SHORT PRODUCT INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

PANOLİMUS 5.0 mg capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is:

Tacrolimus (as monohydrate) 5.0 mg

Adjuvant (s):

124,39 mg lactose anhydrous
Croscarmellose sodium 2.5 mg

For full list of excipients, see section 6.1.
See below for detailed information about the content of excipients. 4.4 Special warnings and precautions.

3. PHARMACEUTICAL FORM

Capsule
With white or off-white granular powder, light yellow / light yellow, No. 5 hard gelatin capsules.

4. CLINICAL FEATURES

4.1 Therapeutic indications

PANOLİMUS, allogeneic liver, kidney and heart transplant patients undergoing immunosuppressive therapies that are resistant to conventional liver, kidney and heart transplant patients treated used.

4.2 Posology and method of administration

PANOLİMUS treatment, by physicians with adequate quality and equipment requires careful monitoring. Medicinal product is prescribed by physicians experienced in immunosuppressive therapy and the treatment of transplant patients and physicians should be applied by the changes in immunosuppressive therapy.

Fast or extended release tacrolimus formulations, careless, unintentional or replacement is not safe to be controlled. This is due to differences in the clinical systemic exposure to tacrolimus, incomplete or excessive immunosuppression, including increased incidence of side effects or may cause graft rejection. Patients, the recommended daily dosage for the formulation with the same formulation of tacrolimus treatment should be continued.

Changes in formulation or regimen only be carried out under the close supervision of the

transplant specialist (see section 4.4 Special warnings and precautions for use and 4.8 Undesirable effects). Applied to any alternative formulation of tacrolimus is changed, and systemic tacrolimus therapeutic drug monitoring performed at the dose adjustments should be made to ensure that the exposure is maintained.

Posology:

Below is the recommended starting doses, should be considered as a guide. PANOLİMUS dosing essentially, with the help of the individual patient clinical assessments of rejection and tolerability should be based on monitoring of blood levels (see below for recommended target whole blood concentrations). If significant clinical signs of rejection, the immunosuppressive regimen should be considered replaced.

PANOLİMUS may be administered intravenously or orally. In general, the dose of oral intake be initiated, if necessary, capsule contents suspended in water were applied by the method of nasogastric tübaj.

With other immunosuppressive agents after the surgery at the beginning of PANOLİMUS used on a regular basis. PANOLİMUS dose may vary depending on the selected immunosuppressive regimen.

Treatment duration:

In order to suppress graft rejection, immunosuppression must be protected, and therefore there is no restriction for the duration of oral therapy.

Application form:

Daily oral dose in the form of two divided doses (morning and evening) are recommended. The capsules should be taken immediately after removal from the blister. The capsules should be taken in conjunction with liquid (preferably water).

In order to achieve maximum absorption, capsules, generally at least one hour before meals or on an empty stomach or taken after 2-3 hours (see 5.2).

Dose recommendations-liver transplantation:

Prophylaxis of transplant rejection - adults:

PANOLİMUS oral treatment, in the form of divided doses twice a day (morning and evening), 0.10 to 0.20 mg / kg dose should be initiated. Application, surgical intervention should begin within about 12 hours after application.

Due to the patient's clinical condition does not get oral dose of 0.01-0.05 mg / kg / day dose and 24-hour continuous infusion of intravenous therapy should be instituted.

Prophylaxis of transplant rejection - children:

0.30 mg / kg / day oral starting dose as two divided doses (morning and evening) should be taken. If you are taking an oral dose, it interferes with the patient's clinical condition, 0.05 mg / kg / day should be in the form of the initial intravenous dose 24-hour continuous infusion.

No dosage adjustment is post-transplant period in adults and children:

Generally PANOLİMUS doses, reduced post-transplant period. In some cases, termination of the co-administered immunosuppressive treatment and is therefore likely to start PANOLİMUS monotherapy. Improvements in clinical status of the patient after transplantation, tacrolimus pharmacokinetic properties and an additional dose adjustments may require change.

Rejection therapy in adults and children:

Increasing the dose of PANOLİMUS additional corticosteroid therapy and mono / short-term administration of polyclonal antibodies, used in the treatment of acute rejection episodes. PANOLİMUS signs of toxicity observed, the dose should be reduced (see 4.8 Undesirable effects).

To be replaced with PANOLİMUS treatment, based on the recommended oral starting dose immunosuppression therapy should be instituted.

For information on the introduction of cyclosporine therapy treatment PANOLİMUS "Special Populations" section.

