SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. NAME OF THE MEDICINAL PRODUCT

Tianke Soft Gelatin Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains: 25mg or 50mg cyclosporine.

Excipients with known effect:

Tianke Soft Gelatin Capsules contain:

Ethanol: 9.5% m/m ethanol (25mg and 50mg capsules).

Propylene glycol: 25mg/capsule (25mg capsules); 50mg/capsule (50mg capsules).

Polyoxyl 40 hydrogenated castor oil: 101.25 mg/capsule (25mg capsules); 202.5 mg/capsule (50mg capsules).

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, Soft

Tianke Soft Gelatin Capsules 25mg: white, oval soft gelatin capsules.

Tianke Soft Gelatin Capsules 50mg: white, oblong soft gelatin capsules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRANSPLANTATION INDICATIONS:

Solid organ transplantation

- Prevention of graft rejection following solid organ transplantation.
- Treatment of transplant cellular rejection in patients previously receiving other immunosuppressive agents.

Bone marrow transplantation

- Prevention of graft rejection following allogeneic bone marrow transplantation.

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

NON-TRANSPLANTATION INDICATIONS:

Endogenous uveitis

- Treatment of sight-threatening intermediate or posterior uveitis of non-infectious aetiology in patients in whom conventional therapy has failed or caused unacceptable side effects.

- Treatment of Behçet uveitis with repeated inflammatory attacks involving the retina in patients of 7 to 70 years old without neurological manifestations.

Nephrotic syndrome

- Patients with steroid-dependent and steroid-resistant nephritic syndrome (most cases are minimal change nephropathy, focal and segmental glomerulosclerosis demonstrated by biospies), in whom traditional cytostatic treatment has failed, but with at least 50% above of normal renal function. Tianke can be used to induce and maintain remissions.

- Tianke can be used to induce and maintain remissions. It can also be used to maintain steroid-induced remission, allowing withdrawal of steroids.

Rheumatoid arthritis

- Treatment of severe, active rheumatoid arthritis.

Psoriasis

- Treatment of severe psoriasis in patients in whom conventional therapy is inappropriate or ineffective.

Atopic dermatitis

- Tianke is indicated in patients with severe atopic dermatitis when systemic therapy is required.

4.2 Posology and method of administration

Posology

The dose ranges given for oral administration are intended to serve as guidelines only. The daily doses of Tianke should be given in two divided doses equally distributed throughout the day. It is recommended that Tianke be administered on a consistent schedule with regard to time of day.

Tianke should only be prescribed by, or in close collaboration with, a physician with experience of immunosuppressive therapy and/or organ transplantation.

TRANSPLANTATION:

Solid organ transplantation

- Treatment with Tianke should be initiated within 12 hours before surgery at a dose of 10 to 15 mg/kg given in 2 divided doses. This dose should be maintained as the daily dose for 1 to 2 weeks post-operatively, being gradually reduced in accordance with blood levels according to local immunosuppressive protocols until a recommended maintenance dose of about 2 to 6 mg/kg given in 2 divided doses is reached.

- In renal transplant patients, when the daily doses is lower than 3 to 4mg/kg, the rejection reaction may increase due to the cyclosporine blood concentration is lower than 50 to 100ng/ml.

- When Tianke is given with other immunosuppressants (e.g. with corticosteroids or as part of a triple or quadruple medicinal product therapy), lower doses (e.g. 3 to 6 mg/kg given in 2 divided doses for the initial treatment) may be used.

Bone marrow transplantation

- The initial dose should be given on the day before transplantation. In most cases, infusion is preferred for this purpose. If Tianke is used to initiate therapy, the recommended daily dose is 12.5 to 15 mg/kg given in 2 divided doses, starting on the day before transplantation. Maintenance treatment with Tianke at daily

doses of about 12.5 mg/kg given in 2 divided doses should be continued for at least 3 months (and preferably for 6 months) before the dose is gradually decreased to zero by 1 year after transplantation.

- Higher doses or intravenous administration of Tianke may be necessary in the presence of gastrointestinal disturbances which might decrease absorption.

- In some patients, GVHD occurs after discontinuation of cyclosporine treatment, but usually responds favourably to re-introduction of therapy. In such cases an initial oral loading dose of 10 to 12.5 mg/kg should be given, followed by daily oral administration of the maintenance dose previously found to be satisfactory. Low doses of Tianke should be used to treat mild, chronic GVHD.

NON-TRANSPLANTATION INDICATIONS:

When using Tianke in any of the established non-transplantation indications, the following general rules should be adhered to:

Before initiation of treatment a reliable baseline level of renal function should be established by at least two measurements. The estimated glomerular filtration rate (eGFR) by the MDRD formula can be used for estimation of renal function in adults and an appropriate formula should be used to assess eGFR in paediatric patients. Since Tianke can impair renal function, it is necessary to assess renal function frequently. If eGFR decreases by more than 30% below baseline at more than one measurement, the dosage of Tianke should be reduced by 25 to 50%. If the eGFR decrease from baseline exceeds 35%, further reduction of the dose of Tianke should be considered. These recommendations apply even if the patient`s values still lie within the laboratory`s normal range. If dose reduction is not successful in improving eGFR within one month, Tianke treatment should be discontinued (see section 4.4).

Regular monitoring of blood pressure is required.

The determination of bilirubin and parameters that assess hepatic function are required prior to starting therapy and close monitoring during treatment is

recommended. Determinations of serum lipids, potassium, magnesium and uric acid are advisable before treatment and periodically during treatment.

Occasional monitoring of cyclosporine blood levels may be relevant in non-transplant indications, e.g. when Tianke is co-administered with substances that may interfere with the pharmacokinetics of cyclosporine, or in the event of unusual clinical response (e.g. lack of efficacy or increased drug intolerance such as renal dysfunction).

The normal route of administration is by mouth.

Except in patients with sight-threatening endogenous uveitis and in children with nephrotic syndrome, the total daily dose must never exceed 5 mg/kg.

For maintenance treatment the lowest effective and well tolerated dosage should be determined individually.

In patients in whom within a given time (for specific information see below) no adequate response is achieved or the effective dose is not compatible with the established safety guidelines, treatment with Tianke should be discontinued.

Endogenous uveitis

- For inducing remission, initially 5 mg/kg/day orally given in 2 divided doses are recommended until remission of active uveal inflammation and improvement in visual acuity are achieved. In refractory cases, the dose can be increased to 7 mg/kg/day for a limited period.

- To achieve initial remission, or to counteract inflammatory ocular attacks, systemic corticosteroid treatment with daily doses of 0.2 to 0.6 mg/kg prednisone or an equivalent may be added if Tianke alone does not control the situation sufficiently. After 3 months, the dose of corticosteroids may be tapered to the lowest effective dose. If no improvement has been observed within 3 months, the Tianke therapy should be discontinued.

