PRODUCT GUIDE

ODVenta

Prolonged release tacrolimus 0.5/1mg capsules

Seize Control for a better tomorrow

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PART I
HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	0.5 mg, 1 mg	Hypromellose, Ethylcellulose *For a complete listing, see Dosage Forms, Composition and Packaging section.*

INDICATIONS

Tacrolimus prolonged release capsules are indicated for prophylaxis of transplant rejection in adult kidney or liver allograft rejection.

Clinical application

De novo

ODVenta ® (tacrolimus extended release capsules) is indicated for prophylaxis of organ rejection in adult patients receiving allogeneic kidney and liver transplants.

ODVenta is to be used concomitantly with adrenal corticosteroids and mycophenolate mofetil (MMF) in de novo renal transplant recipients and adrenal corticosteroids in de novo liver transplants. Antibody induction therapy should also be used in kidney transplant recipients.

Conversion

Stable renal transplant patients may be converted from twice daily Tacrolimus to ODVenta (once daily), in combination with adrenal corticosteroids and MMF, based on equivalent tacrolimus whole blood trough concentrations. Stable liver transplant patients may be converted from immediate release formulation to ODVenta (extended release formulation), in combination with adrenal corticosteroids, based on equivalent tacrolimus whole blood trough concentrations (See Dosage and Administration).

Any changes in immunosuppressive therapy must be initiated by physicians experienced in immunosuppressive therapy and the management of transplant patients.

CONTRAINDICATIONS

ODVenta (tacrolimus extended release capsules) is contraindicated in patients with hypersensitivity to tacrolimus or to any ingredient in the formulation or component of the capsules.

SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Increased susceptibility to infection and the possible development of lymphoma and skin cancer may result from immunosuppression (see Warnings and Precautions – Carcinogenesis and Mutagenesis, and Immune/ Infection).
- Only physicians experienced in immunosuppressive therapy and management of organ transplant should prescribe ODVenta (tacrolimus extended release capsules). Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient and should be consulted if a patient is converted to an alternative formulation so that therapeutic drug monitoring can be instituted.

DOSAGE AND ADMINISTRATION

Dosing Considerations

ODVenta is a once-a-day oral formulation of tacrolimus. ODVenta therapy requires careful monitoring by adequately qualified and equipped personnel. The medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients.

Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate release or extended release tacrolimus formulations, have been observed. This has led to serious adverse events, including graft rejection, or other side effects 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.

Following conversion to any alternative formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained

Patients converting from immediate release formulation to ODVenta extended release formulation should be administered a single daily morning dose of ODVenta equivalent to the patient's previous stable total daily dose of immediate release formulation. Subsequent doses of ODVenta should be adjusted in order to maintain trough concentrations similar to those prior to conversion.

Due to intersubject variability following dosing with tacrolimus, individualization of the dosing regimen is necessary for optimal therapy.

ODVenta is to be used concomitantly with adrenal corticosteroids and mycophenolate mofetil (MMF)/ Azathioprine in de novo renal transplant recipients. Antibody induction therapy should be used in kidney transplant recipients. ODVenta is to be used concomitantly with adrenal corticosteroids in de novo liver transplants

Recommended Dose and Dosage Adjustment

The recommended starting oral dose of Tacrolimus extended release capsules for kidney transplant patients is 0.15 to 0.2 mg/kg and for liver transplant patients 0.10-0.20 mg/kg administered once daily in the morning. The initial dose of ODVenta should be administered within 24 hours of kidney transplantation and within 12-18 hours of liver transplantation. Dosing should be titrated to maintain the whole blood trough concentration levels noted above

Conversion from immediate release formulation to ODVenta (extended release formulation)

Stable kidney and liver transplant recipients can be converted from IR twice daily Tacrolimus formulation to once-daily ODVenta (extended release formulations). Patients converting from IR Tacrolimus to ODVenta should be administered a single daily morning dose of ODVenta (extended release formulation) equivalent to the patient's previous stable total daily dose of IR formulation. The same target trough range and whole blood trough concentration monitoring should be used as with immediate release formulation in order to maintain whole blood trough concentrations of tacrolimus similar to those prior to conversion

In a liver conversion adult study from IR Tacrolimus to extended release formulation (n=62), the ER dose adjustments were needed in approximately 16% of patients in the early conversion period. After conversion, it is strongly recommended that the tacrolimus blood trough be monitored every 4-7 days until stable within the desired therapeutic range

Patients with Hepatic or Renal Dysfunction

Extended release Tacrolimus formulation has not been studied in patients with hepatic or renal dysfunction; the following are based on experiences obtained from use of IR formulation

Due to the reduced clearance and prolonged half-life, patients with severe hepatic impairment (Pugh ≥ 10) may require lower doses of ER Tacrolimus. Close monitoring of blood concentrations is warranted. Due to the potential for nephrotoxicity in patients with renal or hepatic impairment, these patients should receive doses at the lowest value of the recommended oral dosing range. Further reductions in dose below these ranges may be required.

