06-10-2021
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210mm

ARILIO® Capsule
(T a c r o l i m u s)

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS

- Increased risk of development of lymphoma and other malignancies, particularly of the skin, due to immunosuppression.
- Increased susceptibility to bacterial, viral, fungal, and protozoal infections, including opportunistic infections.
- Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe tacrolimus.

QUALITATIVE AND QUANTITATIVE COMPOSITION

ARILIO® Capsule 0.5mg
Each capsule contains:
Tacrolimus (as Monohydrate) USP …. 0.5mg

ARILIO® Capsule 1mg
Each capsule contains:
Tacrolimus (as Monohydrate) USP …. 1mg

PHARMACEUTICAL FORM
Capsule

CLINICAL PARTICULARS
THERAPEUTIC INDICATIONS:

- Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.
- Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.

Limitations of Use: Should not be used simultaneously with cyclosporine. Use with sirolimus is not recommended in liver and heart transplant. The safety and efficacy with sirolimus has not been established in kidney transplant.

POSOLOGY AND METHOD OF ADMINISTRATION:
General considerations: Dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring. If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered. Dosing may commence orally; if necessary, by administering the capsule contents suspended in water, via nasogastric tubing. Tacrolimus is routinely administered in conjunction with other immunosuppressive agents in the initial post-operative period. The dose may vary depending upon the immunosuppressive regimen chosen. The initial dose should be administered no sooner than 6 hours after transplantation in the liver and heart transplant patients. In kidney transplant patients, the initial dose may be administered within 24 hours of transplantation, but should be delayed until renal function has recovered.

Posology: Dosage recommendations-liver transplantation: ***Prophylaxis of transplant rejection-adults:*** 0.10 - 0.20mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence approximately 12 hours after the completion of surgery. ***Prophylaxis of transplant rejection-children:*** Initial oral dose of 0.30mg/kg/day should be administered in two divided doses (e.g. morning and evening). ***Dose adjustment during post-transplant period in adults and children:*** Doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to monotherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments. ***Rejection therapy-adults and children:*** Increased doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted, dose may need to be reduced. For conversion to **ARILIO®** treatment should begin with the initial oral dose recommended for primary immunosuppression.
Dosage recommendations-kidney transplantation: ***Prophylaxis of transplant rejection-adults:*** 0.20-0.30mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence within 24 hours after the completion of surgery.
Prophylaxis of transplant rejection-children: An initial oral dose of 0.30mg/kg/day should be administered in two divided doses (e.g. morning and evening). ***Dose adjustment during post- transplant period in adults and children:*** Doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to tacrolimus based dual-therapy. Post-transplant dose adjustments may be required. ***Rejection therapy–adults and children:*** Increased doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted, the dose of **ARILIO®** may need to be reduced. For conversion to **ARILIO®**, treatment should begin with the initial oral dose recommended for primary immunosuppression.
Dosage recommendations-heart transplantation: ***Prophylaxis of transplant rejection-adults:*** Following antibody induction, oral therapy should commence at a dose of 0.075mg/kg/day administered as two divided doses (e.g. morning and evening). Administration should commence within 5 days after the completion of surgery as soon as the patient's clinical condition is stabilized. If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of 0.01 to 0.02mg/kg/day should be initiated as a continuous 24-hour infusion. Oral tacrolimus administration within 12 hours post transplantation is known to be reserved for patients without organ dysfunction (e.g. renal dysfunction). In that case, an initial oral tacrolimus dose of 2 to 4mg per day was used in combination with mycophenolate mofetil and corticosteroids or in combination with sirolimus and corticosteroids. ***Prophylaxis of transplant rejection-children:*** Tacrolimus is known to be used with or without antibody induction in paediatric heart transplantation. In patients without antibody induction, if therapy is initiated intravenously, the recommended starting dose is 0.03-0.05mg/kg/day as a continuous 24-hour infusion targeted to achieve tacrolimus whole blood concentrations of 15 - 25ng/ml. Patients should be converted to oral therapy as soon as clinically practicable. The first dose of oral therapy should be 0.30 mg/kg/day starting 8 to 12 hours after discontinuing intravenous therapy. Following antibody induction, if therapy is initiated orally, the recommended starting dose is 0.10 - 0.30mg/kg/day administered as two divided doses (e.g. morning and evening). ***Dose adjustment during post-transplant period in adults and children:*** Post-transplant dose adjustments may be required. ***Rejection therapy–adults and children:*** Increased tacrolimus doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. In adult patients converted to tacrolimus, an initial oral dose of 0.15mg/kg/day should be administered in two divided doses (e.g. morning and evening). In paediatric patients converted to, an initial oral dose of 0.20 - 0.30mg/kg/day should be administered in two divided doses (e.g. morning and evening).
Dosage recommendations-rejection therapy, other allografts: Dose recommendations for lung, pancreas and intestinal transplantation are based on limited prospective clinical trial data. In lung-transplanted patients tacrolimus has been used at an initial oral dose of 0.10 - 0.15mg/kg/day, in pancreas-transplanted patients at an initial oral dose of 0.2mg/kg/day and in intestinal transplantation at an initial oral dose of 0.3mg/kg/day.
Dosage adjustments in specific patient populations: ***Patients with liver impairment:*** Dose reduction may be necessary in patients with severe liver impairment. ***Patients with kidney impairment:*** No dose adjustment should be required. Careful monitoring of renal function is recommended. ***Paediatric population:*** In general, paediatric patients require doses 1½ - 2 times higher than the adult doses to achieve similar blood levels. ***Older Population:*** No dose adjustment required in older people. ***Conversion from cyclosporine:*** Dosing should be delayed in the presence of elevated cyclosporine blood levels. In practice, tacrolimus therapy has been initiated 12-24 hours after discontinuation of cyclosporine. Monitoring of cyclosporine blood levels should be continued. ***Target whole blood trough concentration recommendations:*** Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient. In clinical practice, whole blood trough levels have generally been in the range 5-20ng/ml in liver transplant recipients and 10-20ng/ml in kidney and heart transplant patients in the early post-transplant period. Subsequently, during maintenance therapy, blood concentrations have generally been in the range of 5-15ng/ml in liver, kidney and heart transplant recipients.
Method of administration: Oral daily dose be administered in two divided doses (e.g. morning and evening); swallowed with fluid (preferably water). Should generally be administered on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption.
Duration of dosing: To suppress graft rejection, immunosuppression must be maintained; consequently, no limit to the duration of oral therapy can be given.