- For maintenance treatment, the dose should be slowly reduced to the lowest effective level. During the remission phases, this should not exceed 5 mg/kg/day.

- Infectious causes of uveitis should be ruled out before immunosuppressants can be used.

Psoriasis

- For inducing remission, the recommended initial dose is 2.5 mg/kg/day orally given in 2 divided doses. If there is no improvement after 4 weeks, the daily dose may be gradually increased 0.5~1.0mg/kg per month, but should not exceed 5 mg/kg. Treatment should be discontinued in patients in whom sufficient response of psoriatic lesions cannot be achieved within 4 weeks on 5 mg/kg/day, or in whom the effective dose is not compatible with the established safety guidelines (see section 4.4).

- Initial doses of 5 mg/kg/day are justified in patients whose condition requires rapid improvement. Once satisfactory response is achieved, Tianke may be discontinued and subsequent relapse managed with re-introduction of Tianke at the previous effective dose. In some patients, continuous maintenance therapy may be necessary.

- For maintenance treatment, doses have to be titrated individually to the lowest effective level, and should not exceed 5 mg/kg/day.

Atopic dermatitis

Tianke treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis. Due to the variability of this condition, treatment must be individualised.

- The recommended dose range is 2.5 to 5 mg/kg/day given in 2 divided oral doses for adults and teenagers above 16 years old. If a starting dose of 2.5 mg/kg/day does not achieve a satisfactory response within 2 weeks, the daily

dose may be rapidly increased to a maximum of 5 mg/kg. In very severe cases, rapid and adequate control of the disease is more likely to occur with a starting dose of 5 mg/kg/day. Once satisfactory response is achieved, the dose should be reduced gradually and, if possible, Tianke should be discontinued. Subsequent relapse may be managed with a further course of Tianke. Treatment should be discontinued, if satisfactory response is not achieved on the dose of 5mg/kg/day within 1 month.

- The experience in long-term treatment of atopic dermatitis is limited, so the recommended maximum treatment period is not more than 8 weeks.

Rheumatoid arthritis

- For the first 6 weeks of treatment the recommended dose is 3 mg/kg/day orally given in 2 divided doses. If the effect is insufficient, the daily dose may then be increased gradually as tolerability permits, but should not exceed 5 mg/kg. The treatment should be discontinued if satisfactory response is not achieved within 3 months after dose adjustment.

- For maintenance treatment the dose has to be titrated individually to the lowest effective level according to tolerability.

- Tianke can be given in combination with low-dose corticosteroids and/or non-steroidal anti-inflammatory drugs (NSAIDs) (see section 4.4). Tianke can also be combined with low-dose weekly methotrexate in patients who have insufficient response to methotrexate alone, by using 2.5 mg/kg Tianke in 2 divided doses per day initially, with the option to increase the dose as tolerability permits.

Nephrotic syndrome

- For inducing remission, the recommended daily dose is given in 2 divided oral doses.

- If the renal function (except for proteinuria) is normal, the recommended daily dose is the following:

- adults: 5 mg/kg
- children: 6 mg/kg

- In patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg/day (Tinake is not allowed to use when the serum creatinine for adult is exceed 200μmol/L, for child is exceed 140μmol/L).

- The combination of Tianke with low doses of oral corticosteroids is recommended if the effect of Tianke alone is not satisfactory, especially in steroid-resistant patients. If no improvement has been observed within 3 months, Tianke therapy should be discontinued.

- The doses need to be adjusted individually according to efficacy (proteinuria) and safety, but should not exceed 5 mg/kg/day in adults and 6 mg/kg/day in children.

- For maintenance treatment, the dose should be slowly reduced to the lowest effective level.

SWITCHING FROM NON-MICROEMULSION ORAL FORMULATIONS TO TIANKE

- The available data indicate that after a 1:1 switch from non-microemulsion oral formulation to Tianke, the trough concentrations of cyclosporine in whole blood are comparable. In many patients, however, higher peak concentrations (Cmax) and increased exposure to the active substance (AUC) may occur. In a small percentage of patients these changes are more marked and may be of clinical significance. These changes largely depend on intrasubject variability of cyclosporine from previously used non-microemulsion formulations which has high variability of bioavailability. Patients (e.g. patients with cystic fibrosis, cholestasis, poor biliation, children or some renal transplant patients)

with lower than expected cyclosporine blood trough concentrations in relation to the oral dose of non-microemulsion formulations may have poor or inconsistent absorption of cyclosporine from non-microemulsion formulations. After conversion to Tianke following ratio of 1:1, patients tend to have higher cyclosporine concentrations. The dose of Tinake should be titrated individually based on cyclosporine trough concentrations.

- In addition, the absorption of cyclosporine from Tianke is less variable and the correlation between cyclosporine trough concentrations and exposure (in terms of AUC) is stronger than with non-microemulsion oral formulations, which make cyclosporine trough blood concentration is a more stable and reliable monitoring parameter for treatment.

- Since the switch from non-microemulsion oral formulation to Tianke may result in increased exposure to cyclosporine, the following rules must be observed:

  In transplant patients, Tianke should be started at the same daily dose as was previously used with non-microemulsion oral formulation. Cyclosporine trough concentrations in whole blood should be monitored initially within 4 to 7 days after the switch to Tianke. In addition, clinical safety parameters such as serum creatinine and blood pressure must be monitored during the first 2 months after the switch. If the cyclosporine trough blood levels are beyond the therapeutic range, and/or worsening of the clinical safety parameters occurs, the dosage must be adjusted accordingly.

  In patients treated for non-transplantation indications Tianke should be started with the same daily dose as was used with oral Sandimmun. Two, 4 and 8 weeks after the switch, serum creatinine and blood pressure should be monitored. If blood pressure significantly exceed the pre-switch levels or if serum creatinine level increases by more than 30% above the value measured prior to on-microemulsion oral formulation therapy at more than one

measurement, the dose should be reduced (see also 'Additional precautions' in section 4.4). In the event of unexpected toxicity or inefficacy of cyclosporine, blood trough levels should also be monitored.

SWITCHING BETWEEN ORAL CYCLOSPORINE FORMULATIONS

The switch from one oral cyclosporine formulation to another should be made under physician supervision, including monitoring of blood levels of cyclosporine for transplantation patients.

SPECIAL POPULATIONS

Patients with renal impairment

All indications

Cyclosporine undergoes minimal renal elimination and its pharmacokinetics are not extensively affected by renal impairment (see section 5.2). However, due to its nephrotoxic potential (see section 4.8), careful monitoring of renal function is recommended (see section 4.4).