Administration

ODventa can be administered with or without food; however, doses should be administered in a consistent manner (see Action and Clinical Pharmacology).

OVERDOSAGE

For management of a suspected drug overdose, please contact your nearest Health care centre without delay

Limited overdosage experience with tacrolimus is available

An overdosage of 5 times the intended dose has been reported with ER Tacrolimus, followed by an adverse event of hypomagnesaemia that was successfully treated with medication.

Acute overdosages of up to 30 times the intended dose have been reported with IR (immediate release) formulation. Almost all cases have been asymptomatic and all patients recovered with no sequelae. Occasionally, acute overdosage has been followed by adverse reactions consistent with those listed in the adverse reactions section except in one case where transient urticaria and lethargy were observed. Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus is not dialyzable to any significant extent; there is no experience with charcoal hemoperfusion. The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdosage

DOSAGE FORM, STRENGTHS, COMPOSITION AND PACKAGING

ODVenta is available in an extended release capsule, once a day. Each capsule contains 0.5 mg and 1mg of tacrolimus.

Presentation : Pack of 10 capsules

WARNING AND PRECAUTIONS

General

Switching of immediate release formulation or ODventa (extended release formulation) should be done under supervision of a transplant specialist. Inadvertent, unintentional or unsupervised switching of IR or ER formulations of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of side effects, including under- or over-immunosuppression, due to clinically relevant differences in systemic 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 (see Dosage and Administration).

Following conversion to any alternative formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

In de novo kidney and liver transplant patients, AUC0-24 of tacrolimus for ER (extended release) formulation on day 1 is significantly lower in comparison with that for IR (immediate release) formulation at equivalent doses. By day 4, tacrolimus exposure as measured by trough levels is similar for both formulations. All patients in the

clinical kidney de novo studies received antibody induction therapy. All patients in the clinical liver de novo studies received adrenal corticosteroids with ER Tacrolimus formulation. ER Tacrolimus is approved to be used in combination with adrenal corticosteroids and MMF in de novo kidney patients and approved to be used with adrenal corticosteroids in de novo liver patients.

In clinical studies for stable patients converted from immediate release formulation to extended release formulation on 1 : 1 (mg : mg) total daily dose basis, up to one-third of patients required dose adjustment after conversion during the early conversion period due to dosing errors, adverse events, or whole blood trough levels outside the target range. Tacrolimus whole blood trough levels should be measured and closely monitored prior to and after conversion. Conversion to ER Tacrolimus formulation has primarily been studied from immediate release formulation in combination with adrenal corticosteroids and MMF based on equivalent tacrolimus whole blood trough concentrations.

Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P450 system (CYP3A). Tacrolimus does not induce or inhibit CYP3A4 or any other major CYP isoenzymes.

Since tacrolimus is metabolized mainly by the cytochrome P450 3A enzyme systems, substances known to inhibit these enzymes may decrease the metabolism or increase bioavailability of tacrolimus with resultant increases in whole blood or plasma levels. Whole blood concentrations of tacrolimus are markedly increased when co-administered with telaprevir and boceprevir (see Drug Interactions). Drugs known to induce these enzyme systems may result in an increased metabolism of tacrolimus or decreased bioavailability as indicated by decreased whole blood or plasma levels. Monitoring of blood levels and appropriate dosage adjustments in transplant patients are essential when such drugs are used concomitantly (see Drug Interactions).

Carcinogenesis and Mutagenesis

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphomas and carcinomas of the skin. As with other immunosuppressive therapies, the risk of developing lymphomas and other malignancies, particularly of the skin, may be higher in ER Tacrolimus formulation recipients than in the normal, healthy population. This risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

Lymphoproliferative disorders associated with Epstein-Barr Virus infection have been seen with tacrolimus. It has been reported that reduction or discontinuation of immunosuppression may cause the lesions to regress.

No evidence of genotoxicity was seen in bacterial (Salmonella and E. coli) or mammalian (Chinese hamster lung-derived cells) in vitro assays of mutagenicity, the in vitro CHO/HGPRT assay of mutagenicity, or in vivo clastogenicity assays performed in mice; tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.