CONTRAINDICATIONS: Hypersensitivity to tacrolimus or other macrolides.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Medication errors are known to occur; leading to serious adverse events, including graft rejection, or other side effects. During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values, and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered. **Substances with potential for interaction:** When substances with a potential for interaction such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) or rifampicin, rifabutin are being combined with tacrolimus, blood levels should be monitored to adjust the tacrolimus dose. Herbal preparations containing St. John's wort (Hypericum perforatum) or other herbal preparations should be avoided when taking tacrolimus due to the risk of interactions. The combined administration of cyclosporine and tacrolimus should be avoided and care should be taken. High potassium intake or potassium-sparing diuretics should be avoided. **Vaccination:** The use of live attenuated vaccines should be avoided. **Gastrointestinal disorders:** Gastrointestinal perforation has been reported in patients treated with tacrolimus. Adequate treatments should be considered immediately after suspected symptoms or signs occur. **Cardiac disorders:** Tacrolimus may prolong the QT interval and may cause Torsade's de Pointes. Caution should be exercised in patients with risk factors for QT prolongation, including patients with a personal or family history of QT prolongation, congestive heart failure, brady arrhythmias and electrolyte abnormalities. **Lymphoproliferative disorders and malignancies:** Epstein-Barr virus (EBV)-associated lymphoproliferative disorders is known to occur. Patients switched to tacrolimus therapy should not receive anti-lymphocyte treatment concomitantly. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is per se not indicative of lymphoproliferative disease or lymphoma. **Posterior reversible encephalopathy syndrome (PRES):** If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, discontinuation of systemic tacrolimus is advised. **Eye disorder:** Patients should be advised to report changes in visual acuity, changes in colour vision, blurred vision, or visual field defect, and in such cases, prompt evaluation is recommended. **Infections including opportunistic infections:** Increased risk for infections including opportunistic infections (bacterial, fungal, viral and protozoal) such as BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). Patients are also at an increased risk of infections with viral hepatitis (for example, hepatitis B, C and E). **Pure Red Cell Aplasia:** Cases of pure red cell aplasia (PRCA) are known to occur in patients treated with tacrolimus.

