lowest effective levels, not exceeding 5 mg/kg daily during remission phases.

Infectious causes of uveitis should be ruled out before using immunosuppressants.

Nephrotic syndrome
To achieve remission, provided that renal function is normal except for proteinuria, the recommended dose is 5 mg/kg/day for adults and 6 mg/kg/day for children, divided into two doses. In patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg/day.

If adequate results cannot be achieved with LYMUNIR alone, especially in steroid-resistant patients, a combination of LYMUNIR with low-dose corticosteroids is recommended.

The recovery period varies between 3 and 6 months, depending on the type of glomerulopathy. If no improvement is achieved after treatment, LYMUNIR therapy should be discontinued.

Doses should be adjusted according to efficacy (proteinuria) and safety (primarily serum creatinine) in each patient, but doses should not exceed 5 mg/kg/day in adults and 6 mg/kg/day in children.

For maintenance therapy, the dose should be gradually reduced to the lowest effective level.

Rheumatoid arthritis
The recommended dose for the first 6 weeks of treatment is 3 mg/kg/day, administered orally in two divided doses. If adequate efficacy is not achieved, the dose may be gradually increased to the extent tolerated (see Section 4.4 Special warnings and precautions for use), but should

not exceed 5 mg/kg. To achieve full efficacy, LYMUNIR treatment should be continued for up to 12 weeks.

The maintenance dose should be individually adjusted for each patient based on tolerability.

LYMUNIR can be combined with low-dose corticosteroids and/or non-steroidal anti-inflammatory drugs (NSAIDs) (see Section 4.4 Special warnings and precautions for use). LYMUNIR can also be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone. The LYMUNIR dose may be increased from an initial dose of 2.5 mg/kg divided into two daily doses to a dose at which hematological parameters, and particularly serum creatinine clearance, remain within normal limits.

Psoriasis
LYMUNIR therapy should be initiated by physicians experienced in the diagnosis and treatment of psoriasis. Due to the variability of this condition, treatment should be individualized. The recommended starting dose to achieve remission is an oral dose of 2.5 mg/kg/day, divided into two doses. If no improvement is seen after one month, the daily dose may be gradually increased, but should not exceed 5 mg/kg. If an adequate response to psoriatic lesions is not achieved with a dose of 5 mg/kg/day within 6 weeks, or if the effective dose is incompatible with safety data, treatment should be discontinued (see Section 4.4 Special warnings and precautions for use).

A starting dose of 5 mg/kg is recommended in patients whose condition requires rapid improvement. Once improvement is achieved, LYMUNIR may be discontinued, and any subsequent relapse may be treated by re-administering the previously effective dose of LYMUNIR. Some patients may require ongoing maintenance therapy.

For maintenance therapy, doses should be adjusted to the minimum effective dose level for each patient and should not exceed 5 mg/kg/day.

Atopic dermatitis
LYMUNIR treatment should be initiated by physicians experienced in the diagnosis and treatment of atopic dermatitis. Due to the variability of this condition, treatment should be individualized. The recommended dose is 2.5-5 mg/kg/day orally, divided into two doses. If the starting dose of 2.5 mg/kg/day does not produce an adequate response within two weeks, the daily dose may be increased to a maximum of 5 mg/kg. In severe cases, a starting dose of 5 mg/kg/day may be necessary to achieve rapid and adequate control of the disease. Once an adequate response is achieved, the dose should be gradually reduced and LYMUNIR treatment should be discontinued if possible. Consequently, LYMUNIR treatment should be repeated in the event of a subsequent relapse.

An eight-week treatment is sufficient for clearance, but it has been shown that treatment is effective and well tolerated for up to 1 year, provided that follow-up guidelines are followed.

Administration method

The daily dose of LYMUNIR must be divided into two doses.

LYMUNIR soft capsules should be swallowed whole with water.

Switching between oral cyclosporine formulations:
Switching from one oral cyclosporine formulation to another should be done carefully under a doctor's supervision. When switching to a new formulation, blood cyclosporine levels must be monitored to ensure that pre-switch levels are reached.

Additional information for specific populations:
Renal insufficiency:
All indications
The renal elimination of cyclosporine is minimal, and its pharmacokinetics are not significantly affected by renal insufficiency (see Section 5 Pharmacological properties). However, due to its nephrotoxic potential (see Section 4.8 Undesirable effects), careful monitoring of renal function is recommended (see Section 4.4 Special warnings and precautions for use).

Non-transplantation indications
Patients with impaired renal function, except those with nephrotic syndrome, should not receive cyclosporine (see Section 4.4 Special warnings and precautions for use). In patients with nephrotic syndrome and impaired renal function, the initial dose should not exceed 2.5 mg/kg daily.

Hepatic impairment:
Cyclosporine is extensively metabolized by the liver. Approximately a 2-3-fold increase in cyclosporine exposure may be observed in patients with hepatic impairment. In patients with severe hepatic impairment, a dose reduction may be necessary to maintain blood levels within the recommended target range (see Section 4.4 Special warnings for use and Section 5 Pharmacological properties), and monitoring of cyclosporine blood levels is recommended until stable levels are achieved.

Pediatric population:
Children aged 1 year and older were included in clinical studies. In various studies, children required higher doses of cyclosporine (per kg body weight) than those used in adults and tolerated these doses.

The use of LYMUNIR is not recommended in children for non-transplant indications other than nephrotic syndrome (see Section 4.4 Special warnings and precautions for use - Additional precautions for non-transplant indications subsection).

Geriatric population (65 years and older):
Experience with the use of LYMUNIR in the elderly is limited.

When reviewing studies of oral cyclosporine in rheumatoid arthritis, the likelihood of developing systolic hypertension during treatment and serum creatinine levels rising to at least 50% of baseline values after 3-4 months of treatment was found to be higher in patients aged 65 years and older.