Cardiovascular

Heart failure, myocardial hypertrophy and arrhythmia have been reported in association with the administration of IR Tacrolimus formulation

Hypertension is a common adverse effect of tacrolimus therapy (see Adverse Reactions). Mild or moderate hypertension is more frequently reported than severe hypertension. Antihypertensive therapy may be required; the control of blood pressure can be accomplished with any of the common antihypertensive agents. Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics should be avoided. Tacrolimus should be discontinued in patients in whom hypertension and hyperkalemia cannot be controlled.

While calcium-channel blocking agents can be effective in treating tacrolimus-associated hypertension, care should be taken since interference with tacrolimus metabolism may require a dosage reduction (see Drug Interactions).

Myocardial hypertrophy has been reported in association with the administration of tacrolimus as immediate release formulation, and is generally manifested by echocardiographically demonstrated concentric increases in left ventricular posterior wall and interventricular septum thickness. Hypertrophy has been observed in infants, children and adults. This condition appears reversible in most cases following dose reduction or discontinuance of therapy. In a group of 20 patients with pre- and post-treatment echocardiograms who showed evidence of myocardial hypertrophy, mean tacrolimus whole blood concentrations during the period prior to diagnosis of myocardial hypertrophy ranged from 11 to 53 ng/mL in infants (n=10, age 0.4 to 2 years), 4 to 46 ng/mL in children (n=7, age 2 to 15 years) and 11 to 24 ng/mL in adults (n=3, age 37 to 53 years).

In patients who develop renal failure or clinical manifestations of ventricular dysfunction while receiving tacrolimus therapy, echocardiographic evaluation should be considered. If myocardial hypertrophy is diagnosed, dosage reduction or discontinuation of tacrolimus should be considered.

Tacrolimus may prolong the QT interval and may cause Torsade de Pointes. Caution should be exercised in patients with known risk factors for QT prolongation (including but not limited to, congenital or acquired QT prolongation and concomitant medications known to prolong the QT interval or known to increase tacrolimus exposure) (see Drug Interactions).

Gastrointestinal

Gastrointestinal perforation has been reported in patients treated with tacrolimus, although all cases were considered a complication of transplant surgery or were accompanied by infection, diverticulum, or malignant neoplasm. As gastrointestinal perforation may be serious or life-threatening, appropriate medical/surgical management should be instituted promptly (see Adverse Reactions).

Hematologic

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. A mechanism for tacrolimus induced PRCA has not been elucidated. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease or concomitant medications associated with PRCA. If PRCA is diagnosed, discontinuation of tacrolimus should be considered.

Hepatic/Biliary/Pancreatic

ER Tacrolimus was shown to cause new onset diabetes mellitus in clinical trials of kidney transplant patients. New onset diabetes after transplantation (NODAT) may be reversible in some patients. Black and Hispanic kidney transplant patients are at an increased risk. Blood glucose concentrations should be monitored frequently in patients using ODVenta (see Adverse Reactions).

Immune/Infection

A lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. The risk of LPD appears greatest in young children who are at risk for primary EBV infection while immunosuppressed or who are switched to ER formulation following long-term immunosuppression therapy. Because of the danger of oversuppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy other than corticosteroids and MMF is not recommended.

Immunosuppressed patients are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including infection reactivation (e.g. Hepatitis B reactivation) and opportunistic infections, including latent viral infections. These include BK virus-associated nephropathy and JC virus-associated progressive multifocal leukoencephalopathy (PML) which have been observed in patients receiving tacrolimus. These infections are often related to a high immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

Cytomegalovirus (CMV) Infections

Patients receiving immunosuppressants, including ER Tacrolimus, are at increased risk of developing CMV viremia and CMV disease. The risk of CMV disease is highest among transplant recipients seronegative for CMV at time of transplant who receive a graft from a CMV seropositive donor. Therapeutic approaches to limiting CMV disease exist and should be routinely provided. Patient monitoring may help detect patients at risk for CMV disease. Consideration should be given to reducing the amount of immunosuppression in patients who develop CMV viremia and/or CMV disease.