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As tacrolimus contains lactose, special care should be taken in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. In patients who are hypersensitive to peanut or soya, the risk and severity of hypersensitivity should be weighed against the benefit of using tacrolimus.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:
Metabolic interactions: Concomitant use of medicinal products or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels; strongly recommended to closely monitor tacrolimus blood levels. **Inhibitors of metabolism:** Strong interactions are known to occur with ketoconazole, fluconazole, itraconazole voriconazole, and isavuconazole, the macrolide antibiotic erythromycin, HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir), HCV protease inhibitors (e.g. telaprevir, boceprevir, and the combination of ombitasvir and paritaprevir with ritonavir, when used with and without dasabuvir), or the CMV antiviral letermovir, the pharmacokinetic enhancer cobicistat, and the tyrosine kinase inhibitors nilotinib and imatinib. Grapefruit, lansoprazole and cyclosporine may increase tacrolimus whole blood concentrations. **Other interactions potentially leading to increased tacrolimus blood levels:** Possible interactions with other medicinal products known to have high affinity for plasma proteins should be considered (e.g., NSAIDs, oral anticoagulants, or oral antidiabetics). Other potential interactions that may increase systemic exposure of tacrolimus include the metoclopramide, cimetidine and magnesium-aluminium hydroxide. **Inducers of metabolism:** Strong interactions have been observed with rifampicin, phenytoin or St. John's Wort (Hypericum perforatum) which may require increased tacrolimus doses in almost all patients. Clinically significant interactions have also been observed with phenobarbital. Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels. High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels. Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations. **Effect of tacrolimus on the metabolism of other medicinal products:** The half-life of cyclosporine is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of cyclosporine and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received cyclosporine. Tacrolimus has been shown to increase the blood level of phenytoin. As tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure. **Mycophenolic acid:** Therapeutic drug monitoring of mycophenolic acid may be appropriate when switching from cyclosporine to tacrolimus or vice versa. **Other interactions which have led to clinically detrimental effects:** Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole + trimethoprim, NSAIDs, ganciclovir or aciclovir). Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus. As tacrolimus treatment may be associated with hyperkalaemia, or may increase pre-existing hyperkalaemia, high potassium intake, or potassium-sparing diuretics (e.g., amiloride, triamterene, or spironolactone) should be avoided.

PREGNANCY AND LACTATION:
Pregnancy: Pregnancy Category C; human data show that tacrolimus is able to cross the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse effects on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. However, cases of spontaneous abortion have been reported. Due to the need of treatment, tacrolimus can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the potential risk to the fetus. **Breast-feeding:** Human data demonstrate that tacrolimus is excreted into breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if tacrolimus is administered in association with alcohol.

UNDESIRABLE EFFECTS:
Kidney Transplant: The most common adverse reactions (≥ 30%) were infection, tremor, hypertension, abnormal renal function, constipation, diarrhoea, headache, abdominal pain, insomnia, nausea, hypomagnesemia, urinary tract infection, hypophosphatemia, peripheral edema, asthenia, pain, hyperlipidemia, hyperkalaemia, anemia. **Liver Transplant:** The most common adverse reactions (≥ 40%) were tremor, headache, diarrhoea, hypertension, nausea, abnormal renal function, abdominal pain, insomnia, paresthesia, anemia, pain, fever, asthenia, hyperkalaemia, hypomagnesemia, and hyperglycaemia. **Heart Transplant:** The most common adverse reactions (≥ 15%) were abnormal renal function, hypertension, diabetes mellitus, CMV infection, tremor, hyperglycaemia, leukopenia, infection, anemia, bronchitis, pericardial effusion, urinary tract infection and hyperlipemia .
The following are serious and important adverse events: ● Lymphoma and other malignancies. ● Serious infections / polyoma virus infections/ CMV infections. ● New onset diabetes. ● Nephrotoxicity / neurotoxicity. ● Hyperkalaemia / hypertension myocordial hypertrophy. ● Anaphylaxis. ● Pure red cell aplasia. **Cardiovascular:** Atrial fibrillation, atrial flutter, cardiac arrhythmia, cardiac arrest, electrocardiogram T wave abnormal, flushing, myocardial infarction, myocardial ischemia, pericardial effusion, QT prolongation, Torsade de Pointes, venous thrombosis deep limb, ventricular extra systoles, ventricular fibrillation, myocardial hypertrophy. **Gastrointestinal:** Bile duct stenosis, colitis, enterocolitis, gastroenteritis, gastroesophageal reflux disease, hepatic cytolysis, hepatic necrosis, hepatotoxicity, impaired gastric emptying, liver fatty, mouth ulceration, pancreatitis haemorrhagic, pancreatitis necrotizing, stomach ulcer, veno-occlusive liver disease. **Hemic/Lymphatic:** Agranulocytosis, disseminated intravascular coagulation, haemolytic anemia, neutropenia, pancytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pure red cell aplasia **Infections:** Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal; -polyoma virus-associated nephropathy, (PVAN) including graft loss. **Metabolic/Nutritional:** Glycosuria, increased amylase including pancreatitis, weight decreased. **Miscellaneous:** Feeling hot and cold, feeling jittery, hot flushes, multi-organ failure, primary graft dysfunction. **Nervous System:** Carpal tunnel syndrome, cerebral infarction, haemiparesis, leukoencephalopathy, mental disorder, mutism, posterior reversible encephalopathy syndrome (PRES) progressive multifocal leukoencephalopathy (PML), quadriplegia, speech disorder, syncope acute respiratory distress syndrome, interstitial lung disease, lung infiltration, respiratory distress, respiratory failure. **Skin:** Stevens-Johnson syndrome, toxic epidermal necrolysis. **Special Senses:** Blindness, blindness cortical, hearing loss including deafness, photophobia. **Urogenital:** Acute renal failure, cystitis haemorrhagic, haemolytic-uremic syndrome, micturition disorder injury, poisoning and procedural complications: primary graft dysfunction.