In general, caution should be exercised when selecting the dose for an elderly patient. In these patients, it should be considered that liver, kidney, and heart function may be lower than in younger patients. Due to the possibility of other concomitant diseases and the use of other medications, treatment should generally be started with the lowest dose within the dosage range.

4.3. Contraindications

LYMUNIR should not be used in patients with hypersensitivity to cyclosporine or any of its excipients.

Combination with products containing *Hypericum perforatum* (St. John's Wort) (see Section 4.5 "Interaction with other medicinal products and other forms of interaction").

Combination with drugs that are substrates of the multidrug efflux transporter P-glycoprotein or organic anion transporting proteins (OATPs) and drugs such as bosentan, dabigatran etexilate, and aliskiren, whose high plasma concentrations are associated with serious and/or life-threatening events (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4. Special warnings and precautions for use

All indications:

Medical supervision
LYMUNIR should only be used under the supervision of physicians experienced in immunosuppressive therapy and capable of providing adequate monitoring, including control of laboratory safety parameters, regular full physical examinations, and blood pressure measurements. Transplant patients using the drug should be monitored by centers with adequate

equipment, personnel, laboratory, and medical support resources. The physician responsible for maintenance therapy should have complete information for patient follow-up.

Lymphomas and other malignancies
As with other immunosuppressants, cyclosporine increases the risk of developing lymphoma and other malignant events, particularly in the skin. The increased risk is related to the degree and duration of immunosuppression rather than specific drugs. Therefore, treatment regimens containing multiple immunosuppressants (including cyclosporine), which have been reported to be associated with lymphoproliferative disorders, solid organ tumors, and in some cases, death, should be administered with caution. (See Section 4.8 Undesirable effects).

Considering the potential risk of skin malignancy, patients receiving LYMUNIR, especially those with psoriatic or atopic dermatitis, should be warned to avoid excessive exposure to ultraviolet B light and to avoid sun exposure or PUVA photochemotherapy.

Infections
As with other immunosuppressants, cyclosporine causes various bacterial, fungal, parasitic, and viral infections in patients, along with opportunistic pathogens. In patients receiving cyclosporine, activation of latent polyomavirus infections has been observed, leading to polyomavirus-associated nephropathy (PVAN), primarily BK virus nephropathy (BKVN), or progressive multifocal leukoencephalopathy (PML) associated with JC virus. These disorders are often associated with a high total immunosuppressive load and should be considered in the differential diagnosis of immunosuppressed patients with impaired renal function or neurological symptoms. Serious and/or fatal cases have been reported. Effective prophylactic and therapeutic strategies should be implemented, particularly in patients receiving long-term multiple immunosuppressive therapy (including cyclosporine) (see Section 4.8 Undesirable effects).

Renal toxicity
During LYMUNIR treatment, an increase in serum creatinine and urea levels may occur as a frequent and potentially serious complication. These functional changes are dose-dependent and reversible, and generally respond to dose reduction. During long-term treatment, structural changes in the kidney may develop in some patients (e.g., interstitial fibrosis), which should be distinguished from changes caused by chronic rejection in kidney transplant patients (see Section 4.8 Undesirable effects). Parameters assessing renal function for the intended indication should be closely monitored according to local guidelines (see Section 4.2 Posology and method of administration and Section 5.1 Pharmacodynamic properties).

Hepatotoxicity
LYMUNIR may also cause dose-dependent, reversible increases in serum bilirubin and liver enzymes (see Section 4.8 Undesirable effects). Spontaneous post-marketing reports of hepatotoxicity and liver damage, including cholestasis, jaundice, hepatitis, and liver failure,

have been received in patients treated with cyclosporine. Most reports involved patients with other complicating factors, such as significant comorbidities, underlying diseases, infectious complications, and concomitant medications with hepatotoxic potential. Fatal outcomes have been reported in some cases, primarily in transplant patients (see Section 4.8 Undesirable effects). Close monitoring of parameters assessing hepatic function is required. Abnormal values may necessitate a dose reduction (see Section 4.2 Posology and method of administration and Section 5.1 Pharmacodynamic properties).

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

Monitoring of cyclosporine levels in transplant patients
When LYMUNIR is used in transplant patients, monitoring of cyclosporine blood levels is an important safety measure (see Section 4.2 Posology and method of administration).

To determine total blood levels of cyclosporine, a specific monoclonal antibody suitable for measuring the parent drug (parent drug assay) is preferred, although an HPLC method measuring the parent drug may also be used. If plasma or serum is used, a standard separation protocol (time and temperature) should be followed. To determine the dosage that provides adequate immunosuppression in the initial follow-up of liver transplant patients, either specific monoclonal antibodies should be used, or parallel measurements should be performed using both specific and non-specific monoclonal antibodies.
Occasional monitoring of cyclosporine blood levels is recommended in patients other than transplant patients: e.g., when LYMUNIR is administered concomitantly with substances that may affect the pharmacokinetic properties of cyclosporine, or when unusual clinical responses occur (e.g., increased drug intolerance such as ineffectiveness or renal dysfunction).

It should be remembered that the concentration of cyclosporine in blood, plasma, or serum is only one of many factors contributing to the patient's clinical condition. Therefore, results should be evaluated as a guide to posology only within the framework of other clinical and laboratory parameters (see Section 4.2 Posology and method of administration).

Hypertension
Regular blood pressure monitoring is required during LYMUNIR treatment; if hypertension develops, appropriate antihypertensive treatment should be initiated (see Section 4.8 Undesirable effects). An antihypertensive drug that does not affect the pharmacokinetics of cyclosporine, such as isradipine, should be preferred (see Section 4.5 "Interaction with other medicinal products and other forms of interaction").