Neurologic

Tacrolimus can cause neurotoxicity, particularly when used in high doses. Nervous system disorders, including tremor, headache, and other changes in motor function, mental status, and sensory function were reported in 63.1% of de novo kidney transplant recipients. Tremor occurred in 35.0% of ER Tacrolimus formulation-treated kidney transplant patients compared to 19.8% of Cyclosporine treated kidney transplant patients. The incidence of other neurological events in kidney transplant patients was similar in the two treatment groups (see Adverse Reactions). Tremor and headache have been associated with high whole blood concentrations of tacrolimus and may respond to dosage adjustment. Seizures have occurred in adult and pediatric patients receiving tacrolimus as IR formulation. Coma and delirium also have been associated with high plasma concentrations of tacrolimus received as IR formulation

Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). Symptoms indicating PRES include headache, altered mental status, seizures, and visual disturbances. Diagnosis should be confirmed by radiological procedure (e.g., MRI). If PRES is suspected or diagnosed, blood pressure and seizure control and immediate discontinuation of immunosuppression is advised. Most patients completely recover after appropriate measures are taken.

Tacrolimus may cause visual and neurological disturbances. No studies have been performed on the effects of tacrolimus on the ability to drive and use machines.

Renal

Tacrolimus can cause nephrotoxicity, particularly when used in high doses. Renal and urinary disorders were reported in 36.9% of de novo kidney transplantation patients and 50% of de novo liver transplantation patients receiving ER Tacrolimus. In de novo kidney transplant recipients, increased creatinine was reported in 18.7% of ER Tacrolimus -treated patients and 22.6% of Cyclosporine treated patients (see Adverse Reactions). More overt toxicity is seen early after transplantation, characterized by increasing serum creatinine and a decrease in urine output. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced. In patients with persistent elevations of serum creatinine who are unresponsive to dosage adjustments, consideration should be given to changing to another immunosuppressive therapy. Care should be taken in using tacrolimus with other nephrotoxic drugs.

Mild to severe hyperkalemia was reported in 22.0% of kidney de novo transplant recipients treated with ER Tacrolimus and may require treatment (see Adverse Reactions). Serum potassium levels should be monitored. Potassium-sparing diuretics should not be used and high intake of potassium should be avoided during ODVenta therapy

The use of ODVenta (extended release formulation) in liver transplant recipients experiencing post-transplant hepatic impairment may be associated with increased risk of developing renal insufficiency related to high whole blood levels of tacrolimus. These patients should be monitored closely and dose adjustment should be considered (see Dosage and Administration).

Sexual Function/Reproduction

In reproduction studies in rats and rabbits, adverse effects on the fetus were observed mainly at dose levels that were toxic to dams. However, in female rats dosed during organogenesis, embryo toxicity (expressed as reduced

pup weights) was seen at a dose which was one-third of the maternally toxic dose. At this same dose, when administered prior to mating and during gestation, tacrolimus was associated with adverse effects on female reproductive parameters and embryolethality. This dose was equivalent to 0.5X the clinical dose. (See Warnings and Precautions - Special Populations).

Special Populations

Pregnant Women

ODVenta (extended release formulation) should not be used during pregnancy unless the potential benefit to the mother outweighs potential risk to the fetus (See Detailed Pharmacology - Human Studies and Toxicology - Reproductive and Developmental Toxicity). There are no adequate and well-controlled studies in pregnant women. Tacrolimus is transferred across the placenta and infants exposed to tacrolimus in utero may be at a risk of prematurity, birth defects/congenital anomalies, low birth weight, and fetal distress. The use of tacrolimus during pregnancy has been associated with preterm delivery, neonatal hyperkalemia and renal dysfunction.

Tacrolimus may increase hyperglycemia in pregnant women with diabetes (including gestational diabetes). Monitor maternal blood glucose levels regularly.

Tacrolimus may exacerbate hypertension in pregnant women and increase pre-eclampsia. Monitor and control blood pressure. Females and males of reproductive potential should consider the use of appropriate contraception prior to starting treatment with tacrolimus.

Breast feeding

Tacrolimus is excreted in human milk. The effects of tacrolimus on the breastfed infant, or on milk production have not been assessed. As detrimental effects on the newborn cannot be excluded, women should not breastfeed while receiving tacrolimus.

Pediatrics (< 18 years of age)

Heart failure, cardiomegaly and increased thickness of the myocardium have been reported in patients taking tacrolimus.

Geriatrics (≥ 65 years of age)

No formal studies have been performed to evaluate the effect of tacrolimus specifically in the geriatric population.

Monitoring and Laboratory Tests

Serum creatinine, potassium, and fasting glucose should be assessed regularly. Routine monitoring of metabolic and hematologic systems should be performed as clinically warranted.