Non-transplantation indications

With the exception of patients being treated for nephrotic syndrome, patients with impaired renal function should not receive cyclosporine (see subsection on additional precautions in non-transplantation indications in section 4.4). In nephrotic syndrome patients with impaired renal function, the initial dose should not exceed 2.5 mg/kg/day.

Patients with hepatic impairment

Cyclosporine is extensively metabolised by the liver. An approximate 2- to 3-fold increase in cyclosporine exposure may be observed in patients with hepatic impairment. Dose reduction may be necessary in patients with severe liver impairment to maintain blood levels within the recommended target range (see sections 4.4 and 5.2) and it is recommended that cyclosporine blood levels are monitored until stable levels are reached.

Paediatric population

The experience with cyclosporine treatment on children is limited, however, there is no unusual adverse reactions found on the children above 1 years old who have been given standard dose of non-microemulsion formulation. In several studies, paediatric patients required and tolerated higher doses of cyclosporine per kg body weight than those used in adults.

Use of Tianke in children for non-transplantation indications other than nephrotic syndrome cannot be recommended (see section 4.4).

Elderly population (age 65 years and above)

Experience with Tianke in the elderly is limited.

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

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

Method of administration

Oral use

Tianke capsules should be swallowed whole.

4.3 Contraindication

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Combination with products containing Hypericum perforatum (St John´s Wort) (see section 4.5).

- Concomitant use of cyclosporine and tacrolimus should be avoided (see section 4.5).

- Use of Tianke in children under 3 years old or teenagers under 18 years old for Rheumatoid Arthritis is not allowed.

- Rheumatoid arthritis patients with abnormal renal function, uncontrolled hypertension, or malignancies should not receive Tianke.

- Psoriasis patients who are treated with Tianke should not receive concomitant PUVA or UVB therapy, methotrexate or other immunosuppressive agents, coal tar or radiation therapy. Psoriasis patients with abnormal renal function, uncontrolled hypertension, or malignancies should not receive Tianke.

- Combination with medicines that are substrates for the multidrug efflux transporter P-glycoprotein or the organic anion transporter proteins (OATP) and for which elevated plasma concentrations are associated with serious and/or life-threatening events, e.g. bosentan, dabigatran etexilate and aliskiren (see section 4.5).

4.4 Special warnings and precautions for use

Medical supervision

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

Because Tianke is not bioequivalent to non-microemulsion cyclosporine soft capsules, switch from Tianke to non-microemulsion cyclosporine soft capsules using a 1:1 ratio (mg/kg/day) may result in lower cyclosporine blood concentrations. Switch from Tianke to non-microemulsion cyclosporine soft capsules should be made with increased monitoring to avoid the potential of underdosing.

Lymphomas and other malignancies

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

A treatment regimen containing multiple immunosuppressants (including cyclosporine) should therefore be used with caution as this could lead to lymphoproliferative disorders and solid organ tumours, some with reported fatalities.

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

Infection

Like other immunosuppressants, Cyclosporine predisposes patients to the development of a variety of bacterial, fungal, parasitic and viral infections, often with opportunistic pathogens. Activation of latent polyomavirus infections that may lead to polyomavirus associated nephropathy (PVAN), especially to BK virus nephropathy (BKVN), or to JC virus associated progressive multifocal leukoencephalopathy (PML), have been observed in patients receiving Cyclosporine. These conditions are often related to a high total immunosuppressive burden and should be considered in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. Serious and/or fatal outcomes have been reported.

Effective pre-emptive and therapeutic strategies should be employed, particularly in patients on multiple long-term immunosuppressive therapy.

Renal toxicity

A frequent and potentially serious complication, an increase in serum creatinine and urea, may occur during Tianke therapy. These functional changes are dose-dependent and are initially reversible, usually responding to dose reduction. During long-term treatment, some patients may develop structural changes in the kidney (e.g. interstitial fibrosis) which, in renal transplant patients, must be differentiated from changes due to chronic rejection. Frequent monitoring of renal function is therefore required according to local guidelines for the indication in question (see sections 4.2 and 4.8).

Hepatotoxicity

Tianke may also cause dose-dependent, reversible increases in serum bilirubin and in liver enzymes (see section 4.8). There have been solicited and spontaneous reports of hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure in patients treated with cyclosporine. Most reports included patients with significant co-morbidities, underlying conditions and other confounding factors including infectious complications and co-medications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (see section 4.8). Close monitoring of parameters that assess hepatic function is required and abnormal values may necessitate dose reduction (see sections 4.2 and 5.2).

Thrombotic Microangiopathy

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure. The vasculopathy can occur in the absence of rejection and is accompanied by avid platelet consumption within the graft as demonstrated by Indium111 labeled platelet studies. Neither the pathogenesis nor the management of this syndrome is clear. Though resolution has occurred after reduction or discontinuation of cyclosporine and 1) administration of streptokinase and heparin or 2) plasmapheresis, this appears to depend upon early detection with Indium111 labeled platelet scans. (*see 4.8*)

Neurotoxicity

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

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

Elderly population (age 65 years and above)

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

Monitoring cyclosporine levels (see section 4.2)

When Tianke is used in transplant patients, routine monitoring of cyclosporine blood levels is an important safety measure. For monitoring cyclosporine levels in whole blood, a specific monoclonal antibody (measurement of parent compound) is preferred; a high-performance liquid chromatography (HPLC) method, which also measures the parent compound, can be used as well. If plasma or serum is used, a standard separation protocol (time and temperature) should be followed. For the initial monitoring of liver transplant patients, either the specific monoclonal antibody should be used, or parallel measurements using both the specific monoclonal antibody and the non-specific monoclonal antibody should be performed, to ensure a dosage that provides adequate immunosuppression.

In non-transplant patients, occasional monitoring of cyclosporine blood levels is recommended, e.g. when Tianke is co-administered with substances that may interfere with the pharmacokinetics of cyclosporine, or in the event of unusual clinical response (e.g. lack of efficacy or increased drug intolerance such as renal dysfunction).

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

Hypertension

Regular monitoring of blood pressure is required during Tianke therapy. If hypertension develops, appropriate antihypertensive treatment must be instituted. Preference should be given to an antihypertensive agent that does not interfere with the pharmacokinetics of cyclosporine, e.g. isradipine (see section 4.5).

Blood lipids increased

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

Hyperkalaemia

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

Hypomagnesaemia

Cyclosporine enhances the clearance of magnesium. This can lead to symptomatic hypomagnesaemia, especially in the peri-transplant period. Control of serum magnesium levels is therefore recommended in the peri-transplant period, particularly

in the presence of neurological symptom/signs. If considered necessary, magnesium supplementation should be given.

Hyperuricaemia

Caution is required when treating patients with hyperuricaemia.

