ESOT CONGRESS 2019 in COPENHAGEN
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INVITATION TO CHIESI INDUSTRY SYMPOSIUM

Monday, September 16th | h 13 to 14 | Room A15

Adapting our approach to patients' need: can sensitivity to tacrolimus PK become a potential driver in clinical practice?

Chair: **R. Oberbauer** (Austria)

With:

L. Furian (Italy):
Early identification of tacrolimus PK sensitivity in kidney transplanted patients

F. Saliba (France):
Exploring new aspects of clinical PK sensitivity: management of liver transplanted patients

Sandwich boxes will be available for attendees

Envarsus® 0.75mg, 1mg, 4mg Prolonged-Release Tablet Tacrolimus (as monohydrate) Abbreviated Prescribing Information

Please refer to Summary of Product Characteristics (SPC) before prescribing.

Presentation: Each Envarsus prolonged-release tablets contains 0.75mg, 1mg and 4mg of tacrolimus. **Indications:** Prophylaxis of transplant rejection in adult kidney or liver allograft recipients and treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients. **Dosage and administration:** Once-a-day oral formulation. Requires careful monitoring by adequately qualified and equipped personnel. This medicinal product should only be prescribed, and changes in immunosuppressive therapy be initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist. The recommended initial doses presented below are intended to act solely as a guideline. Envarsus 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. 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. As tacrolimus is a substance with low clearance, adjustments to the Envarsus dose regimen may take several days before steady state is achieved. Envarsus doses are usually reduced in the post-transplant period. Post-transplant changes in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments. *Prophylaxis of kidney transplant rejection:* Therapy should commence at a dose of 0.17 mg/kg/day administered once daily in the morning. Administration should commence within 24 hours after the completion of surgery. *Prophylaxis of liver transplant rejection:* Therapy should commence at a dose of 0.11–0.13 mg/kg/day administered once daily in the morning. Administration should commence within 24 hours after the completion of surgery. *Conversion of Prograf- or Advagraf-treated patients to Envarsus - allograft transplant patients:* Allograft transplant patients maintained on twice daily Prograf (immediate-release) or Advagraf (once daily) dosing requiring conversion to once daily Envarsus should be converted on a 1:0.7 (mg:mg) total daily dose basis and the Envarsus maintenance dose should, therefore, be 30% less than the Prograf or Advagraf dose. Envarsus should be administered in the morning. When converting from tacrolimus immediate-release products (e.g. Prograf capsules) or from Advagraf prolonged-release capsules to Envarsus, trough levels should be measured prior to conversion and within two weeks after conversion. Dose adjustments should be made to ensure that similar systemic exposure is maintained after the switch. In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels. In clinical studies patients converted from twice daily Prograf were converted to Envarsus using a 1:0.85 (mg:mg) conversion. *Conversion from ciclosporin to tacrolimus:* Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy. The combined administration of ciclosporin and tacrolimus is not recommended. Envarsus therapy should be initiated after considering ciclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated ciclosporin blood levels. In practice, tacrolimus-based therapy has been initiated 12 to 24 hours after discontinuation of ciclosporin. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin might be affected. *Treatment of allograft rejection:* Increased doses of tacrolimus, supplemental corticosteroid therapy, and introduction of short courses of monoclonal/polyclonal antibodies have been used to manage rejection episodes. If signs of toxicity such as severe adverse reactions are noted, the dose of Envarsus may need to be reduced. *Treatment of allograft rejection after kidney or liver transplantation:* For conversion from other immunosuppressants to once daily Envarsus, treatment should begin with the initial oral dose recommended in kidney and liver transplantation respectively for prophylaxis of transplant rejection. **Therapeutic drug monitoring:** Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient aided by whole blood tacrolimus trough level monitoring. As an aid to optimise dosing, several immunoassays are available for determining tacrolimus concentrations in whole blood. Comparisons of concentrations from the published literature to individual values in clinical practice should be assessed with care and knowledge of the assay methods employed. In current clinical practice, whole blood levels are monitored using immunoassay methods. The relationship between tacrolimus trough levels and systemic exposure (AUC0-24) is well