Blood Concentration Monitoring

Monitoring of tacrolimus blood levels in conjunction with other laboratory and clinical parameters is considered an essential aid to transplant patient management. During the immediate post-operative period, trough blood concentrations should be measured every 1-3 days. Tacrolimus doses are usually reduced in the post-transplant period. In patients with hepatic or renal dysfunction, or in those receiving or discontinuing concomitant interacting medications, more intensive monitoring may be required, since tacrolimus clearance may be affected under each of these circumstances. More frequent monitoring may also be required in patients early after transplantation since it is at this time patients experience the highest risk of rejection. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies. Following discharge from the hospital, the frequency of patient monitoring will decrease with time post-transplant.

Methods commonly used for the assay of tacrolimus include high performance liquid chromatography with tandem mass spectrometric detection (HPLC/MS/MS), enzyme immunoassay (EIA), microparticle enzyme immunoassay (MEIA), and enzyme-linked immunosorbent assay (ELISA). Comparison of the concentrations in

published literature to patient concentrations using the current assays must be made with detailed knowledge of the assay methods and biological matrices employed. Whole blood is the matrix of choice and specimens should be collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anti-coagulant. Heparin anti-coagulation is not recommended because of the tendency to form clots on storage. Samples which are not analyzed immediately should be stored at room should be deep frozen at -20°C for up to 12 months.

Data from kidney and liver transplant recipients receiving tacrolimus administered as IR (immediate release) formulation indicate that trough concentrations of tacrolimus in whole blood, as measured by IMx® MEIA (kidney) and ELISA (liver), were most variable during the first week of dosing, and the relative risk of toxicity is increased with higher whole blood trough concentrations. Therefore, monitoring of whole blood trough concentrations is recommended to assist in the clinical evaluation of toxicity. Long-term post-transplant patients often are maintained at the low end of the recommended target range. For stable transplant recipients converted from IR (immediate release) formulation to ODVenta (extended release formulation), the same type of therapeutic monitoring can be used.

ADVERSE REACTIONS

Overview

The most common adverse reactions reported were infection, tremor, hypertension, decreased renal function, constipation, diarrhea, headache, abdominal pain and insomnia. Many of these adverse reactions were mild and responded to a reduction in dosage. Insulin-dependent post-transplant diabetes mellitus (PTDM) was related to increased whole blood trough concentrations of tacrolimus and higher doses of corticosteroids. The median time to onset of PTDM was 68 days.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Kidney

In a large (n=668), phase III, randomized, comparative trial, de novo kidney transplant recipients received either extended release Tacrolimus formulation plus mycophenolate mofetil (MMF) or immediate release Tacrolimus formulation plus MMF or Cyclosporine plus MMF. All three regimens included corticosteroids and basiliximab induction. The incidence of adverse events that occurred in ≥15% of ER Tacrolimus-treated de novo kidney transplant recipients is shown in Table 2 below.

Table 2 : De Novo Kidney Transplantation : Adverse Events Occurring in ≥ 15% of ER Tacrolimus (tacrolimus extended release capsules) + MMF Treated Patients

	Immediate release + MMF N = 212 (% Patients)	Extended release + MMF N = 214 (% Patients)	Cyclosporine + MMF N = 212 (% Patients)
Gastrointestinal Disorders			
Diarrhea	44.3%	45.3%	25.5%
Nausea	38.7%	42.1%	46.7%
Constipation	35.8%	41.6%	41.0%
Vomiting	25.5%	26.2%	24.5%
Dyspepsia	17.9%	15.0%	15.1%

Injury, Poisoning and Procedural Complications			
Post-procedural pain	28.8%	29.4%	27.4%
Incision site complication	28.3%	20.6%	23.1%
Metabolism and Nutritional Disorders			
Hypomagnesemia	28.3%	25.7%	22.2%
Hypophosphatemia	27.8%	23.8%	21.2%
Hyperkalemia	25.5%	22.0%	19.3%
Hyperglycemia	21.2%	19.2%	15.1%
Hyperlipidemia	17.5%	16.4%	24.5%
Hypokalemia	16.0%	15.9%	17.5%
Infections and Infestations			
Urinary tract infection	25.5%	15.9%	22.2%
General Disorders and Administration Site Conditions			
Edema peripheral	34.9%	35.5%	45.8%
Fatigue	10.8%	15.9%	12.3%
Nervous System Disorder			
Tremor	34.4%	35.0%	19.8%
Headache	24.1%	21.5%	24.5%
Investigations			
Blood creatinine increased	23.1%	18.7%	22.6%
Blood and Lymphatic System Disorders			
Anemia	30.2%	33.6%	27.8%
Leukopenia	15.6%	16.4%	11.8%
Vascular Disorders			
Hypertension	32.1%	29.9%	34.9%
Musculoskeletal and Connective Tissue Disorders			
Back pain	12.7%	15.0%	14.2%
Psychiatric Disorders			
Insomnia	30.2%	25.7%	21.2%