Dosage recommendations - Kidney transplantation:

Prophylaxis of transplant rejection - adults:

PANOLİMUS oral treatment, in the form of divided doses twice a day (morning and evening), 0.20 to 0.30 mg / kg dose should be initiated. Application, surgical intervention should begin within approximately 24 hours after application. Due to the clinical condition of the patient does not get oral dose, 0.05 to 0.10 mg / kg / day dose and a 24-hour intravenous infusion of continuity of treatment should be initiated.

Prophylaxis of transplant rejection - children:

0.30 mg / kg / day oral starting dose as two divided doses (morning and evening) should be taken. If you are taking an oral dose, it interferes with the patient's clinical condition, 0.075 to 0.100 mg / kg / day starting dose 24-hour continuous intravenous infusion should be applied.

No dosage adjustment is post-transplant period in adults and children:

Generally PANOLİMUS doses, reduced post-transplant period. In some cases, termination of the co-administered immunosuppressive treatment and is therefore likely to PANOLİMUS based dual initiation of treatment. Improvements in clinical status of the patient after transplantation, change the properties of tacrolimus pharmacokinetics and extra dose adjustments may be required.

Rejection therapy in adults and children:

Increasing the dose of PANOLİMUS additional corticosteroid therapy and mono / short-term administration of polyclonal antibodies, used in the treatment of acute rejection

episodes. PANOLİMUS signs of toxicity observed, the dose should be reduced (see 4.8 Undesirable effects). To be replaced with PANOLİMUS treatment, based on the recommended oral starting dose immunosuppression therapy should be instituted.

For information on the introduction of cyclosporine therapy treatment PANOLİMUS "Special Populations" section.

Dosage recommendations - Heart transplantation:

Prophylaxis of transplant rejection-adults:

PANOLİMUS, combined with antibody induction (late initiation of therapy, leading to tacrolimus), or, alternatively, can be used without induction of antibodies in patients with stable clinical condition.

Following induction of antibodies, oral PANOLİMUS treatment, in the form of divided doses twice a day (morning and evening), 0.075 mg / kg dose should be initiated. Application, or within five days after applying surgical stabilization in conjunction with the patient's clinical condition should be initiated as soon as possible. Due to the clinical condition of the patient does not get oral dose, 0.01 to 0.02 mg / kg / day dose and 24-hour continuous infusion of intravenous therapy should be instituted.

Oral tacrolimus An alternative strategy is applied within 12 hours after transplantation have been published. This approach organ dysfunction (e.g. renal dysfunction) are not reserved for patients. In this case, starting from day 2 to 4 mg oral dose of tacrolimus, mycophenolate mofetil and corticosteroids or used in combination with sirolimus and corticosteroids.

Prophylaxis of transplant rejection - children:

PANOLİMUS, pediatric heart transplantation, antibody induction with or without induction of antibody used. In patients without antibody induction, if you will start PANOLİMUS recommended starting dose of intravenous treatment, tacrolimus whole blood concentrations of 15-25 ng / ml in 24-hour continuous infusion targeted to be 0.03 to 0.05 mg / kg / day. Patients were clinically appropriate oral therapy as soon as possible, should not be. The first dose of oral therapy discontinuation of intravenous therapy to begin within the next 8-12 hours daily 0.30 mg / kg should be.

Following induction of antibodies, PANOLİMUS treatment starts orally, the recommended starting dose as two divided doses (morning and evening) daily from 0.10 to 0.30 mg / kg.

No dosage adjustment is post-transplant period in adults and children:

Generally PANOLİMUS doses, reduced transplant period. Improvements in clinical status of the patient after transplantation, tacrolimus pharmacokinetic properties and an additional dose adjustments may require change.

Rejection therapy - adults and children:

Increasing the dose of PANOLİMUS additional corticosteroid therapy and mono / short-term administration of polyclonal antibodies, used in the treatment of acute rejection episodes.

PANOLİMUS modified by treatment in adult patients since oral dosage form two divided doses (morning and evening) a day of 0.15 mg / kg applied.

PANOLİMUS modified by treatment in pediatric patients, doses in the form of two divided oral doses starting from (morning and evening) daily from 0.20 to 0.30 mg / kg applied.

For information on the introduction of cyclosporine therapy treatment PANOLİMUS "Special Populations" section.

Target whole blood concentrations suggestions:

Dosing primarily, rejection and tolerability in each patient should be based on clinical assessment.

The best way to do dosing, as well as tacrolimus whole blood concentrations of semi-automated microparticle enzyme immunoassay test to determine (MEIA) immunologic testing must be done as a couple. Concentration values obtained from published literature and clinical experience to compare individual values, should be evaluated carefully and to those skilled in the methods of analysis used. Current clinical experience, complete blood levels should be monitored using immunoassay methods.