correlated and is similar between the immediate-release formulation and Envarsus. Blood trough levels of tacrolimus should be monitored during the post-transplantation period. Tacrolimus blood trough levels should be determined approximately 24 hours post-dosing of Envarsus, just prior to the next dose. Blood trough levels of tacrolimus should also be closely monitored following conversion from tacrolimus products, dose adjustments, changes in the immunosuppressive regimen, or co-administration of substances which may alter tacrolimus whole blood concentrations. The frequency of blood level monitoring should be based on clinical needs. As tacrolimus is a substance with low clearance, following adjustments to the Envarsus dose regimen it may take several days before the targeted steady state is achieved. Data from clinical studies suggest that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels. In clinical practice, whole blood trough levels have generally been in the range of 5 20 ng/ml in kidney transplant patients in the early post-transplant period, and 5 15 ng/ml during subsequent maintenance therapy. *Method of administration:* Taken once daily in the morning, swallowed whole with fluid (preferably water) immediately following removal from the blister. Generally taken on an empty stomach to achieve maximal absorption. **Contraindications:** Hypersensitivity to active substance or excipients. Hypersensitivity to macrolides. **Warnings and precautions:** Medication errors have led to serious adverse reactions, including graft rejection, or other adverse reactions which could be a consequence of either under- or over-exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist. Not recommended for use in children below 18 years of age due to the limited data on safety and/or efficacy. 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. Gastrointestinal perforation has been reported in patients treated with tacrolimus, adequate treatments should be considered immediately after suspected symptoms or signs occur. Extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea. Eye disorders, sometimes progressing to loss of vision, have been reported in patients treated with tacrolimus. Some cases have reported resolution on switching to alternative immunosuppression. Prompt evaluation and referral for changes in visual acuity or colour vision, blurred vision, or visual field defect. Cardiomyopathies have been observed in tacrolimus treated patients on rare occasions. Most cases have been reversible, occurring with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at 3 months and then at 9 12 months). If abnormalities develop, dose reduction or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval, caution should be exercised in patients with diagnosed or suspected Congenital Long QT Syndrome. Patients treated with tacrolimus have been reported to develop EBV-associated lymphoproliferative disorders. Risk factors include using a combination of immunosuppressives, such as antilymphocytic antibodies (e.g. basiliximab, daclizumab) concomitantly, or EBV-Viral Capsid Antigen (VCA)-negative patients. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with Envarsus. 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. The risk of secondary cancer is unknown. Exposure to sunlight and UV light should be limited. At increased risk for opportunistic infections (bacterial, fungal, viral, and protozoal). Among these conditions are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If 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, adequate blood pressure and seizure control, and immediate discontinuation of systemic tacrolimus is advised. Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease or concomitant medicinal product associated with PRCA. Dose reduction may be necessary in patients with severe liver impairment. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product (refer to SPC for further information). **Interaction with other medicinal products and other forms of interaction:** Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is strongly recommended to closely monitor tacrolimus blood levels, as well as renal function and other side effects, whenever substances which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly, and to interrupt or adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure. Caution should be exercised when switching combination therapy from ciclosporin, which interferes with enterohepatic recirculation of mycophenolic acid, to tacrolimus, which is devoid of this effect, as this might result in changes of mycophenolic acid exposure. Drugs which interfere with mycophenolic acid's enterohepatic cycle have potential to reduce the plasma level and efficacy of mycophenolic acid. **Fertility, pregnancy and lactation:** *Pregnancy:* Human data show that tacrolimus crosses the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse events on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. However, cases of