Live-attenuated vaccines

During treatment with cyclosporine, vaccination may be less effective. The use of live attenuated vaccines should be avoided (see section 4.5).

Interactions

Caution should be observed when co-administering cyclosporine with drugs that substantially increase or decrease cyclosporine plasma concentrations, through inhibition or induction of CYP3A4 and/or P-glycoprotein (see section 4.5).

Renal toxicity should be monitored when initiating cyclosporine use together with active substances that increase cyclosporine levels or with substances that exhibit nephrotoxic synergy (see section 4.5).

Concomitant use of cyclosporine and tacrolimus should be avoided (see section 4.5).

Cyclosporine is an inhibitor of CYP3A4, the multidrug efflux transporter P-glycoprotein and organic anion transporter proteins (OATP) and may increase plasma levels of co-medications that are substrates of this enzyme and/or transporter. Caution should be observed while co-administering cyclosporine with such drugs or concomitant use should be avoided (see section 4.5). Cyclosporine increases the exposure to HMG-CoA reductase inhibitors (statins). When concurrently administered with cyclosporine, the dosage of the statins should be reduced and concomitant use of certain statins should be avoided according to their label recommendations. Statin therapy needs to be temporarily withheld or discontinued in patients with signs and symptoms of myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis (see section 4.5).

Following concomitant administration of cyclosporine and lercanidipine, the AUC of lercanidipine was increased three-fold and the AUC of cyclosporine was increased 21%. Therefore the simultaneous combination of cyclosporine and lercanidipine

should be avoided. Administration of cyclosporine 3 hours after lercanidipine yielded no change of the lercanidipine AUC, but the cyclosporine AUC was increased by 27%. This combination should therefore be given with caution with an interval of at least 3 hours.

Special excipients: Polyoxyl 40 hydrogenated castor oil

Tianke contains polyoxyl 40 hydrogenated castor oil, which may cause stomach upsets and diarrhoea.

Special excipients: Ethanol

Tianke contains around 9.5% m/m ethanol. A 500 mg dose of Tianke contains 500 mg ethanol, equivalent to nearly 15 ml beer or 5 ml wine. This may be harmful in alcoholic patients and should be taken into account in pregnant or breast-feeding women, in patients presenting with liver disease or epilepsy, or if the patients is a child.

Additional precautions in non-transplantation indications

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

Before initiation of treatment a reliable baseline assessment of renal function should be established by at least two measurements of eGFR. Renal function must be assessed frequently throughout therapy to allow dosage adjustment (see section 4.2).

Additional precautions in endogenous uveitis

Tianke should be administered with caution in patients with neurological Behcet`s syndrome. The neurological status of these patients should be carefully monitored.

There is only limited experience with the use of Tianke in children with endogenous uveitis.

Additional precautions in nephrotic syndrome

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

In some patients, it may be difficult to detect cyclosporine-induced renal dysfunction because of changes in renal function related to the nephrotic syndrome itself. This

explains why, in rare cases, cyclosporine-associated structural kidney alterations have been observed without increases in serum creatinine. Renal biopsy should be considered for patients with steroid-dependent minimal-change nephropathy, in whom cyclosporine therapy has been maintained for more than 1 year.

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

Additional precautions in rheumatoid arthritis

Before initiating treatment, at least two creatinine levels to estimate baseline should be performed. Serum creatinine should be evaluated every 2 weeks during the initial 3 months and then monthly if the patient is stable.

After 6 months of therapy, renal function needs to be assessed every 4 to 8 weeks depending on the stability of the disease, its co- medication, and concomitant diseases. More frequent checks are necessary when the Tianke dose is increased, or concomitant treatment with an NSAID is initiated or its dosage increased. Discontinuation of Tianke may also become necessary if hypertension developing during treatment cannot be controlled by appropriate therapy.

As with other long-term immunosuppressive treatments, an increased risk of lymphoproliferative disorders must be borne in mind. Special caution should be observed if Tianke is used in combination with methotrexate due to nephrotoxic synergy.

Additional precautions in psoriasis

Discontinuation of Tianke therapy is recommended if hypertension developing during treatment cannot be controlled with appropriate therapy.

Elderly patients should be treated only in the presence of disabling psoriasis, and renal function should be monitored with particular care.

There is only limited experience with the use of Tianke in children with psoriasis.

In psoriatic patients on cyclosporine, as in those on conventional immunosuppressive therapy, development of malignancies (in particular of the skin) has been reported. Skin lesions not typical for psoriasis, but suspected to be malignant or pre-malignant

should be biopsied before Tianke treatment is started. Patients with malignant or pre-malignant alterations of the skin should be treated with Tianke only after appropriate treatment of such lesions, and if no other option for successful therapy exists.

In a few psoriatic patients treated with cyclosporine, lymphoproliferative disorders have occurred. These were responsive to prompt discontinuation.

Patients on Tianke should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy.

Additional precautions in atopic dermatitis

Discontinuation of Tianke is recommended if hypertension developing during treatment cannot be controlled with appropriate therapy.

Experience with Tianke in children with atopic dermatitis is limited.

Elderly patients should be treated only in the presence of disabling atopic dermatitis and renal function should be monitored with particular care.

Benign lymphadenopathy is commonly associated with flares in atopic dermatitis and invariably disappears spontaneously or with general improvement in the disease.

Lymphadenopathy observed on treatment with cyclosporine should be regularly monitored.

Lymphadenopathy which persists despite improvement in disease activity should be examined by biopsy as a precautionary measure to ensure the absence of lymphoma.

Active herpes simplex infections should be allowed to clear before treatment with Tianke is initiated, but are not necessarily a reason for treatment withdrawal if they occur during therapy unless infection is severe.

Skin infections with *Staphylococcus aureus* are not an absolute contraindication for Tianke therapy, but should be controlled with appropriate antibacterial agents. Oral erythromycin, which is known to have the potential to increase the blood concentration of cyclosporine (see section 4.5), should be avoided. If there is no alternative, it is recommended to closely monitor blood levels of cyclosporine, renal function, and for side effects of cyclosporine.

Patients on Tianke should not receive concomitant ultraviolet B irradiation or PUVA photochemotherapy.

Paediatric use in non-transplantation indications

Except for the treatment of nephrotic syndrome, there is no adequate experience available with Tianke. Its use in children under 16 years of age for non-transplantation indications other than nephrotic syndrome cannot be recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions

Of the many drugs reported to interact with cyclosporine, those for which the interactions are adequately substantiated and considered to have clinical implications are listed below.

Various agents are known to either increase or decrease plasma or whole blood cyclosporine levels usually by inhibition or induction of enzymes involved in the metabolism of cyclosporine, in particular CYP3A4.