Tacrolimus blood trough levels should be monitored post-transplant period. Dose when given orally, blood trough levels measured 12 hours after the last application (immediately prior to the next dose) should be performed. Blood levels of measurement frequency, arranged according to clinical requirements. Klerensli PANOLİMUS a medicinal product is low, the blood levels of the adjustment of dosage regimen may take several days before the changes become clear. Blood trough levels in the early period after transplantation and after approximately two times a week during maintenance therapy should be monitored periodically. Dose adjustment and immunosuppressive regimen of tacrolimus whole blood concentrations, or change the following changes with the use of the following substances, blood trough levels of tacrolimus should be monitored (see section 4.5 Interactions with other medicinal products and other forms of interaction).

Analysis of clinical trials, tacrolimus blood trough levels 20ng/ml under 'is maintained, the vast majority of patients can be treated successfully shows. Whole blood levels should be taken into consideration assessing the patient's clinical status.

Clinical experience, in the early period after transplantation, whole blood trough levels of patients treated with liver transplantation is usually 5-20 mg / ml in kidney and heart transplant patients treated, usually 10-20 ng / ml can vary. During subsequent maintenance therapy, liver, kidney and heart transplant recipients blood concentrations are generally 5-15 ng / ml in the range.

Additional information on special populations:

Renal impairment:

The pharmacokinetics of tacrolimus in renal function is not affected by the dose adjustment is required. However, because of the potential nephrotoxicity of tacrolimus, renal function (serum creatinine concentration measurement, calculation of creatinine clearance and monitoring of urine output included) Careful monitoring is recommended.

Hepatic impairment:

To achieve the recommended target range of blood trough levels, in patients with severe hepatic impairment, dose reduction may be necessary.

Paediatric population:

Generally, pediatric patients, the adult dose in adults in order to achieve similar blood levels of 1 ½ -2 times the dose to be used.

Elderly:

There are no data indicating dosage adjustment is necessary in elderly patients.

Other

Cyclosporine, tacrolimus therapy treatment, transition

Patients should be careful crossing the cyclosporine-based therapy PANOLİMUS-based therapy (see 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicinal products and other forms of interaction). After taking into account the patient's clinical status and blood concentrations of cyclosporine therapy should be initiated PANOLİMUS. Should be postponed in patients with high blood levels of cyclosporine therapy. In practice, discontinuation of cyclosporine therapy initiated 12-24 hours after the treatment PANOLİMUS. May be affected by clearance of cyclosporine, cyclosporine or cyclosporine blood levels after discontinuation of therapy should be continued monitoring.

4.3 Contraindications

PANOLİMUS, takrolimusa other macrolide immunosuppressive or be used in patients known to be hypersensitive to other substances contained in the composition.

4.4 Special warnings and precautions for use

The start of treatment and changes to the immunosuppressive treatment PANOLİMUS only physicians specializing in the treatment of patients who have undergone organ transplantation and immunosuppressive therapy should decide. PANOLİMUS treatment, with adequate laboratory and medical support facilities and specialized staff in centers should be initiated. As a result of suppression of the immune system, may increase susceptibility to infection and the possible development of lymphoma may occur. Claimed responsibility for the maintenance treatment the doctor, the patient must have all the necessary information to keep track of.
Specializes in treating patients who have undergone organ transplants, and without the knowledge of the patient's treatment, termination or similar drugs, physicians have the responsibility to continue treatment or changing the treatment may cause serious conditions.

In the first period after transplantation as a routine follow-up of the following parameters must be very closely: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, hematological parameters, coagulation values, and plasma protein determination.

Clinically significant changes are observed, immunosuppressive therapy should be considered. Fast or extended release tacrolimus formulations, careless, unintentional errors in medication were observed, including the replacement of, or be controlled. This condition develops as a result of organ rejection or less, or excessive exposure to tacrolimus, including serious adverse events may cause other side effects. The recommended daily dose for patients with the formulation, but should continue treatment with the formulation of tacrolimus.

Changes in formulation or regimen only be carried out under the close supervision of the transplant specialist. (See 4.2 Posology and method of administration and 4.8 Undesirable effects).

Resulting in a reduction in clinical efficacy of tacrolimus blood concentrations and the risk of interactions, depending on the receiving PANOLİMUS St. St. John's Wort (Hypericum perforatum), a herbal preparations should be avoided (see section 4.5 Interactions with other medicinal products and other forms of interaction).

Tacrolimus blood levels may change significantly during episodes of diarrhea, diarrhea episodes during the more careful monitoring of tacrolimus concentrations is recommended.

The combined use of cyclosporine and tacrolimus should be avoided and patients who received cyclosporine, tacrolimus Caution should be exercised before. (See 4.2 Posology and method of administration and 4.5 Interactions with other medicinal products and other forms of interaction).