Elevation in blood lipid levels
Since cyclosporine has been reported to cause reversible increases in blood lipid levels, monitoring of lipid levels is recommended before treatment and during the first month of

treatment. If an increase in lipid levels is observed, dietary fat restriction and, if deemed appropriate, dose reduction should be considered (see Section 4.8 Undesirable effects).

Hyperkalemia
Cyclosporine increases the risk of hyperkalemia, particularly in patients with impaired renal function (see Section 4.8 Undesirable effects). Caution is advised when cyclosporine is used concomitantly with potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and potassium-containing drugs, and in patients on a potassium-rich diet (see Section 4.5 "Interaction with other medicinal products and other forms of interaction"). In such cases, monitoring of potassium levels is recommended.

Hypomagnesemia
Cyclosporine increases magnesium clearance. This leads to symptomatic hypomagnesemia, especially during the perioperative period (see Section 4.8 Undesirable effects). Therefore, monitoring serum magnesium levels is recommended during the perioperative period, especially in the presence of neurological symptoms/signs. If deemed necessary, supplemental magnesium should be administered.

Hyperuricemia
Caution should be exercised when treating patients with hyperuricemia (see Section 4.8 Undesirable effects).

Live-attenuated vaccines
Vaccinations administered during cyclosporine therapy may be less effective than expected; live-attenuated vaccines should be avoided (see Section 4.5 "Interaction with other medicinal products and other forms of interaction").

Interactions
Caution should be exercised when cyclosporine is administered concomitantly with drugs that significantly increase or decrease cyclosporine plasma concentrations through CYP3A4 and/or P-glycoprotein inhibition or induction (see Section 4.5 "Interaction with other medicinal products and other forms of interaction").

Renal toxicity should be monitored when initiating cyclosporine in combination with active substances that increase cyclosporine levels or substances that exhibit nephrotoxic synergy (see Section 4.5 "Interaction with other medicinal products and other forms of interaction").

Concomitant use of cyclosporine and tacrolimus should be avoided (see Section 4.5 "Interaction with other medicinal products and other forms of interaction").

Cyclosporine is an inhibitor of CYP3A4, the multidrug efflux transporter P-glycoprotein, and organic anion transporting proteins (OATPs), and may increase the plasma levels of

concomitantly administered substances that are substrates of these enzymes and/or transporters. Caution should be exercised when administering such drugs concomitantly with cyclosporine, or concomitant administration should be avoided (see Section 4.5 "Interaction with other medicinal products and other forms of interaction"). Cyclosporine increases exposure to HMG-CoA reductase inhibitors (statins). When administered concomitantly with cyclosporine, the dosage of statins should be reduced, and concomitant administration with certain statins should be avoided in accordance with their labels. Statin therapy should be temporarily discontinued in patients with myopathy signs and symptoms or in patients with factors such as rhabdomyolysis-secondary renal failure that predispose them to severe renal impairment (see Section 4.5 "Interaction with other medicinal products and other forms of interaction").

Following concomitant administration of cyclosporine and lerkanidipine, the AUC of lerkanidipine increased threefold and the AUC of cyclosporine increased (by 21%). Therefore, concomitant combination of cyclosporine and lerkanidipine should be avoided. Administration of cyclosporine three hours after lerkanidipine did not cause any change in the lerkanidipine AUC value, but the cyclosporine AUC value increased by 27%. Therefore, this combination should be administered with caution, at least 3 hours apart.

Ethanol
LYMUNIR should be given to pregnant or breastfeeding women, patients with liver disease or epilepsy, alcoholics, or to a child, taking into account its ethanol content (see Section 2 Qualitative and quantitative composition).

This medicinal product contains 11.79% anhydrous ethanol (alcohol) by volume; for example, up to 125 mg per dose, equivalent to 0.747 mL of beer per dose, or 1.79 mL of wine per dose.

It may be harmful to those with alcohol dependence.

It should be considered in pregnant or breastfeeding women, children, and patients at high risk such as those with liver disease or epilepsy.

LYMUNIR contains polyoxyl hydrogenated castor oil. This ingredient may cause nausea and diarrhea.

This medicinal product contains glycerol. However, due to the dosage, no warning is necessary.
This medicinal product contains propylene glycol. However, due to the dosage, no warning is necessary.

Additional warnings for autoimmune diseases:

Cyclosporine should not be administered in patients with renal insufficiency (except for patients with nephrotic syndrome with a certain degree of renal insufficiency) in cases of uncontrolled hypertension, uncontrolled infections, or any type of malignancy.

Before starting treatment, a reliable baseline assessment of renal function should be performed using at least two eGFR (estimated glomerular filtration rate) measurements. Renal function should be evaluated frequently throughout treatment to allow for dose adjustment (see Section 4.2 Posology and method of administration).

Except for the treatment of nephrotic syndrome, use in children under 16 years of age for autoimmune diseases is not recommended. Except for the treatment of nephrotic syndrome, there is insufficient experience with LYMUNIR.

Additional warnings for endogenous uveitis:
LYMUNIR should be used with caution in individuals with neurological Behçet's syndrome. The neurological status of patients with Behçet's syndrome should be closely monitored.

Experience with the use of LYMUNIR in children with endogenous uveitis is limited.

Additional warnings in nephrotic syndrome:
Patients with abnormal baseline renal function should be treated with an initial daily dose of 2.5 mg/kg and monitored very carefully.

In some patients, changes in renal function may be due to the nephrotic syndrome itself, making it difficult to identify LYMUNIR-induced renal impairment. This explains why, in some rare cases, LYMUNIR-induced structural kidney changes may be seen without an increase in serum creatinine. Renal biopsy should be considered in patients with steroid-dependent minimal change nephropathy who have been treated with LYMUNIR for more than one year.