Cyclosporine is also an inhibitor of CYP3A4, the multidrug efflux transporter P-glycoprotein and organic anion transporter proteins (OATP) and may increase plasma levels of co-medications that are substrates of this enzyme and/or transporters. Medicinal products known to reduce or increase the bioavailability of cyclosporine: In transplant patients frequent measurement of cyclosporine levels and, if necessary, cyclosporine dosage adjustment is required, particularly during the introduction or withdrawal of the co-administered medication. In non-transplant patients the relationship between blood level and clinical effects is less well established. If medicinal products known to increase cyclosporine levels are given concomitantly, frequent assessment of renal function and careful monitoring for cyclosporine-related side effects may be more appropriate than blood level measurement.

Drugs that decrease cyclosporine levels

All inducers of CYP3A4 and/or P-glycoprotein are expected to decrease cyclosporine levels. Examples of drugs that decrease cyclosporine levels are:

Barbiturates, carbamazepine, oxcarbazepine, Phenobarbital, phenytoin; nafcillin, intravenous sulfadimidine, probucol, orlistat, hypericum perforatum (St. John's wort), ticlopidine, sulfinpyrazone, terbinafine, bosentan.

Products containing *Hypericum perforatum* (St John´s Wort) must not be used concomitantly with Tianke due to the risk of decreased blood levels of cyclosporine and thereby reduced effect (see section 4.3).

Rifampicin induces cyclosporine intestinal and liver metabolism. Cyclosporine doses may need to be increased 3- to 5-fold during co-administration.

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

Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system. The interaction between rifabutin and cyclosporine has not been studied. Care should be exercised when these two drugs are administered concomitantly.

<u>Drugs that increase cyclosporine levels</u>

All inhibitors of CYP3A4 and/or P-glycoprotein may lead to increased levels of cyclosporine. Examples are:

Nicardipine, metoclopramide, oral contraceptives, methylprednisolone (high dose), allopurinol, cholic acid and derivatives, protease inhibitors, imatinib, colchicine, bromocriptine, nefazodone.

Macrolide antibiotics: *Erythromycin* can increase cyclosporine exposure 4- to 7-fold, sometimes resulting in nephrotoxicity. *Clarithromycin* has been reported to double the exposure of cyclosporine. *Azitromycin* increases cyclosporine levels by around 20%.

Azole antibiotics: Ketoconazole, fluconazole, itraconazole and voriconazole could more than double cyclosporine exposure.

Verapamil increases cyclosporine blood concentrations 2- to 3-fold.

Co-administration with *telaprevir* resulted in approximately 4.64-fold increase in cyclosporine dose normalised exposure (AUC).

Amiodarone substantially increases the plasma cyclosporine concentration concurrently with an increase in serum creatinine. This interaction can occur for a long time after withdrawal of amiodarone, due to its very long half-life (about 50 days).

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

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

Imatinib could increase cyclosporine exposure and C_{max} by around 20%.

HIV Protease inhibitors The HIV protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, and saquinavir) are known to inhibit cytochrome P-450 3A and thus could potentially increase the concentrations of cyclosporine, however no formal studies of the interaction are available. Care should be exercised when these drugs are administered concomitantly.

Food interactions

The concomitant intake of grapefruit and grapefruit juice has been reported to increase the bioavailability of cyclosporine.

Combinations with increased risk for nephrotoxicity

Care should be taken when using cyclosporine together with other active substances that exhibit nephrotoxic synergy such as: *aminoglycosides (including gentamycin, tobramycin), amphotericin B, ciprofloxacin, vancomycin, trimethoprim (+ sulfamethoxazole); fibric acid derivatives (e.g. bezafibrate, fenofibrate); NSAIDs (including diclofenac, naproxen, sulindac, azapropazon); melphalan histamine H2-receptor antagonists (e.g. cimetidine, ranitidine); methotrexate* (see section 4.4).

During the concomitant use of a drug that may exhibit nephrotoxic synergy, close monitoring of renal function should be performed. If a significant impairment of renal function occurs, the dosage of the co-administered medicinal product should be reduced or alternative treatment considered.

Concomitant use of cyclosporine and tacrolimus should be avoided due to the risk for nephrotoxicity and pharmacokinetic interaction via CYP3A4 and/or P-gp (see section 4.4).

Effects of cyclosporine on other drugs

Cyclosporine is an inhibitor of CYP3A4, the multidrug efflux transporter P-glycoprotein (P-gp) and organic anion transporter proteins (OATP). Co-administration of drugs that are substrates of CYP3A4, P-gp and OATP with cyclosporine may increase plasma levels of co-medications that are substrates of this enzyme and/or transporter.

Some examples are listed below:

Cyclosporine may reduce the clearance of *digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins), and, repaglinide, NSAIDs, sirolimus, etoposide, aliskiren, bosentan, dabigatran, and* other drugs. If any of these drugs are used concurrently with cyclosporine, close clinical observation is required in order to enable early detection of toxic manifestations of the medicinal products, followed by reduction of its dosage or its withdrawal. When concurrently administered with cyclosporine, the dosage of the statins should be reduced and concomitant use of certain statins should be avoided according to their label recommendations. Exposure changes of commonly used statins with cyclosporine are summarised in Table 1. Statin therapy needs to be temporarily withheld or discontinued in patients with signs and symptoms of myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis.

Table 1 Summary of exposure changes of commonly used statins with cyclosporine

Statin	**Doses available**	**Fold change in exposure with cyclosporine**
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 is recommended when co-administering cyclosporine with lercanidipine (see section 4.4).

Concomitant administration of *dabigatran* and cyclosporine may result in increased plasma dabigatran concentrations due to the P-gp inhibitory activity of cyclosporine. Coadministration of cyclosporine with dabigatran should be avoided.

Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking *digoxin*. If digoxin is used concurrently with cyclosporine, serum digoxin concentrations should be monitored.

There are reports on the potential of cyclosporine to enhance the toxic effects of *colchicine* such as myopathy and neuropathy, especially in patients with renal dysfunction. Concomitant administration of cyclosporine and colchicine results in significant increases in colchicine plasma concentrations. If colchicine is used concurrently with cyclosporine, a reduction in the dosage of colchicine is recommended.

Cyclosporine may increase the plasma concentrations of *repaglinide* and thereby increase the risk of hypoglycemia. In 12 healthy male subjects who received two doses of 100 mg cyclosporine capsule orally 12 hours apart with a single dose of 0.25 mg repaglinide tablet (one-half of a 0.5mg tablet) orally 13 hours after the cyclosporine initial dose, the repaglinide mean C_{max} and AUC were increased 1.8 fold (range: 0.6 to –3.7 fold) and 2.4 fold (range 1.2 to 5.3 fold), respectively. Close monitoring of blood glucose level is advisable for a patient taking cyclosporine and repaglinide concomitantly.