Reported cardiomyopathy, ventricular hypertrophy or hypertrophy of the septum was observed in rare cases. Most of these cases becomes reversible and in particular, tacrolimus blood trough konsatrasyonları maximum recommended values are higher in children. A pre-existing heart disease, corticosteroid use, hypertension, renal or hepatic dysfunction, infections, fluid overload, and other factors, including edema, increased risks of clinical conditions were observed. Accordingly, patients receiving immunosuppressant, especially small children and large amounts of, before and after transplant (eg initially and after 3 months, 9-12 months) using procedures such as echocardiography or ECG should be monitored. If treatment-related abnormalities develop, dose reduction or treatment, other immunosuppressive agents through PANOLİMUS replacement therapy should be considered. Tacrolimus can prolong the QT interval, but, however, there is insufficient evidence that it is the development of Torsades de Pointes. The presence of congenital long QT syndrome should be treated with caution in patients with suspected or diagnosed.

In patients treated with tacrolimus, Epstein-Barr Virus (EBV) lymphoproliferative disorders associated with, development of. Treatment with anti-lymphocyte therapy should be administered in patients with PANOLİMUS passed. Very small (under 2 years), EBV-VCA sero-negative children are reported to be higher than the risk of developing lymphoproliferative disorders. PANOLİMUS Therefore, before initiating therapy in this patient group, EBV-VCA serology should be investigated. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may continue for several months, and on its own does not indicate a lymphoproliferative disease or lymphoma.

Treated with tacrolimus in patients with posterior reversible encephalopathy syndrome (PRES) have been reported. If patients taking tacrolimus, headache, altered mental status, such as visual disturbances and symptoms related to Pres if there is a radiological

procedures (eg, MRI) should be performed. If PRES is being diagnosed, adequate blood pressure control to ensure immediate cessation of systemic tacrolimus is recommended. Most patients completely recover after appropriate measures.

Including tacrolimus, immünosüpresanlarla treated patients, opportunistic infections (bacterial, fungal, viral and protozoal) high risk. Of these conditions, BK virus-associated nephropathy and Creutzfeld Jacobs virus associated with progressive multifocal leukoencephalopathy (PML) are available. These infections are often subject to high total immunosuppressive burden and deteriorating renal function or neurological symptoms, physicians should consider patients may lead to serious or fatal conditions.

As with other immunosuppressive agents, because of the risk of malignant skin changes, exposure to sunlight and UV light, protective clothing and using a high protection factor sun cream should be reduced.

Other effective as immunosuppressive compounds, the risk of secondary cancer is unknown (see 4.8 Undesirable effects).

Sodium:

PANOLİMUS each capsule contains 2.5 mg croscarmellose sodium. This dose is not expected to have any side effects sodium-dependent.

Lactose:

Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine with problems.

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

Metabolic interactions:

Available tacrolimus is metabolised by hepatic CYP3A4 isoenzyme systemically. In addition, the gastrointestinal metabolism by CYP3A4 is evidence that the intestinal wall are also available. Medicinal products known to inhibit CYP3A4, or induce or herbal medications affect the metabolism of tacrolimus and thereby increase tacrolimus blood levels or be degraded. Therefore, when taken together with substances that have the potential to change CYP3A4 metabolism of tacrolimus and other similar tacrolimus exposure monitoring blood levels in order to provide a suitable adjustment of the dose of tacrolimus is recommended (see sections 4.2 and 4.4 Dosage and Administration Special Precautions).

Metabolic inhibitors:

Clinically, following substances shown to increase tacrolimus blood levels:

Ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin or HIV protease inhibitors (eg, ritonavir) with the strong interactions, such as has been observed with antifungal agents. With the use of these substances, the dose of tacrolimus may be required to reduce almost all patients.

Clotrimazole, clarithromycin, josamisin, nifedipine, nicardipine, diltiazem, verapamil,

danazol, oral contraceptives containing ethinylestradiol, omeprazole and weak interactions observed with nefazodone.

Potential inhibitors of tacrolimus metabolism in vitro the following substances is shown to be the following: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mefenitoin, miconazole, midazolam, nilvadipin, norethisterone, quinidine, tamoxifen, troleandomycin.

Grapefruit juice, has been reported to increase tacrolimus blood levels and therefore should be avoided drinking grapefruit juice.

Metabolism inducers:

Clinically, the following substances are shown to reduce blood levels of tacrolimus.

Rifampicin, phenytoin or St. St. John's Wort (Hypericum perforatum), along with the need to increase the dose of tacrolimus in patients with almost all significant interactions strong interactions gözlenmektedir.Klinik also been observed with phenobarbital. Maintenance doses of corticosteroids are shown to reduce tacrolimus blood levels.

High dose prednisolone or methylprednisolone for the treatment of acute rejection, has the potential to increase or decrease tacrolimus blood levels.