Malignancies (including Hodgkin's lymphoma) have been reported rarely in patients with nephrotic syndrome treated with immunosuppressants (including cyclosporine).

Additional warnings in rheumatoid arthritis:
After 6 months of treatment, serum creatinine should be measured every 4-8 weeks, depending on the stability of the disease, the medications being administered, and any accompanying diseases. More frequent measurements should be performed when the LYMUNIR dose is increased, when treatment with a non-steroidal anti-inflammatory drug is initiated, or when the dose of this drug is increased (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

If hypertension developing during LYMUNIR treatment cannot be controlled with appropriate antihypertensive agents, discontinuation of LYMUNIR may be necessary (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

As with other long-term immunosuppressive therapies (including cyclosporine), the increased risk of lymphoproliferative disorders should be considered. If LYMUNIR is used in combination with methotrexate, special caution should be exercised (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Additional warnings for psoriasis:
During LYMUNIR treatment, discontinuation of LYMUNIR is recommended if hypertension develops that cannot be controlled with appropriate treatment (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Elderly patients should only be treated if psoriasis is present to an extent that impairs the patient's daily activities, and renal function should be monitored with particular care.

Experience with the use of LYMUNIR in children with psoriasis is limited.

As with conventional immunosuppressive therapy, malignancy (particularly cutaneous) has been reported in psoriatic patients receiving cyclosporine therapy. A biopsy should be performed before initiating LYMUNIR therapy in cases of skin lesions that are atypical for psoriasis but suspected to be malignant or premalignant. LYMUNIR should only be administered to patients with malignant or premalignant skin changes if no other effective treatment options remain after appropriate treatment of these lesions.

Lymphoproliferative disorders have occurred in a few psoriatic patients treated with cyclosporine. These resolved upon discontinuation of the drug.

Patients receiving LYMUNIR should not concurrently receive ultraviolet B radiation or PUVA photochemotherapy.

Additional warnings for atopic dermatitis:
During LYMUNIR treatment, discontinuation of LYMUNIR is recommended if uncontrolled hypertension develops despite appropriate treatment (see Section 4.8 Undesirable effects).

Experience with LYMUNIR in children with atopic dermatitis is currently limited.

Elderly patients should only be treated if they have atopic dermatitis that interferes with their daily activities, and renal function should be monitored with particular care.

Benign lymphadenopathy is often associated with exacerbations of atopic dermatitis and resolves spontaneously following general improvement in the disease. Lymphadenopathy occurring with cyclosporine therapy should be monitored regularly. If adenopathy persists despite improvement in the disease, a biopsy should be performed to rule out lymphoma.

Active herpes simplex infections should be treated before starting treatment with LYMUNIR. However, infections developing during treatment do not require discontinuation of the drug unless they are serious.

Skin infections caused by *Staphylococcus aureus* do not constitute an absolute contraindication for LYMUNIR treatment, but they should be treated with appropriate antibacterial drugs. The use of erythromycin, which is known to increase cyclosporine blood concentrations (see section on interactions with other medicinal products and other forms of interaction), should be avoided or, if no other option is available, close monitoring of cyclosporine blood levels, renal function, and cyclosporine-related side effects is recommended.

Patients taking LYMUNIR should not also receive ultraviolet B radiation or PUVA photochemotherapy.

Modified cyclosporine formulations have higher bioavailability than non-modified formulations. Therefore, switching from a modified formulation to a non-modified formulation should only be done under medical supervision, as it will cause a decrease in cyclosporine blood levels.

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

Drug interactions
Among the many drugs that interact with cyclosporine, those for which the interaction has been definitively established and which are clinically significant are listed below.

It is known that various agents generally increase or decrease cyclosporine levels in plasma and whole blood through the inhibition and induction of enzymes involved in cyclosporine metabolism, particularly CYP3A4.

Cyclosporine is also an inhibitor of the multidrug efflux transporter P-glycoprotein, CYP3A4, and organic anion transporter proteins (OATP), and may increase the plasma levels of concomitantly administered drugs that are substrates of these enzymes and/or transporters.

Medical products known to decrease or increase the bioavailability of cyclosporine: In transplant patients, cyclosporine levels should be measured frequently, especially when starting or discontinuing concomitant medication, and the cyclosporine dosage should be adjusted as necessary. In patients other than transplant patients, the relationship between blood levels and

clinical efficacy is less well established. If medicinal products known to increase cyclosporine levels are administered concomitantly, frequent assessment of renal function and careful monitoring of cyclosporine-related side effects may be more meaningful than measuring blood levels.

Interactions that decrease cyclosporine levels:
All CYP3A4 and/or P-glycoprotein inducers are expected to decrease cyclosporine levels. Examples of drugs that decrease cyclosporine levels:
Barbiturates, carbamazepine, oxcarbazepine, phenytoin; nafcillin, sulfadimidine IV; rifampicin; octreotide; probucol; orlistat, Hypericum perforatum (St. John's wort); ticlopidine, sulfinpyrazone, terbinafine, bosentan.

Due to the risk of decreased cyclosporine blood levels and consequently decreased effect, products containing Hypericum perforatum (St. John's wort) should not be used concomitantly with LYMUNIR (see Section 4.3 Contraindications).

Rifampicin induces the intestinal and hepatic metabolism of cyclosporine. Cyclosporine doses may need to be increased by 3 to 5 times during concomitant administration.

Octreotide reduces the oral absorption of cyclosporine, and a 50% increase in the cyclosporine dose or a switch to intravenous administration may be necessary.

Interactions that increase cyclosporine levels:
All CYP3A4 and/or P-glycoprotein inducers may cause an increase in cyclosporine levels. Examples of drugs that increase cyclosporine levels:
Nicardipine, metoclopramide, oral contraceptives, methylprednisolone (high dose), allopurinol, colic acid and its derivatives, protease inhibitors, imatinib, colchicine, and nefazodone.