Liver

In a phase III (n=467), randomized, double-blind comparative trial, de novo liver transplant recipients received either ER Tacrolimus (0.2 mg/kg/day) or IR Tacrolimus (0.1 mg/kg/day in two divided doses). Both regimens included corticosteroids. The incidence of adverse events that occurred in ≥ 15% of ER Tacrolimus -treated de novo liver transplant recipients is shown in Table 3. The most common events among recipients who received ER Tacrolimus (≥ 15% of patients in the ER Tacrolimus group) were anemia, diarrhea, hyperglycemia, hypertension, pleural effusion, pyrexia, renal insufficiency and thrombocytopenia

Table 3 : De novo liver transplantation : Adverse events occurring in ≥ 15% of ER Tacrolimus or IR Tacrolimus treated patients incidence of most frequently reported adverse events regardless of relationship to study medication

	ER Tacrolimus (N=237) Patients (%)	IR Tacrolimus (N=234) Patients (%)
Blood and lymphatic system disorders		
Anaemia	31.2%	30.8%
Thrombocytopenia	15.2%	16.2%
Gastrointestinal disorders		
Diarrhoea	24.9%	18.4%
General disorders and administration site conditions		
Pyrexia	17.3%	17.5%
Metabolism and nutrition disorders		
Hyperglycaemia	18.6%	22.6%
Renal and urinary disorders		
Renal insufficiency	24.5%	23.1%
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	15.2%	17.9%
Vascular disorders		
Hypertension	30.8%	32.5%

The following adverse events were also reported in clinical studies of solid organ transplant recipients who were treated with ER Tacrolimus at a frequency of ≥ 3% to <15%.

Blood and Lymphatic System Disorders : leukopenia, secondary anemia, leukocytosis, pancytopenia

Cardiac Disorders : atrial fibrillation, tachycardia

Gastrointestinal Disorders : abdominal pain, abdominal pain upper, ascites, constipation, dyspepsia, flatulence, gastroenteritis, nausea, vomiting

General Disorders and Administration Site Conditions : asthenia, chest pain, edema, peripheral edema, pyrexia, pain

Hepatobiliary Disorders : bile duct stenosis, cholestasis, cytolytic hepatitis, hepatic artery stenosis, hyperbilirubinemia

Infections and Infestations : bacterial urinary tract infection, bacterial pneumonia, bacterial sepsis, biliary tract infection, cytomegalovirus infection, hepatitis C, herpes simplex, influenza, nasopharyngitis, pneumonia, sinusitis, upper respiratory tract infection, wound infection

Injury, Poisoning and Procedural Complications : graft dysfunction, incision site complication, necrotic preservation injury or graft, post-procedural bile leak

Investigations : abnormal liver function test, increased blood glucose, increased blood creatinine, hepatic enzyme increased, hepatitis C virus

Metabolism and Nutrition Disorders : dehydration, metabolic acidosis, hyperkalemia, hyperuricemia, noninsulin-dependent diabetes mellitus, hypoalbuminemia, hypocalcemia, hypokalemia, diabetes mellitus, hypomagnesemia, hyperlipidemia, hyponatremia, insulin-dependent diabetes mellitus

Musculoskeletal and Connective Tissue Disorders : arthralgia, back pain, muscle spasm, pain in extremity including Calcineurin-Inhibitor Induced Pain Syndrome (CIPS)

Nervous System Disorders (see Warnings and Precautions) : dizziness, tremor, and headache

Psychiatric Disorders : agitation, anxiety, depression, confusional state, insomnia, psychotic disorder

Renal and Urinary Disorders (see Warnings and Precautions) : acute renal failure, hematuria, oliguria, renal impairment, renal insufficiency

Respiratory, Thoracic and Mediastinal Disorders : cough, dyspnea, pharyngolaryngeal pain, respiratory failure

Skin and Subcutaneous Tissue Disorders : acne, pruritus

Vascular Disorders : hypotension, hemorrhage.