Carbamazepine, metamizole and isoniazid have the potential to reduce concentrations of tacrolimus.

Tacrolimus on the metabolism of other medicinal effect:

Tacrolimus is a known inhibitor of CYP3A4, therefore tacrolimus with medicinal products known to be metabolised by CYP3A4 use of such products may affect the metabolism.

Cyclosporine A half-life is prolonged when tacrolimus with it. In addition, the synergistic / additive nephrotoxic effects can occur. Therefore, the combined use of cyclosporine and tacrolimus tacrolimus is not recommended and should not be administered to patients already used cyclosporine is recommended (see 4.2 Posology and method of administration and 4.4 Special warnings and precautions for use).

Been shown to increase tacrolimus blood levels of phenytoin.

Tacrolimus, the clearance of steroid-based contraceptives, may reduce due to increased hormone exposure, special care must be taken when deciding on contraceptive measures.

There is limited information about the interaction between tacrolimus and statins. The present data farmokokinetiklerinin largely unchanged tacrolimus used in combination with statins has been suggested. Animal data, tacrolimus, and potentially decrease the clearance of pentobarbital and antipirin'in can increase the half-time show.

Clinically, the harmful effects of the other interactions:

Medicinal products known to have nephrotoxic or neurotoxic effects (eg, aminoglycosides, gyrase inhibitors, sulfamethoxazole + trimethoprim, non-steroidal anti-inflammatory drugs (NSAIDs), such as ganciclovir or acyclovir) may lead to increased effects with the

concomitant use of tacrolimus.

Amphotericin B and ibuprofen, when used in combination with tacrolimus nephrotoxicity was observed in residues. Be associated with tacrolimus treatment of hyperkalemia or exacerbate pre-existing hyperkalemia, too much potassium intake, or potassium-sparing diuretics (amiloride, triamterene, or spironolactone, etc.) should be avoided.

During treatment response affect immunization and vaccination İmmunosupresanlar tacrolimus may be less effective. The use of live attenuated vaccines should be avoided.

Protein binding:

Tacrolimus is extensively connected to plasma proteins. Other medicinal products known to have high affinities to plasma proteins (eg, NSAIDs, oral anticoagulants, or oral antidiabetics) may be taken into consideration along with possible interactions.

4.6. Pregnancy and lactation

General advice

Pregnancy Category: C

Women of childbearing potential / birth control (contraception)

Animal studies, pregnancy / and-or / embryonal / fetal development / ve-veya/doğum / ve-veya/doğum insufficient in terms of the effects on postnatal development.

Gestation

Human data showed that tacrolimus may pass the placenta. Limited data from organ transplant recipients, tacrolimus treatment compared with other medicinal products immuosüpresif increased risk of side effects during and after pregnancy, a finding that it is up to göstermemektedir.Bugüne, did not appear in any other epidemiological data. Due to the need for treatment, it is not a safe alternative to the fetus and the benefits to be obtained from the use of tacrolimus meets the potential risk to pregnant women considered. In case of in utero exposure, the possible side effects of tacrolimus (in particular effects on the kidneys) against neonatal monitoring is recommended. Premature delivery (<37 weeks) and at the same time, there is a risk of hyperkalaemia in the newborn is usually returned to normal by itself.

PANOLİMUS be used during pregnancy unless it is necessary.

Lactation:

Human data have shown that tacrolimus excreted in breast milk. Due to the harmful effects on the newborn can not be ignored, women should not breast feed while PANOLİMUS patients.

Reproductive ability / Fertility

Maternal toxicity observed in rats and rabbits at doses of tacrolimus caused embryo-fetal toxicity (see section 5.3 Preclinical safety data). Tacrolimus effect on male fertility in rats

(see section 5.3 Preclinical safety data).

4.7. Effects on ability to drive and use machines

Tacrolimus, may cause visual and neurological disturbances. These effects are taken together with alcohol PANOLİMUS improved.

4.8. Undesirable effects

With the presence of underlying disease, and multiple drug use, due to the side effect profile associated with immunosuppressive agents is difficult to determine.

Most of the following side effects are reversible and / or by reducing the dose is reduced. The frequency of adverse events observed during the use of oral administration of IV gözükmektedir.Yan effects observed during the observation of their frequency of side effects, such as less as follows:
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 (can not be estimated from the available data).