Cyclosporine alters the pharmacokinetics of *aliskiren*, a substrate of P-glycoprotein and CYP3A4. In 14 healthy subjects who received concomitantly single doses of cyclosporine (200 mg) and reduced dose aliskiren (75 mg), the mean C_{max} of aliskiren was increased by approximately 2.5-fold (90% CI: 1.96 to 3.17) and the mean AUC by approximately 4.3 fold (90% CI: 3.52 to 5.21), compared to when these subjects received aliskiren alone. The concomitant administration of aliskiren with cyclosporine prolonged the median aliskiren elimination half-life (26 hours versus 43

to 45 hours) and the T_{max} (0.5 hours versus 1.5 to 2.0 hours). The mean AUC and C_{max} of cyclosporine were comparable to reported literature values. Coadministration of cyclosporine and aliskiren in these subjects also resulted in an increase in the number and/or intensity of adverse events, mainly headache, hot flush, nausea, vomiting, and somnolence. The coadministration of cyclosporine with aliskiren is not recommended. Concomitant administration of dabigatran extexilate is not recommended due to the P-gp inhibitory activity of cyclosporine (see section 4.3).

Cyclosporine should not be used with *potassium-sparing diuretics* because hyperkalemia can occur. Caution is also required when cyclosporine is coadministered with potassiumsparing drugs (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists), potassium-containing drugs as well as in patients on a potassium rich diet. Control of potassium levels in these situations is advisable.

Clinical status and serum creatinine should be closely monitored when cyclosporine is used with *NSAIDs* in rheumatoid arthritis patients.

Pharmacodynamic interactions have been reported to occur between cyclosporine and both naproxen and sulindac, in that concomitant use is associated with additive decreases in renal function, as determined by ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) and (p-aminohippuric acid) PAH clearances. Although concomitant administration of diclofenac does not affect blood concentrations of cyclosporine, it has been associated with approximate doubling of diclofenac blood concentrations and occasional reports of reversible decreases in renal function. Consequently, the dose of diclofenac should be in the lower end of the therapeutic range.

Preliminary data indicate that when methotrexate and cyclosporine were coadministered to rheumatoid arthritis patients (N=20), methotrexate concentrations (AUCs) were increased approximately 30% and the concentrations (AUCs) of its metabolite, 7-hydroxy methotrexate, were decreased by approximately 80%. The clinical significance of this interaction is not known. Cyclosporine concentrations do not appear to have been altered (N=6).

Elevations in serum creatinine were observed in studies using sirolimus in combination with full-dose cyclosporine. This effect is often reversible with cyclosporine dose reduction. Simultaneous coadministration of cyclosporine significantly increases blood levels of sirolimus. To minimize increases in sirolimus concentrations, it is recommended that sirolimus be given 4 hours after cyclosporine administration.

The concurrent administration of *nifedipine* with cyclosporine may result in an increased rate of gingival hyperplasia compared with that observed when cyclosporine is given alone.

Convulsions when high dose *methylprednisolone* is given concurrently with cyclosporine have been reported.

Psoriasis patients receiving other immunosuppressive agents or radiation therapy (including PUVA and UVB) should not receive concurrent cyclosporine because of the possibility of excessive immunosuppression.

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Pregnancy, Lactation & Fertility

Pregnancy

- Animal studies have shown reproductive toxicity in rats and rabbits.
- Experience with micro-emulsified cyclosporine in pregnant women is limited. Pregnant women receiving immunosuppressive therapies after transplantation, including cyclosporine and cyclosporine-containing regimens, are at risk of premature delivery (<37 weeks).
- A limited number of observations in children exposed to cyclosporine *in utero* are available, up to an age of approximately 7 years. Renal function and blood

pressure in these children were normal. However, there are no adequate and well-controlled studies in pregnant women and therefore Tianke should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus. The ethanol content of the Tianke formulations should also be taken into account in pregnant women (see section 4.4).

Breast-feeding

- Cyclosporine passes into breast milk. The ethanol content of the Tianke formulations should also be taken into account in women who are breast-feeding (see section 4.4). Mothers receiving treatment with Tianke should not breast-feed because of the potential of Tianke to cause serious adverse drug reactions in breast-fed newborns/infants. A decision should be made whether to abstain from breast-feeding or to abstain from using the medicinal drug, taking into account the importance of the medicinal product tothe mother.

Fertility

- There is limited data on the effect of Tianke on human fertility. No impairment in fertility was demonstrated in studies in male and female rats. (see section 5.3).

4.7 Effects on ability to drive and use machines

- No data exist on the effects of Tianke on the ability to drive and use machines

4.8 Undesirable effects

Summary of the safety profile

- The principal adverse reactions observed in clinical trials and associated with the administration of Cyclosporine include renal dysfunction, tremor, hirsutism, hypertension, anorexia, nausea and vomiting.

- Many side effects associated with Cyclosporine therapy are dose-dependent and responsive to dose reduction. In the various indications the overall

spectrum of side effects is essentially the same; there are, however, differences in incidence and severity. As a consequence of the higher initial doses and longer maintenance therapy required after transplantation, side effects are more frequent and usually more severe in transplant patients than in patients treated for other indications.

- Anaphylactoid reactions have been observed following intravenous administration, such as face and flushing, asthma and short of breath etc.

Infections and infestations

- Patients receiving immunosuppressive therapies, including Cyclosporine and Cyclosporine-containing regimens, are at increased risk of infections (viral, bacterial, fungal, parasitic) (see section 4.4). Both generalized and localized infections can occur. Pre-existing infections may also be aggravated and reactivation of polyomavirus infections may lead to polyomavirus-associated nephropathy (PVAN) or to JC virus associated progressive multifocal leukopathy (PML). Serious and/or fatal outcomes have been reported.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

- Patients receiving immunosuppressive therapies, including Cyclosporine and Cyclosporine containing regimens, are at increased risk of developing lymphomas or lymphoproliferative disorders and other malignancies, particularly of the skin. The frequency of malignancies increases with the intensity and duration of therapy (see section 4.4). Some malignancies may be fatal.

Tabulated summary of adverse drug reactions from clinical trials

- Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition the corresponding frequency category for

each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000) very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1: Adverse drug reactions from clinical trials

Blood and lymphatic system disorders	
Common	Leucopenia
Metabolism and nutrition disorders	
Very common	anorexia
Nervous system disorders	
Very common	Tremor, headache
Common	Convulsions, paraesthesia
Vascular disorders	
Very common	Hypertension
Common	Flushing
Gastrointestinal disorders	
Very Common	Nausea, vomiting, abdominal discomfort/pain, diarrhoea, gingival hyperplasia,
Common	peptic ulcer
Hepatobiliary disorders	
Common	Hepatotoxicity
Skin and subcutaneous tissue disorders	
Very common	Hirsutism
Common	Acne, Allergic rashes
Renal and urinary disorders	
Very common	Renal dysfunction
Reproductive system and breast disorders	
Rare	Menstrual disturbances

General disorders and administration site conditions	
Common	Pyrexia, Oedema

Other adverse drug reactions from post-marketing experience

The following adverse drug reactions from spontaneous reports from post-marketing and literatures. These ADR frequency is not known due to the lack of a real denominator.