spontaneous abortion have been reported. Tacrolimus treatment can be considered in pregnant women when there is no safer alternative, and when the perceived benefit justifies the potential risk to the foetus. *Breast-feeding:* Human data demonstrate that tacrolimus is excreted in breast milk. As detrimental effects on the newborn cannot be excluded, women should not breast-feed. *Fertility:* A negative effect of tacrolimus on male fertility in the form of reduced sperm count and motility was observed in rats. **Effects on ability to drive and use machines:** May have a minor influence and may cause visual and neurological disturbances. This effect may be enhanced if administered in association with alcohol. No studies on the effects of tacrolimus (Envarsus) on the ability to drive and use machines have been performed. **Side effects:** *Very common:* tremor, renal impairment, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, infections, hypertension, insomnia, headache, diarrhoea, nausea, liver function tests abnormal Common: anaemia, thrombocytopenia, leukopenia, red blood cell analyses abnormal, leukocytosis, anorexia, metabolic acidoses, other electrolyte abnormalities, hyponatraemia, fluid overload, hyperuricaemia, hypomagnesaemia, hypokalaemia, hypocalcaemia, appetite decreased, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypophosphataemia, confusion and disorientation, depression, anxiety symptoms, hallucination, mental disorders, depressed mood, mood disorders and disturbances, nightmare, nervous system disorders, seizures, disturbances in consciousness, peripheral neuropathies, dizziness, paraesthesias and dysaesthesias, writing impaired, eye disorders, blurred vision, photophobia, tinnitus, ischaemic coronary artery disorders, tachycardia, thromboembolic and ischaemic events, vascular hypotensive disorders, haemorrhage, peripheral vascular disorders, parenchymal lung disorders, dyspnoea, pleural effusion, cough, pharyngitis, nasal congestion and inflammations, gastro-intestinal (GI) signs and symptoms, vomiting, GI and abdominal pains, GI inflammatory conditions, GI haemorrhages, GI ulceration and perforation, ascites, stomatitis and ulceration, constipation, dyspeptic signs and symptoms, flatulence, bloating and distension, loose stools, bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice, rash, pruritus, alopecias, acne, sweating increased, arthralgia, back pain, muscle cramps, pain in limb, renal failure, renal failure acute, nephropathy toxic, renal tubular necrosis, urinary abnormalities, oliguria, bladder and urethral symptoms, febrile disorders, pain and discomfort, asthenic conditions, oedema, body temperature perception disturbed, blood alkaline phosphatase increased, weight increased, primary graft dysfunction. *Uncommon:* coagulopathies, pancytopenia, neutropenia, abnormal coagulation and bleeding analyses, hypoglycaemia, psychotic disorder, encephalopathy, central nervous system haemorrhages and cerebrovascular accidents, coma, paralysis and paresis, cataract, heart failures, ventricular arrhythmias and cardiac arrest, supraventricular arrhythmias, cardiomyopathies, abnormal ECG investigations, ventricular hypertrophy, palpitations, abnormal heart rate and pulse investigations, deep limb venous thrombosis, shock, infarction, respiratory failures, respiratory tract disorders, asthma, acute and chronic pancreatitis, peritonitis, paralytic ileus, dermatitis, haemolytic uraemic syndrome, influenza like illness, increased blood lactate dehydrogenase, multi-organ failure. Rare: thrombotic, microangiopathy, thrombocytopenic purpura, hypoprothrombinaemia, blindness, deafness neurosensory, pericardial effusion, acute respiratory distress syndrome, pancreatic pseudocyst, subileus, veno-occlusive liver disease, hepatic artery thrombosis, toxic epidermal necrolysis (Lyell's syndrome), ulcer. Very rare: myasthenia, hearing impaired, echocardiogram abnormal, hepatic failure, Stevens Johnson Syndrome, nephropathy, cystitis haemorrhagic. *Not Known Frequency:* pure red cell aplasia, agranulocytosis, haemolytic anaemia, optic neuropathy, allergic and anaphylactoid reactions (refer to SPC for full list of side effects). **Prescription group:** BEGR. **Reimbursement:** None. **Prices and Packs:** 0.75mg 1x90 depot tablets, 1mg 1x90 depot tablets, 4mg 1x30 tablets. See www.medicinpriser.dk for current prices. **Marketing authorization holder:** Chiesi Farmaceutici S.p.A. **This abbreviated prescribing information (26. June 2019) has been shortened/rewritten from the EMA SmPC (11. April 2017) which can be requested from the local representative for Denmark:** Chiesi Pharma AB, Kungstensgatan 38, 4 tr, SE-113 59 Stockholm, Sweden.

Adverse events should be reported.
Reporting forms and information can be found at www.meldenbivirkning.dk or reported the Danish Medicines Agency, Axel Heides Gade 1, DK-2300 Copenhagen S, Denmark at dkma@dkma.dk.
Adverse events should also be reported to Chiesi Pharma AB at pharmacovigilancenordic@chiesi.com.