Cardiac disorders

Common: ischemic coronary artery disorders, tachycardia
Uncommon: Ventricular arrhythmias and cardiac arrest, heart failure, kardiyomiyopatikler, ventricular hypertrophy, supraventricular arrhythmias, palpitations, ECG tests abnormalities, abnormal heart rate and pulse tests
Rare: Pericardial effusion,
Very rare: abnormal echocardiogram

Blood and lymphatic system disorders

Common: anemia, leukopenia, thrombocytopenia, leukocytosis, abnormal red blood cell analysis
Uncommon: coagulopathy, coagulation and bleeding analyzes abnormal, pancytopenia, neutropenia
Rare: Thrombotic thrombocytopenic purpura, hypoprothrombinemia

Nervous system disorders:

Very common: tremor, headache,
Common: Episodes, confusion, paresthesia and dysesthesia, peripheral neuropathy, dizziness, writing impaired, nervous system disorders
Uncommon: coma, central nervous system hemorrhage and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language disorders, amnesia
Rare: hypertonia
Very rare: Myasthenia

Eye diseases

Common: Vision disturbances, photophobia, eye disorders

Uncommon: Cataract
Rare: Blindness

Ear and labyrinth disorders

Common: Tinnitus
Uncommon: hypoacuousia
Rare: deafness Nörosensoriel
Very rare: Hearing impairment

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammation
Uncommon: Respiratory failure, respiratory disorders, asthma
Rare: acute respiratory distress syndrome

Gastrointestinal Disorders

Very common: diarrhea, nausea,
Common: gastrointestinal inflammatory conditions, gastrointestinal ulceration, and perforation, gastrointestinal hemorrhage, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic symptoms, constipation, flatulence, bloating and distension, infrequent stools, gastrointestinal signs and symptoms
Uncommon: Paralytic ileus, peritonitis, acute and chronic pancreatitis, blood amylase increased, gastroesophageal reflux disease, gastric emptying disorders
Rare: partial intestinal obstruction, pancreatic pseudocyst

Renal and urinary disorders:

Very common: Renal dysfunction
Common: Renal failure, acute renal failure, oliguria, renal tubular necrosis, toxic nephropathy, urinary abnormalities, bladder and urethral symptoms
Uncommon: Anuria, hemolytic uremic syndrome
Very rare: nephropathy, hemorrhagic cystitis

Skin and subcutaneous tissue disorders

Common: pruritus, rash, alopecia, acne, excessive sweating
Uncommon: dermatitis, sensitivity to light
Rare: Toxic epidermal necrolysis (Lyell's syndrome)
Very rare: Stevens-Johnson syndrome

Musculo-skeletal disorders, connective tissue and bone disorders

Common: Arthralgia, muscle cramps, limb pain, back pain
Uncommon: joint disorders

Endocrine disorders

Rare: hirsutism Metabolism and nutrition disorders

Very common: hyperglycemic conditions, diadetes mellitus, hyperkalaemia
Common: hypomagnesemia, hypophosphatemia, hypokalemia, hypocalcemia, hyponatremia, excess fluid overload, hyperuricaemia, loss of appetite, anorexia, metabolic asidozlar, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, and other electrolyte abnormalities
Uncommon: dehydration, hypoproteinemia, hyperphosphatemia, hypoglycemia

Infections and infestations

It is well known for other potent immunosuppressive agents, patients using tacrolimus are often at risk of infection (viral, bacterial, fungal, and protozoal). Pre-existing infections flammable. Both common, as well as localized infections can occur.

PANOLİMUS including immünosüpresanlarla patients treated cases of BK virus-associated nephropathy, as well as Creutzfeld Jacobs virus associated with progressive multifocal leukoencephalopathy (PML) reported.

Injury, poisoning and procedural complications

Common: Primary graft dysfunction

Fast or extended release tacrolimus formulations, careless, unintentional errors in medication were observed, including the replacement of, or be controlled. Associated with transplant rejection have been reported in some cases (data out of the existing frequencies can not be determined).

Benign, malignant neoplasms, and an unidentified

In patients receiving immunosuppressive therapy, an increased risk of developing malignancy. Tacrolimus therapy, depending on the EBV-related lymphoproliferative disorders, including malignant and benign neoplasms, and skin malignancies have been reported observed.

Vascular diseases

Very common: hypertension
Common: haemorrhage, thromboembolic and ischemic events, peripheral vascular disorders, vascular hypotensive disorders
Uncommon: infarction, deep venous thrombosis risk, shock

General disorders and administration site conditions

Common: Asthenic conditions, febrile disorders, edema, pain and discomfort, blood alkaline phosphatase increase, weight gain, body temperature distortion in the perception of
Uncommon: Multiple organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased, weight decreased
Uncommon: thirst, lethargy, chest tightness, mobility decreased, ulcer

Very rare: increase in adipose tissue

Immune System Disorders

Patients treated with tacrolimus, allergic and anaphylactoid reactions have been observed (see section 4.4 Special warnings and precautions for use).