OVERDOSE: No specific antidote to tacrolimus therapy is available. If over dosage occurs, general supportive measures and symptomatic treatment should be conducted. In cases of oral intoxication, gastric lavage and/or the use of adsorbents (such as activated charcoal) may be helpful, if used shortly after intake.

PHARMACOLOGICAL PROPERTIES
PHARMACODYNAMIC PROPERTIES: Pharmacotherapeutic group: Immunosuppressants, calcineurin inhibitors, **ATC code:** L04AD02.
Mechanism of action and pharmacodynamic effects: Tacrolimus is a highly potent immunosuppressive agent; inhibits the formation of cytotoxic lymphocytes, which are mainly responsible for graft rejection; suppresses T-cell activation and T-helper-cell dependent B-cell proliferation, as well as the formation of lymphokines (such as interleukins-2, -3, and γ-interferon) and the expression of the interleukin-2 receptor.

PHARMACOKINETIC PROPERTIES:
Absorption: Following oral administration of tacrolimus capsules peak concentrations (C_{max}) of tacrolimus in blood are achieved in approximately 1-3 hours. In some patients, tacrolimus appears to be continuously absorbed. Mean oral bioavailability of tacrolimus is in the range of 20% - 25%. After oral administration (0.30mg/kg/day) to liver transplant patients, steady-state concentrations of tacrolimus were achieved within 3 days in the majority of patients. The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases both the rate and extent of absorption of tacrolimus, the effect being most pronounced after a high-fat meal. The effect of a high-carbohydrate meal is less pronounced. A strong correlation exists between AUC and whole blood trough levels at steady-state. **Distribution and Elimination:** In the systemic circulation, tacrolimus binds strongly to erythrocytes in plasma, tacrolimus is highly bound (> 98.8%) to plasma proteins. Tacrolimus is extensively distributed in the body. Tacrolimus is a low-clearance substance. Paediatric liver transplant recipients have a TBC approximately twice that of adult liver transplant patients. The half-life of tacrolimus is long and variable. In healthy subjects, the mean half-life in whole blood is approximately 43 hours. In adult and paediatric liver transplant patients, it averaged 11.7 hours and 12.4 hours, respectively, compared with 15.6 hours in adult kidney transplant recipients. Increased clearance rates contribute to the shorter half-life observed in transplant recipients. **Metabolism and biotransformation:** Tacrolimus is widely metabolized in the liver, primarily by the cytochrome P_{450}-3A4. Tacrolimus is also considerably metabolized in the intestinal wall. There are several metabolites identified mostly do not contribute to pharmacological activity of tacrolimus. **Excretion:** Following oral administration of ^{14}C-labelled tacrolimus, most of the radioactivity was eliminated in the feces; approximately 2% was eliminated in the urine. Less than 1% of unchanged tacrolimus was detected in the urine and feces, indicating that tacrolimus is almost completely metabolized prior to elimination: bile being the principal route of elimination.

SHELF LIFE
See expiry on the pack.

AVAILABILITY
ARILIO® capsule 0.5mg in a pack of 30's
ARILIO® capsule 1mg in a pack of 30's

INSTRUCTIONS
Dosage: As advised by the physician.
To be sold on the prescription of registered medical practitioner only.
Keep out of the reach of children.
Avoid exposure to heat, light and humidity.
Store between 15 to 30°C.
Improper storage may deteriorate the medicine.

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

ایریلیو® کیپسول
(ٹیکروولمس)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری
سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہوجائیگی۔

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