Macrolide antibiotics: Erythromycin can increase cyclosporine exposure by 4-7 times, which can sometimes result in nephrotoxicity. Clarithromycin has been reported to double cyclosporine exposure. Azithromycin increases cyclosporine levels by approximately 20%.

Azole antibiotics: Ketoconazole, fluconazole, itraconazole, and voriconazole can increase cyclosporine exposure by more than twofold.

Verapamil increases cyclosporine blood concentrations by 2-3 times.

Co-administration with telaprevir has resulted in an approximately 4.64-fold increase in dose-normalized AUC for cyclosporine.

Amiodarone increases plasma cyclosporine concentrations concurrently with an increase in serum creatinine. Due to its very long half-life (approximately 50 days), this interaction may persist for a long time after discontinuation of amiodarone.

Danazol has been reported to increase cyclosporine blood concentrations by approximately 50%.

Diltiazem (at a dose of 90 mg/day) can increase cyclosporine plasma concentrations by up to 50%.

Imatinib may increase cyclosporine exposure and Cmax by 20%.
Other relevant drug interactions

Drug-food interactions:
Grapefruit juice and grapefruit consumption have been reported to increase the bioavailability of cyclosporine (see Section 4.2 Posology and method of administration).

Interactions that may increase potential nephrotoxicity:
Aminoglycosides showing nephrotoxic synergy (including gentamicin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); non-steroidal anti-inflammatory drugs (including diclofenac, naproxen, sulindac), melphalan, histamine H2 receptor antagonists (e.g., cimetidine, ranitidine), methotrexate should be used with caution when combined with cyclosporine (see Section 4.4 Special warnings and precautions for use).

Concomitant use with other drugs may result in nephrotoxic synergy. Close monitoring of renal function (primarily serum creatinine) is required. If a significant deterioration in renal function occurs, the dose of the concomitant drug should be reduced or an alternative treatment should be used.

Due to the increased potential for nephrotoxicity and interactions mediated by CYP3A4 and/or P-glycoprotein, the concomitant use of cyclosporine with tacrolimus should be avoided.

Interactions causing increases in the levels of other drugs:
Cyclosporine is also an inhibitor of the CYP3A4 enzyme and P-glycoprotein, which is an efflux transporter for many drugs, and may increase plasma levels of organic anion transporting proteins (OATPs) and concomitantly administered drugs that are substrates of this enzyme and/or transporter.

Cyclosporine may also decrease the clearance of digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins), and etoposide.

If digoxin, colchicine, or HMG-CoA reductase inhibitors (statins) are used with cyclosporine, close clinical monitoring should be performed to detect the toxic effects of the drug early, and the dose should be reduced or the drug discontinued if necessary.

If these statins are to be used with cyclosporine, the dosage of the statins in question should be reduced in accordance with the summary of product characteristics (SPC) recommendations. Changes in exposure to commonly used statins with cyclosporine are summarized in Table 1. Statin therapy may need to be temporarily discontinued or discontinued altogether in patients with myopathy signs and symptoms or in those with risk factors predisposing them to severe kidney damage, including renal failure, due to rhabdomyolysis.

Table 1: Changes in exposure to commonly used statins with cyclosporine

Statin	Applicable doses	Change in exposure in the presence of cyclosporine (fold)
Atorvastatin	10-80 mg	8-10
Simvastatin	10-80 mg	6-8
Fluvastatin	20-80 mg	2-4
Lovastatin	20-40 mg	5-8
Pravastatin	20-80 mg	5-10
Rosuvastatin	5-40 mg	5-10
Pitavastatin	1-4 mg	4-6

Caution should be exercised when administering lercanidipine concomitantly with cyclosporine (see Section 4.4 Special warnings and precautions for use).

Following concomitant administration of *aliskiren*, a P-gp substrate, with cyclosporine, the Cmax value of aliskiren increased approximately 2.5-fold and the AUC value increased approximately 5-fold. On the other hand, the pharmacokinetic profile of cyclosporine did not

change significantly. The concomitant use of cyclosporine and aliskiren is not recommended (see Section 4.3 Contraindications).
Due to the P-gp inhibitory activity of cyclosporine, concomitant administration of dabigatran etexilate is not recommended (see Section 4.3 Contraindications).

Concomitant administration of nifedipine with cyclosporine may result in a higher incidence of gingival hyperplasia than that observed with cyclosporine alone.

The combined use of diclofenac and cyclosporine has been observed to result in a significant increase in diclofenac bioavailability, with possible consequent reversible renal impairment. The increase in diclofenac bioavailability is most likely due to a decrease in the first-pass effect. When NSAIDs with low first-pass effect (e.g., acetylsalicylic acid) are administered with cyclosporine, an increase in bioavailability is not expected.

In studies where microemulsion-based, full-dose cyclosporine was used in combination with everolimus or sirolimus, elevated serum creatinine levels were observed. Reducing the cyclosporine dose often eliminates this toxic effect. Everolimus and sirolimus have only a minor effect on the pharmacokinetics of cyclosporine. Concomitant use of cyclosporine significantly increases serum levels of everolimus and sirolimus.
Caution should be exercised when cyclosporine is used with potassium-sparing drugs (e.g., potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists) or potassium-containing drugs, as they may cause a significant increase in serum potassium. (see Section 4.4 Special warnings and precautions for use).

Cyclosporine may increase repaglinide plasma concentrations and, in this context, the risk of hypoglycemia.

In healthy volunteers, concomitant administration of bosentan and cyclosporine resulted in approximately a 2-fold increase in bosentan exposure and a 35% decrease in cyclosporine exposure. Concomitant administration of bosentan and cyclosporine is not recommended (see Section 4.3 Contraindications).