Hepato-billier diseases

Common: hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis
Rare: Hepatic artery thrombosis, veno-occlusive liver disease
Very rare: hepatic impairment, biliary duct narrowing

Reproductive system and breast disorders

Uncommon: dysmenorrhoea and uterine bleeding

Psychiatric disorders

Very common: Insomnia
Common: anxiety symptoms, confusion and disorientation, depression, anxiety disorders, mood swings and confusion, nightmares, hallucinations, mental disorders
Uncommon: psychotic disorder

4.9 Overdose and treatment

There is limited experience with overdose. Several reported cases of accidental overdose, tremor, headache, nausea and vomiting, infections, urticaria, lethargy, and blood urea nitrogen, serum creatinine concentration, and increased alanine aminotransferase shales.

There is no specific antidote therapy PANOLİMUS. To overdose, general supportive measures and symptomatic treatment should be the case.
High molecular weight, depending on the solubility in water is small and is connected to the plasma proteins and erythrocytes strong tacrolimus said uzaklaştırılamayacağı dialysis. Isolated in patients with high plasma levels, haemofiltration or diyafiltrasyon, has been effective in reducing toxic concentrations. Cases of oral intoxication, if applied immediately after, gastric lavage and / or the use of absorbents such as activated charcoal may be useful.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: calcineurin inhibitors
ATC code: L04AD02

Mechanism of action

At the molecular level, the effects of tacrolimus in the composition which is responsible for the intracellular accumulation of cytosolic protein (FKBP-12) is thought to be through

connected. Tacrolimus as FKBP-12 complex-specific and competitive binding and kalsinörini kalsinörine to inhibit the calcium-dependent inhibition of T-cell signal transduction paths is caused, and therefore a different set of lymphokine gene transcription is blocked.

Tacrolimus, kanıtlanış activity in vitro and in vivo experiments, the immunosuppressive agent is very strong.

Particular, tacrolimus, inhibits the formation of cytotoxic lymphocyte which is responsible for graft rejection. Tacrolimus is a T-cell-dependent B cell activation and proliferation of T-helper cells prints. Also, interleukin-2, 3, and the formation of lymphokines, such as γ-interferon and interleukin-2 receptor expression of prints.

5.2 Pharmacokinetic properties

General characteristics

Absorption:

Shown to be absorbed gastrointestinal route of tacrolimus in humans. Following oral administration of tacrolimus capsules, peak plasma concentrations of tacrolimus in the blood (Cmax) is reached approximately 1-3 hours. In some patients, tacrolimus, and constantly absorbed in a longer time than the flat absorption profile can be revealed. Mean oral bioavailability of tacrolimus in the range of 20-25%.

Liver transplant patients, 0.30 per day mg / kg oral tacrolimus after applying, the majority of patients takrolimus'un constant plasma concentrations were reached within 3 days.

In healthy volunteers, tacrolimus 0.5 mg, 1 mg and 5 mg capsules equivalent doses shown to be bioequivalent.

Rate and degree of absorption of tacrolimus, most likely an empty stomach. The presence of food, both the speed and extent of tacrolimus absorption decreases, this effect is stated that the more high-fat meal hours. If the effect of high-carbohydrate meal is less than specified.
Stable liver transplant patients with a moderate fat meal (34% of calories) is received after the oral bioavailability of tacrolimus decreased. Full blood, AUC (27%) and Cmax'ta (50%) decrease in T max 'ta (173%) increase in the clear.

The standard tacrolimus in stable renal transplant patients after a traditional breakfast is included in the study, the effect of oral bioavailability is less than specified. Whole blood, AUC (2% - 12%) and Cmax'ta (15% - 38%) decrease and Tmax'ta (38% - 80%) increase is evident.

Takrolimus'un affect the absorption of bile flow.

Steady-state area under the curve, and is a strong correlation between the levels of whole blood. Thus, monitoring of whole blood trough levels, provides better estimation in systemic exposure.

Distribution and elimination:

In humans, the distribution of tacrolimus after intravenous infusion described as biphasic.

A strong connection of the erythrocytes in the systemic circulation of tacrolimus whole blood concentrations / plasma concentration range that results in a ratio of about 20:1.

Tacrolimus plasma, plasma proteins, mainly serum albumin and alpha-1-acid glycoprotein, a high percentage (> 98.8%) are connected.

Tacrolimus, a widely distributed to the body. Volume of distribution at steady-state plasma concentrations in healthy volunteers due to approximately 1300 liters. This value corresponds to an average of 47.6 liters of whole blood.