Less Common Clinical Trial Adverse Drug Reactions (≥ 1% to < 3%)

The following adverse events were reported in clinical trials of solid organ transplant recipients treated with ER Tacrolimus at a frequency rate of ≥ 1% and < 3% :

Blood and Lymphatic System Disorders : bone marrow depression, coagulopathy, febrile neutropenia, neutropenia, polycythemia, thrombocytopenia

Cardiac Disorders : cardiac failure

Eye Disorders : vision blurred

Gastrointestinal Disorders : abdominal discomfort, abdominal distension, abdominal pain lower, gastritis, gastrooesophageal reflux disease, hemorrhoids, hernial eventration, loose stools, esophagitis, post-procedural nausea, toothache, umbilical hernia

General Disorders and Administration Site Conditions : anasarca, chest discomfort, fatigue, multi-organ failure, impaired healing, rigors

Hepatobiliary Disorders : hepatic artery thrombosis, hepatic steatosis, hepatic fibrosis, abnormal hepatic function, jaundice

Infections and Infestations : ascites, bacterial infections, bronchitis, candidiasis, cellulitis, diarrhea infections, Escherichia urinary tract infection, fungal infection, herpes zoster, herpes virus infection, human polyomavirus infection, liver abscess, lower respiratory tract infection, oral candidiasis, pharyngeal candidiasis, pharyngitis, pyelonephritis, respiratory moniliasis, respiratory tract infection, respiratory tract infection bacterial, sepsis, upper respiratory fungal infection

Injury, Poisoning, and Procedural Complications : anemia postoperative, anastomotic stenosis, complications of transplant surgery, contusion, drug toxicity, fall, hepatic hematoma, incisional hernia, overdose, post-procedural discharge, procedural hypotension, post-procedural hemorrhage, post-procedural pain, therapeutic agent toxicity, wound dehiscence, wound secretion

Investigations : blood alkaline phosphatase increased, blood bilirubin increased, blood glucose fluctuation, blood magnesium decreased, blood phosphorus decreased, blood potassium decreased, c-reactive protein increased, cardiac murmur, drug level decreased, drug level increased, gamma-glutamyltransferase increased, international normalized ratio increased, platelet count decreased, urine output decreased, weight decreased, weight increased, white blood cell count increased

Metabolism and Nutrition Disorders : acidosis, anorexia, decreased appetite, dehydration, dyslipidemia, fluid overload, glucose tolerance impaired, gout, hypercalcemia, hypercholesterolemia, hyperhomocysteinemia, hyperphosphatemia, hypophosphatemia, hypoglycemia, hypertriglyceridaemia

Musculoskeletal and Connective Tissue Disorders : joint swelling, myalgia, osteopenia, osteoporosis

Nervous System Disorders : convulsion, disturbance in attention, hypoesthesia, neurotoxicity, neuropathy, neuropathy peripheral, paraesthesia

Psychiatric Disorders : delirium, hallucination, restlessness

Renal and Urinary Disorders : dysuria, nephropathy toxic, proteinuria, pollakiuria, renal cyst, urethral pain

Reproductive System and Breast Disorders : erectile dysfunction, prostatic hypertrophy

Respiratory, Thoracic and Mediastinal Disorders : atelectasis, dyspnea exertional, epistaxis, hydrothorax, lung disorder, nasal congestion, pneumothorax, productive cough, pulmonary edema

Skin and Subcutaneous Tissue Disorders : alopecia, ecchymosis, hyperhidrosis, night sweats, rash, skin lesion, scar pain

Vascular Disorders : hematoma, hemodynamic instability, hot flush, orthostatic hypotension.

Post-Market Adverse Drug Reactions

The following adverse events have been reported from worldwide marketing experience with tacrolimus (Extended release formulation and/or immediate release formulation). Because these events are reported voluntarily from a population of uncertain size, are associated with concomitant diseases and multiple drug therapies and surgical procedures, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors : (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to the drug :

Blood and Lymphatic System Disorders : agranulocytosis, disseminated intravascular coagulation, eosinophilia, febrile neutropenia, hemolytic anemia, hemolytic-uremic syndrome, pure red cell aplasia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura

Cardiac Disorders : atrial flutter, cardiac arrhythmia, cardiac arrest, cardiac disorder, congestive cardiomyopathy, electrocardiogram T wave abnormal, myocardial infarction, myocardial ischemia, pericardial effusion, QT prolongation with or without Torsade de Pointes, venous thrombosis deep limb, ventricular extrasystoles, ventricular fibrillation

Ear and Labyrinth Disorders : hearing loss including deafness, tinnitus

Endocrine Disorders : hypothyroidism

Eye Disorders : blindness, blindness cortical, diplopia, eyelid edema, optic neuropathy, photophobia