Multiple-dose administration of ambrisentan and cyclosporine in healthy volunteers resulted in an approximately twofold increase in ambrisentan exposure and a marginal increase in cyclosporine exposure (approximately 10%).

In oncology patients receiving very high doses of cyclosporine in combination with anthracycline antibiotics (e.g., doxorubicin, mitoxantrone, daunorubicin), a significant increase in anthracycline antibiotic exposure has been observed.

Vaccination may be less effective during cyclosporine therapy, and live attenuated vaccines should be avoided.

Additional information for specific populations
No clinical interaction studies have been conducted in special populations.

Pediatric population
No clinical interaction studies have been conducted in the pediatric population.

4.6. Fertility, pregnancy and lactation

General recommendation
Pregnancy category C.

Women of childbearing potential/ Contraception
There are no specific recommendations for women of childbearing potential.

Pregnancy
Animal studies have shown reproductive toxicity in rats and rabbits.

There is a reasonable amount of data on the use of LYMUNIR in pregnant patients. Pregnant women receiving immunosuppressive therapy, including cyclosporine and cyclosporine-containing regimens after transplantation, are at risk of premature delivery (<37 weeks).

There are a limited number of studies in children up to approximately 7 years of age who were exposed to cyclosporine *in utero*. Renal function and blood pressure were normal in these children.

However, as there are no adequate and well-controlled studies in pregnant women, LYMUNIR should not be used unless the expected benefit to the mother outweighs the expected risk to the fetus.

In pregnant women, the ethanol content should also be taken into account (see Section 4.4 Special warnings and precautions for use).

Lactation
Cyclosporine passes into breast milk. In addition, the ethanol content of LYMUNIR formulations should also be taken into account (see Section 4.4 Special warnings and precautions for use). Therapeutic doses of LYMUNIR administered to lactating women are excreted in amounts that could potentially affect the infant.

Mothers receiving LYMUNIR treatment should not breastfeed.
Due to the potential for LYMUNIR to cause serious adverse drug reactions in breastfed newborns/infants, a decision should be made whether to avoid breastfeeding or to avoid using

this medicinal product, taking into account the importance of this medicinal product for the mother.

Reproductive ability/Fertility
There is limited data on the effects of LYMUNIR on human fertility.

4.7. Effects on the ability to drive and use machines

There is no information available on the effects of LYMUNIR on the ability to operate machinery and vehicles.

4.8. Undesirable effects

Summary of safety profile
The main adverse reactions observed in clinical studies and associated with cyclosporine administration include renal dysfunction, tremor, hirsutism, hypertension, diarrhea, anorexia, nausea, and vomiting.

Many side effects associated with cyclosporine therapy are dose-dependent and respond to dose reduction. In most indications, the detailed spectrum of side effects is actually the same, with only differences in incidence and severity. As a result of high initial doses and the long maintenance therapy required after transplantation, side effects are more frequent and more severe in transplant patients than in patients treated for other indications.

Anaphylactoid reactions have been observed following intravenous administration (see Section 4.4 Special warnings and precautions for use).

Infections and Infestations
The risk of infection (viral, bacterial, fungal, parasitic) is increased in patients receiving immunosuppressive therapy, including cyclosporine and cyclosporine-containing regimens (see Section 4.4 Special warnings and precautions for use). Both systemic and localized infections may occur. Additionally, pre-existing infections may worsen, and reactivation of Polyomavirus infections may lead to Polyomavirus-associated nephropathy (PVAN) or JC virus-associated progressive multifocal leukoencephalopathy (PML). Serious and/or fatal cases have been reported.

Benign, malignant, and neoplasms of undetermined group (including cysts and polyps)
The risk of developing lymphomas or lymphoproliferative disorders, and other malignancies, particularly of the skin, is increased in patients receiving immunosuppressive therapy, including cyclosporine and cyclosporine-containing regimens. The incidence of malignancies increases with the intensity and duration of treatment (see Section 4.4 Special warnings and precautions for use). Some malignancies may be fatal.

Summary of adverse drug reaction information from clinical studies:

Adverse drug reactions are listed below in order of frequency, with the most common adverse reaction listed first. Within each frequency group, adverse reactions are listed in order of decreasing severity.

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
Common: Leukopenia
Uncommon: Anemia, thrombocytopenia.
Rare: Microangiopathic hemolytic anemia, hemolytic uremic syndrome.
Not known*: Thrombotic microangiopathy, thrombotic thrombocytopenic purpura

Metabolic and nutritional disorders
Very common: Hyperlipidemia.
Common: Hyperglycemia, anorexia, hyperuricemia, hyperkalemia, and hypomagnesemia.

Nervous system disorders
Very common: Tremor, headache.
Common: Paresthesia, convulsions
Uncommon: Encephalopathy, including Posterior Reversible Encephalopathy Syndrome (PRES), convulsions, confusion, disorientation, decreased responsiveness to external stimuli, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis, cerebellar ataxia.
Rare: Motor polyneuropathy.
Very rare: Optic disc edema, including papilledema, possibly associated with visual disturbances secondary to benign intracranial hypertension.
Not known*: Migraine

Vascular diseases
Very common: Hypertension (see Section 4.4 Special warnings and precautions for use).
Common: Facial flushing.

Gastrointestinal disorders
Common: Nausea, vomiting, abdominal discomfort/pain, diarrhea, gingival hyperplasia, peptic ulcer

Rare: Pancreatitis.

Hepatobiliary disorders
Common: Liver function disorders (see Section 4.4 Special warnings and precautions for use warnings and precautions).
Not known*: Liver damage and hepatotoxicity, some of which may be fatal, such as cholestasis, jaundice, hepatitis, and liver failure (see Section 4.4 Special warnings and precautions)

Skin and subcutaneous tissue disorders
Very common: Hirsutism
Common: Acne, hypertrichosis.
Uncommon: Allergic rash.