Tacrolimus is a low klerensli substance. In healthy volunteers, the average total body clearance of whole blood concentrations of L was found to be 2.25 per hour. In adult liver transplantation in adult renal transplant patients, patients with total body klerensli hours, 6.7 hours, 4.1 l L and 3.9 L have been observed in adult heart transplant patients per hour. Pediatric liver transplant recipients, the total body clearance is about 2 times that of adult liver transplant patients. Higher clearance rates observed after transplantation, tacrolimus resulting in an increase in the free portion of the low hematocrit and protein levels, or factors such as corticosteroid-induced increased metabolism is thought to be responsible. The long and variable half-life of tacrolimus. Average half-life of about 43 hours of whole blood in healthy volunteers. Compared to an average 15.6 hours in adult patients with recent kidney transplantation, liver transplantation in adult patients, 11.7, 04.12 hours of liver transplantation in pediatric patients. Increased clearance rates observed in transplant recipients leads to a shorter half-life.

Metabolism:

Tacrolimus is mainly cytochrome P450 (CYP3A4) by is largely metabolized in the liver. Tacrolimus is metabolized in the bowel wall quite. There are described several metabolites. Only one of these metabolites takrolimusunkine immunosuppressive activity similar to that shown in the in vitro. There is weak or no immunosuppressive activity of the other metabolites. The systemic circulation, only one of the low concentrations of metabolites are inactive. Therefore, it is not caused by the pharmacological activity of tacrolimus metabolites.

Breakthrough:

After intravenous and oral administration of 14C-labeled tacrolimus, most of the radioactivity was eliminated in the faeces. Approximately 2% of the radioactivity was eliminated in the urine. Tacrolimus has a low rate of less than 1% unchanged in the urine and faeces were taken, and this is almost completely metabolised prior to elimination suggests that tacrolimus. The main way of elimination of bile.

Additional information on special populations:

Renal impairment:

Tacrolimus pharmacokinetic properties is not affected by renal function, dosage adjustment is not required. However, because of the potential nephrotoxicity of tacrolimus, renal function (serum creatinine concentration measurement, calculation of creatinine clearance and monitoring of urine output included) Careful monitoring is recommended.

Hepatic impairment:

Compared to people with normal liver function, higher concentrations of tacrolimus in patients with impaired liver function, the plasma half-life may be longer and the clearance lower levels.

PANOLİMUS is mainly metabolized in the liver, patients with liver dysfunction should be carefully monitored and dosage adjustment is necessary.

Paediatric population:

In pediatric liver transplant recipients of adult liver transplant recipients based on the total body clearance is approximately two times higher. After transplantation, the high clearance rates, resulting in an increase in part connected to the low hematocrit and protein levels of tacrolimus factors or factors such as corticosteroids increase the metabolism of tacrolimus is thought to be responsible. (See 4.2 Posology and method of administration).

Elderly:

A limited number of data shows that the elderly have not changed PANOLİMUS'un pharmacokinetic properties.

5.3 Preclinical safety data

Toxicity studies performed in rats and baboons, have been affected by the major organs, kidneys and pancreas. In rats, tacrolimus caused toxic effects in the central nervous system and eyes. After intravenous administration of tacrolimus, reversible cardiotoxic effects have been observed in rabbits.

Toxicity was observed in rats and rabbits, embryo-fetal and maternal toxicity in animals with certain doses is limited. In rats, female reproductive function including birth toxic doses disturbed and low birth weight offspring, survival skills and growth was observed.

In rats, tacrolimus, reduced sperm count and male üremesindeki negative effects were observed as the movement.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hypromellose
Lactose anhydrous
Croscarmellose sodium
Magnesium stearate

Capsule coating mixture:

Titanium dioxide E171
Yellow Iron (III) oxide E172
Gelatin

6.2. Incompatibilities

Tacrolimus is incompatible with PVC. Suspension of capsules used in preparing and implementing PANOLİMUS tubes, syringes and other materials must not contain PVC.

6.3. Shelf life

36 months

6.4. Special precautions for storage

30 ° C, kept at room temperature.

Blisters should be stored in a dry place.

6.5. Nature and contents of container

Al-Al foil blisters. In the fifth box in the blister, each blister 10 pills. Are available in packages of 50 capsules.

6.6. Medicinal Special precautions for disposal and other handling the product, the remaining

No special requirements.

Any unused product or waste material "Medical Waste Control Regulation" and "Packaging Waste Control Regulation" tion must be disposed of in accordance with.

7. LICENCE HOLDER

BIEM Drug San.ve Tic. Inc.
Turgut Reis Cad No: 21 06570
Tandogan-Ankara
Tel: 0.312230 29 29
Fax: 0.312230 68 00

8. LICENSE NUMBER

132/78

9. DATE OF FIRST AUTHORISATION / RENEWAL OF LICENCE

Date of first authorization: 23/02/2012
Registration Date of renovation:

10. The renewal date of short product information