Table 2 Adverse drug reactions from spontaneous reports and literature

Blood and lymphatic system disorders
Thrombotic microangiopathy, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, anaemia, thrombocytopenia
Metabolism and nutrition disorders
Hyperlipidaemia, hyperuricaemia, hyperkalaemia, hypomagnesaemia
Nervous system disorders
Encephalopathy including Posterior Reversible Encephalopathy Syndrome (PRES), signs and symptoms such as convulsions, confusion, disorientation, decreased responsiveness, agitation, insomnia, visual disturbances, cortical blindness, coma, paresis and cerebellar ataxia; optic disc oedema, including papilloedema, with possible visual impairment secondary to benign intracranial hypertension; Motor polyneuropathy; Migraine
Gastrointestinal disorders
Acute pancreatitis
Hepatobiliary disorders
Hepatotoxicity and liver injury including cholestasis, jaundice, hepatitis and liver failure with some fatal outcome;
Skin and subcutaneous tissue disorders
Hypertrichosis
Musculoskeletal and connective tissue disorders

Myopathy, muscle cramps, myalgia, muscle weakness, pain of lower extremities

Reproductive system and breast disorders

Gynaecomastia

General disorders and administration site conditions

Fatigue, weight increase

There have been solicited and spontaneous reports of hepatotoxicity and liver injury including cholestasis, jaundice hepatitis and liver failure in patients treated with cyclosporine. Most reports included patients with significant co-morbidities, underlying conditions and other confounding factors including infectious complications and co-medications with hepatotoxic potential. In some cases, mainly in transplant patients, fatal outcomes have been reported (see section 4.4).

Acute and chronic nephrotoxicity

Patients receiving calcineurin inhibitor (CNI) therapies, including cyclosporine and cyclosporine-containing regimens, are at increased risk of acute or chronic nephrotoxicity. There have been reports from clinical trials and from the post-marketing setting associated with the use of cyclosporine. Cases of acute nephrotoxicity reported disorders of ion homeostasis, such as hyperkalaemia, hypomagnesaemia, and hyperuricaemia most of the cases happened in the first month treatment. Cases reporting chronic morphological changes included arteriolar hyalinosis, tubular atrophy and interstitial fibrosis (see section 4.4).

BK virus nephropathy have been observed in patients receiving immunosuppressive agents, including cyclosporine, resulting in serious outcomes, including deteriorating renal function and graft loss.

Pain of lower extremities

Isolated cases of pain of lower extremities have been reported in association with cyclosporine. Pain of lower extremities has also been noted as part of Calcineurin-Inhibitor Induced Pain Syndrome (CIPS).

4.9 Overdose

The oral LD50 of cyclosporine is 2,329 mg/kg in mice, 1,480 mg/kg in rats and > 1,000 mg/kg in rabbits. The intravenous LD50 is 148 mg/kg in mice, 104 mg/kg in rats, and 46 mg/kg in rabbits.

Symptoms

Experience with acute overdosage of cyclosporine is limited. Oral doses of cyclosporine of up to 10 g (about 150 mg/kg) have been tolerated with relatively minor clinical consequences, such as vomiting, drowsiness, headache, tachycardia and in a few patients moderately severe, reversible impairment of renal function. However, serious symptoms of intoxication have been reported following accidental parenteral overdosage with cyclosporine in premature neonates.

Treatment

In all cases of overdosage, general supportive measures should be followed and symptomatic treatment applied. Forced emesis and gastric lavage may be of value within the first few hours after oral intake. Cyclosporine is not dialysable to any great extent, nor is it well cleared by charcoal haemoperfusion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Immunosuppressive agents, calcineurin inhibitors

ATC code: L04AD01

- Cyclosporine (also known as Cyclosporine A) is a cyclic polypeptide consisting of 11 amino acids. It is a potent immunosuppressive agent, which in animals prolongs survival of allogeneic transplants of skin, heart, kidney, pancreas, bone marrow, small intestine or lung. Studies suggest that Cyclosporine inhibits the development of cell-mediated reactions, including allograft immunity, delayed cutaneous hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, graft-versus-host disease (GVHD), and also T-cell dependent antibody production. At the cellular level

it inhibits production and release of lymphokines including interleukin 2 (T-cell growth factor, TCGF).

- Cyclosporine appears to block the resting lymphocytes in the G0 or G1 phase of the cell cycle, and inhibits the antigen-triggered release of lymphokines by activated T-cells.

- All available evidence suggests that Cyclosporine acts specifically and reversibly on lymphocytes. Unlike cytostatic agents, it does not depress haemopoiesis and has no effect on the function of phagocytic cells.

- Successful solid organ and bone marrow transplantations have been performed in man using Cyclosporine to prevent and treat rejection and GVHD. Cyclosporine has been used successfully both in hepatitis C virus (HCV) positive and HCV negative liver transplants recipients. Beneficial effects of Cyclosporine therapy have also been shown in a variety of conditions that are known, or may be considered to be of autoimmune origin.

- Paediatric population: Cyclosporine has been shown to be efficacious in steroid-dependent nephrotic syndrome

5.2 Pharmacokinetic properties

Absorption

Following oral administration of Cyclosporine peak blood concentrations of Cyclosporine are reached within 3-4 hours. The absolute oral bioavailability of Cyclosporine following administration of Cyclosporine is 20 to 50%. About 13 and 33% decrease in AUC and C_{max} was observed when Cyclosporine was administered with a high-fat meal. The relationship between administered dose and exposure (AUC) of Cyclosporine is linear within the therapeutic dose range. The Tianke Soft Gelatin Capsules and Cyclosporine Oral Solution are bioequivalent.

Tianke administration results in a 59% higher Cmax and approximately 29% higher bioavailability than non-microemulsion formulation (Cmax appears 1 to 6 hours after

administration). The available data indicate that following a 1:1 switch from non-microemulsion foumulation to Tianke Soft Gelatin Capsules trough concentrations in whole blood are comparable and remain in the desired therapeutic range. Tianke administration improves dose linearity in cyclosporine exposure (AUCB). It provides a more consistent absorption profile with less influence from concomitant food intake or from diurnal rhythm than non-microemulsion formulation.Distribution

Cyclosporine is distributed largely outside the blood volume, the highest concentration in fat, followed by liver, adrenal gland and pancreas. In the blood, 33 to 47% is present in plasma, 4 to 9% in lymphocytes, 5 to 12% in granulocytes, and 41 to 58% in erythrocytes. In plasma, approximately 90% is bound to proteins, mostly lipoproteins.