Musculoskeletal disorders, connective tissue and bone diseases
Common: Muscle cramps, myalgia.
Rare: Muscle weakness and myopathy.
Not known*: Pain in the lower limbs.

Kidney and urinary tract disorders
Very common: Renal insufficiency (see Section 4.4 Special warnings and precautions for use).

Reproductive system and breast disorders
Rare: Menstrual disorders, gynecomastia.

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

* Adverse events reported from post-marketing experience for which the frequency of ADRs is unknown due to the lack of a real denominator.

Definition of specific adverse drug reactions

Hepatotoxicity and liver damage:
There have been spontaneous post-marketing reports of liver damage and hepatotoxicity, such as jaundice, hepatitis, and liver failure, in patients treated with cyclosporine. Most reports involved patients with factors that could influence the assessment, such as significant concomitant diseases, underlying diseases, infectious complications, or the concomitant use of other drugs with hepatotoxic potential. Death has been reported in some cases, primarily in transplant patients (see Section 4.4 Special warnings and precautions for use).

Acute and chronic nephrotoxicity:
Patients receiving treatment with calcineurin inhibitors (CNI's), including cyclosporine and cyclosporine-containing regimens, are at higher risk for acute and chronic nephrotoxicity. Reports associated with the use of LYMUNIR have been received from clinical trials and post-marketing conditions. Reported cases of acute nephrotoxicity included electrolyte disturbances such as hyperkalemia, hypomagnesemia, and hyperuricemia, most of which developed within the first month of treatment. Cases reporting chronic morphological changes included arteriolar hyalinosis, tubular atrophy, and interstitial fibrosis (see Section 4.4 Special warnings and precautions for use).

Lower limb pain:
Isolated cases of lower limb pain associated with cyclosporine have been reported. Lower limb pain has also been noted within the context of Calcineurin Inhibitor-Induced Pain Syndrome (CIPS).

Pediatric population:
Children over 1 year of age were included in clinical studies, and a safety profile similar to that in adults was observed with standard cyclosporine dosing.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with local requirements.

4.9. Overdose

The oral LD_{50}value of cyclosporine is 2,329 mg/kg in mice, 1,480 mg/kg in rats, and >1,000 mg/kg in rabbits. The IV LD_{50}value is 148 mg/kg in mice, 104 mg/kg in rats, and 46 mg/kg in rabbits.

Symptoms:
Experience with acute cyclosporine overdose is limited. Oral doses of up to 10 g (approximately 150 mg/kg) of cyclosporine have been tolerated with minor clinical consequences such as vomiting, drowsiness, headache, tachycardia, and, in a small number of patients, moderate and reversible renal dysfunction. However, serious intoxication symptoms have been reported following accidental parenteral overdose in premature neonates.

Treatment:
In all cases of overdose, general supportive measures should be followed and symptomatic treatment should be administered. Inducing vomiting and gastric lavage within the first few

hours after oral ingestion may be beneficial. Cyclosporine is largely undialysable and cannot be effectively removed by carbon hemoperfusion.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressive agents, calcineurin inhibitors
ATC code: L04A D01

Cyclosporine (also known as cyclosporine A) is a cyclic polypeptide consisting of 11 amino acids. It is a potent immunosuppressive agent that prolongs the life of allogeneic skin, heart, kidney, pancreas, bone marrow, small intestine, or lung transplants in animals.

Various studies have shown that cyclosporine inhibits the development of cell-mediated reactions such as allograft immunity, delayed cutaneous hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, and graft-versus-host disease (GVHD), as well as T-cell-dependent antibody formation. It also inhibits lymphokine production and release at the cellular level, including interleukin-2 (T-cell growth factor, TCGF). Cyclosporine has been shown to block resting lymphocytes in the G_0 or G_1 phases of the cell cycle and to inhibit antigen-stimulated lymphokine release by active T cells.

All available data indicate that cyclosporine acts specifically and reversibly on lymphocytes. Unlike cytostatic agents, cyclosporine does not depress hematopoiesis and has no effect on the functions of phagocytic cells.

The use of cyclosporine for the prevention and treatment of organ rejection and GVHD has resulted in successful organ and bone marrow transplants. Cyclosporine has been used successfully in liver transplant patients who are both Hepatitis C Virus (HCV) positive and HCV negative. Positive responses have also been demonstrated with cyclosporine therapy in various cases known or thought to be related to immunological mechanisms.

Pediatric population: Cyclosporine has been found to be effective in steroid-dependent nephrotic syndrome.

5.2. Pharmacokinetic properties

General characteristics

Absorption

After oral administration, peak blood concentrations of cyclosporine are reached within 1-2 hours. The absolute oral bioavailability of cyclosporine after LYMUNIR administration is 20-50%. When cyclosporine is administered with a high-fat meal, approximately 13% and 33%

decreases in AUC and Cmax values, respectively, have been observed. The relationship between the administered dose of cyclosporine and exposure (AUC) is linear within the therapeutic dose range. Inter- and intra-individual variability in AUC and Cmax values is approximately 10-20%.

After oral administration of cyclosporine, blood levels measured throughout the day (AUC_B) show greater parallelism with the administered dose, a more stable absorption profile, and less influence from food and daily rhythm compared to IV cyclosporine. The combination of these properties reduces the variability observed in the pharmacokinetics of cyclosporine in the same patient and provides a better correlation between the trough level (blood level measured immediately before the patient takes the drug during treatment) and AUC_B(area under the blood level-time curve). As a result of these added advantages, it is not necessary to consider meal times when adjusting cyclosporine dosing times. In addition, cyclosporine provides more stable blood levels throughout the day and between days during maintenance therapy.

It has been shown that trough blood levels are similar when switching from the IV form of cyclosporine to oral cyclosporine, and thus the desired therapeutic trough level limits are maintained. Compared to other oral formulations, oral cyclosporine is absorbed more rapidly (peak blood concentration is achieved within 1-6 hours) (mean $t_{max}$is reduced by 1 hour and mean C_{max}increases by 59%) and exhibits a mean bioavailability that is 29% higher.

Distribution

Cyclosporine shows widespread distribution outside the blood volume with an average apparent volume of distribution of 3.5 L/kg. In the blood, it is found in plasma at 33-47%, in lymphocytes at 4-9%, in granulocytes at 5-12%, and in erythrocytes at 41-58%. Approximately 90% is bound to proteins in plasma, primarily to lipoproteins.

Biotransformation

Cyclosporine is extensively metabolized into approximately 15 metabolites. There is no single major metabolic pathway. Metabolism occurs in the liver via the cytochrome P450-dependent monooxygenase system (e.g., CYP3A4), and the main metabolic pathway involves mono- and dihydroxylation and N-demethylation at various positions on the molecule. Compounds known to inhibit or induce the cytochrome P450 enzyme system have been shown to increase or decrease cyclosporine levels. The metabolites identified to date are intact peptide structures of the parent compound, and some have been found to have weak immunosuppressive activity (about one-tenth that of the unchanged compound).

Elimination

Elimination occurs primarily via the bile duct, with only 6% of the oral dose excreted in the urine, and only 0.1% of this is excreted unchanged.

The terminal half-life of cyclosporine shows high variability depending on the method used to determine the administered amount and the group being measured. The terminal half-life ranges from 6.3 hours (in healthy volunteers) to 20.4 hours (in patients with severe liver disease) (see Section 4.2 Posology and method of administration and Section 4.4 Special warnings and precautions for use). In kidney transplant patients, the elimination half-life was found to be approximately 11 hours, ranging from 4 to 25 hours.

Characteristic features in patients

Renal insufficiency:

In a study conducted with patients with end-stage renal failure, systemic clearance was found to be approximately two-thirds of the average systemic clearance in patients with normal kidney function. Less than 1% of the administered dose was removed by dialysis.

Liver failure:

Approximately a 2-3-fold increase in cyclosporine exposure may be observed in patients with liver dysfunction. In a study conducted with patients with severe liver disease and biopsy-proven cirrhosis, the terminal half-life was observed to be 20.4 hours (range 10.8 to 48.0 hours; the same value in healthy volunteers was 7.4 to 11.0 hours).

Pediatric population:

Pharmacokinetic data on pediatric patients receiving oral or IV cyclosporine are very limited. In 15 renal transplant patients aged 3-16 years, the total blood clearance of cyclosporine after IV administration was 10.6±3.7 ml/min/kg (assay: Cyclo-trac specific RIA). In a study involving 7 renal transplant patients aged 2-16 years, the clearance of cyclosporine ranged from 9.8 to 15.5 ml/min/kg. In 9 liver transplant patients aged 0.65-6 years, the clearance was 9.3±5.4 ml/min/kg (determined by HPLC). Compared to adult transplant populations, the differences in bioavailability between orally administered cyclosporine and intravenously administered cyclosporine in pediatric patients are the same as those observed in adults.

5.3. Preclinical safety data

Cyclosporine did not show mutagenic or teratogenic effects in standard test systems following oral administration (up to 17 mg/kg daily in rats and up to 30 mg/kg daily in rabbits). At toxic doses (30 mg/kg/day orally in rats and 100 mg/kg/day orally in rabbits), embryotoxic and fetotoxic effects, such as increased prenatal and postnatal mortality, associated skeletal abnormalities, and low fetal weight, have been identified.

Two published research studies have demonstrated a reduced number of nephrons, renal hypertrophy, systemic hypertension, and progressive renal failure in rabbits up to 35 weeks of age exposed to cyclosporine in utero (10 mg/kg/day subcutaneously).

Pregnant rats administered cyclosporine intravenously at 12 mg/kg/day (twice the recommended human intravenous dose) had fetuses with a high incidence of ventricular septal defects.

These findings have not been demonstrated in other species and their relevance to humans is unknown. Studies in male and female rats showed no impairment of fertility.

Cyclosporine has been tested for genotoxicity in a series of *in vitro* and *in vivo* tests, and no evidence of clinically relevant mutagenic potential has been found.
Carcinogenicity studies have been conducted in male and female mice and rats. In a 78-week study in mice, at daily doses of 1, 4, and 16 mg/kg, a statistically significant trend for lymphocytic lymphomas was demonstrated in females, and at the medium dose, the incidence of hepatocellular carcinomas exceeded the control value in males. In a 24-month rat study at daily doses of 0.5, 2, and 8 mg/kg, the incidence of pancreatic islet adenoma significantly exceeded the control rate at the low dose level. Hepatocellular carcinoma and pancreatic islet adenoma were not dose-dependent.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Anhydrous ethanol
α-Tocopherol racemate
Glycerol monolinoleate
Macrogol glycerol hydroxystearate
Propylene glycol

Gelatin capsule
Gelatin (bovine gelatin)
Glycerin
Propylene glycol
Purified water
Black iron oxide
Titanium dioxide

6.2. Incompatibilities

None.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Should be stored at room temperature below 25°C.

LYMUNIR capsules should be kept in their blister packs until use. When a blister is opened, a characteristic odor is noticeable. This is normal and does not indicate any problem with the capsule.

6.5. Nature and contents of container

The primary packaging material used for our product is a blister pack consisting of OPA/ALU/PVC foil and aluminum foil. Blister packs containing 50 capsules per box are supplied with a package leaflet.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

2022/713

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 08.12.2022
Date of renewal of authorization:

10. DATE OF REVISION OF THE TEXT