Biotransformation

Cyclosporine is extensively metabolized to approximately 15 metabolites. Metabolism mainly takes place in the liver via cytochrome P450 3A4 (CYP3A4), and the main pathways of metabolism consist of mono- and dihydroxylation and N-demethylation at various positions of the molecule. All metabolites identified so far contain the intact peptide structure of the parent compound; some possess weak immunosuppressive activity (up to one-tenth that of the unchanged drug)

Elimination

The excretion is primarily biliary, with only 6% of the oral dose excreted in the urine; only 0.1% is excreted in the urine as unchanged parent compound.

There is a high variability in the data reported on the terminal half-life of cyclosporine depending on the assay applied and on 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 (see sections 4.2 and 4.4). The elimination half-life in kidney-transplanted patients was approximately 11 hours, with a range between 4 and 25 hours.

Special populations

Patients with renal impairment

In a study performed in patients with terminal renal failure, an intravenous infusion of 3.5 mg/kg of cyclosporine over 4 hours administered at the end of a hemodialysis session resulted in a mean Cmax level of whole blood of 1,800 ng/mL (range 1,536～2,331 ng/mL), mean volume of distribution (Vdss) of 3.49 L/kg and systemic clearance (CL) of 0.369 L/hr/kg. This systemic CL (0.369 L/hr/kg) was approximately two thirds of the mean systemic CL (0.56 L/hr/kg) of cyclosporine in historical control subjects with normal renal function.

Patients with hepatic impairment

An approximate 2- to 3-fold increase in cyclosporine exposure may be observed in patients with hepatic impairment. In a study performed in severe liver disease patients with biopsy-proven cirrhosis, the terminal half-life was 20.4 hours (range between 10.8 to 48.0 hours) compared to 7.4 to 11.0 hours in healthy subjects.

Pediatric population

Pharmacokinetic data from pediatric patients administered Tianke or non-microemulsion formulation are very limited. In 15 renal transplant patients aged 3-16 years, cyclosporine whole blood clearance after IV administration of cyclosporine was 10.6±3.7 mL/min/kg (assay: Cyclo-trac specific RIA). In a study of 7 renal transplant patients aged 2-16, the cyclosporine clearance ranged from 9.8-15.5 mL/min/kg. In 9 liver transplant patients aged 0.6-5.6 years, clearance was 9.3±5.4 mL/min/kg (assay: HPLC).

In the pediatric population, Tianke also demonstrates an increased bioavailability as compared to non-microemusion formulation. In 7 liver de novo transplant patients aged 1.4-10 years, the absolute bioavailability of Tianke was 43% (range 30%-68%) and for non-microemusion formulation in the same individuals absolute bioavailability was 28% (range 17%-42%).

Pediatric Pharmacokinetic Parameters (mean±SD)

Patient population	**Dose/day (mg/d)**	**Dose/weight (mg/kg/d)**	**AUC[1] (ng·hr/mL)**	**C_{max} (ng/mL)**	**CL/F (mL/min)**	**CL/F (mL/min/kg)**
Stable liver transplant[2]						
Age 2～8, Dosed TID (N=9)	101±25	5.95±1.32	2163±801	629±219	285±94	16.6±4.3
Age 8～15, Dosed TID	188±55	4.96±2.09	4272±1462	975±281	378±80	10.2±4.0

(N=8)

Stable liver transplant [3] Age 3, Dosed BID (N=1)	120	8.33	5832	1050	171	11.9
Age 8～15, Dosed BID (N=5)	158±55	5.51±1.91	4452±2475	1013±635	328±121	11.0±1.9
Stable liver transplant [3] Age 7～15, Dosed BID (N=5)	328±83	7.37±4.11	6922±1988	1827±487	418±143	8.7±2.9

[1] AUC was measured over one dosing interval

[2] Assay: Cycto-trac specific monoclonal radioimmunoassay

[3] Assay: TDx specific monoclonal fluorescence polarization immunoassay

Elderly population

Comparison of single dose data from both normal elderly volunteers (N=18, mean age 69 years) and elderly rheumatoid arthritis patients (N=16, mean age 68 years) to single dose data in young adult volunteers (N=16, mean age 26 years) showed no significant difference in the pharmacokinetic parameters.

5.3 Preclinical safety data

- Cyclosporine gave no evidence of mutagenic or teratogenic effects in the standard test systems with oral application (rats up to 17 mg/kg/day and rabbits up to 30 mg/kg/day orally). At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day orally), cyclosporine was embryo- and foetotoxic as indicated by increased prenatal and postnatal mortality, and reduced foetal weight together with related skeletal retardations.

- In two published research studies, rabbits exposed to Cyclosporine *in-vitro* (10 mg/kg/day subcutaneously) demonstrated reduced numbers of nephrons, renal hypertrophy, systemic hypertension, and progressive renal insufficiency up to 35 weeks of age. Pregnant rats which received 12 mg/kg/day of Cyclosporine intravenously (twice the recommended human intravenous dose) had fetuses with an increased incidence of ventricular septal defect. These findings have not been demonstrated in other species and their relevance for humans is

unknown. No impairment in fertility was demonstrated in studies in male and female rats.

- Cyclosporine was tested in a number of *in vitro* and *in vivo* tests for genotoxicity with no evidence for a clinically relevant mutagenic potential.

- Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-month rat study conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate at the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Propylene glycol

Absolute ethanol

Polyoxyl40 hydrogenated castor oil

Glyceryl monolinoleate

Vitamin E

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

- Tianke Soft Gelatin Capsules should be preserved in tight container, and store at a temperature not exceeding 30℃.
- Tianke Soft Gelatin Capsules should be left in the blister pack until required for use.
- When a blister is opened, a characteristic smell is noticeable. This is normal and does not mean that there is anything wrong with the capsule.
- Keep the medicine out of reach of the children

6.5 Nature and contents of container

- Tianke Soft Gelatin Capsules are available in 10 x 5 (25mg and 50mg) blister packs of double-sided aluminium consisting of an aluminium foil on the bottom side and an aluminium on the upper side.

6.6 Special precautions for disposal and other handling

Not applicable

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

7. MARKETING AUTHORIZATION HOLDER

North China Pharmaceutical Co., Ltd.

8. MARKETING AUTHORIZATION NUMBER(S)

08403/08938/NMR/2021

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Jan 31, 2023

10. DATE OF REVISION OF THE TEXT

December 2019