Gastrointestinal Disorders : colitis, enterocolitis, gastrointestinal obstruction, gastrointestinal perforation, granulomatous liver disease, hepatocellular injury, impaired gastric emptying, liver fatty, mouth ulceration, Mikulicz's syndrome, pancreatitis hemorrhagic, pancreatitis necrotizing, stomach ulcer

General Disorders and Administration Site Conditions : disease recurrence, drug effect delayed, drug effect increased, drug ineffective, drug interaction, drug intolerance, fatigue, Feeling of body temperature change, feeling jittery, hot flushes, mobility decreased, multi-organ failure, thirst

Hepatobiliary Disorders : cholestasis of pregnancy, hepatic cytolysis, hepatic necrosis, hepatotoxicity, venoocclusive liver disease

Infections and Infestations : eczema infected, Escherichia, urinary tract infection, BK virus associated nephropathy

Injury, Poisoning and Procedural Complications : drug dispensing error, drug prescribing error, maternal exposure during pregnancy, medication error, primary graft dysfunction

Investigations : blood urea increased, drug level below therapeutic, drug level fluctuating, immunosuppressant drug level decreased, platelet count increased, transaminases increased

Metabolism and Nutrition Disorder : appetite disorder, diabetes mellitus inadequate control, glycosuria, hyperammonaemia, amylase increased, ketoacidosis

Musculoskeletal and Connective Tissue Disorders : immunoglobulin G4 related sclerosing disease, muscular weakness

Neoplasms benign, malignant and unspecified (including cysts and polyps) : breast cancer, haematological malignancy, hepatic neoplasm malignant, lung neoplasm malignant, pharyngeal cancer stage unspecified

Nervous System Disorders : aphasia, balance disorder, brachial plexopathy, carpal tunnel syndrome, cerebrovascular accident, cerebral infarction, encephalopathy, hemiparesis, incoherent, leukoencephalopathy, mononeuropathy multiplex, mutism, neuralgia, neurotoxicity, paraesthesia, peripheral nerve lesion, peripheral sensory neuropathy, polyneuropathy, posterior reversible encephalopathy syndrome (PRES), progressive multifocal leukoencephalopathy (PML), quadriplegia, somnolence, speech disorder, syncope, tremor

Psychiatric Disorders : intentional drug misuse, mental disorder

Renal and Urinary Disorders : albuminuria, cystitis hemorrhagic, glycosuria, hemolytic-uremic syndrome, micturition disorder, renal failure, renal failure chronic

Respiratory, Thoracic and Mediastinal Disorders : acute pulmonary edema, acute respiratory distress syndrome, interstitial lung disease, lung infiltration, respiratory distress

Skin and Subcutaneous Tissue Disorders : dermatosis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Vascular Disorders : flushing.

There have been rare spontaneous reports of myocardial hypertrophy associated with clinically manifested ventricular dysfunction in patients receiving (immediate release formulation) therapy (see Warnings and Precautions).

DRUG INTERACTIONS

Overview

Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P450 system (CYP3A). Tacrolimus does not induce or inhibit CYP3A4 or any other major CYP isoenzymes. Tacrolimus dose reductions and prolongation of dosing interval may be required when co-administered with strong CYP3A4 inhibitors, particularly telaprevir and boceprevir (Refer to Table 4). Close monitoring of tacrolimus blood levels, renal function and other side effects (including ECG monitoring for QT prolongation) is strongly recommended when administered with strong CYP3A4 inhibitors.

Drug-Drug Interactions

Drug Interactions Potentially Affecting Renal Function

Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering ODVenta with drugs that may be associated with renal dysfunction. These include, but are not limited to, aminoglycosides, amphotericin B, ganciclovir, acyclovir and cisplatin. NSAIDs may interact with ER Tacrolimus causing deteriorations in blood pressure (BP) control and serum creatinine levels. The half-life of cyclosporine has been shown to increase when tacrolimus is given simultaneously. Initial clinical experience with immediate release formulation and cyclosporine resulted in additive/synergistic nephrotoxicity when both agents were co-administered. 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.

Drug Interactions Potentially Affecting Tacrolimus Blood Concentrations

Since tacrolimus is metabolized mainly by the CYP3A (cytochrome P450 3A) enzyme systems, substances known to inhibit these enzymes may decrease the metabolism or increase bioavailability of tacrolimus with resultant increases in whole blood or plasma concentrations. Drugs known to induce these enzyme systems may result in an increased metabolism of tacrolimus or decreased bioavailability as indicated by decreased whole blood or plasma concentrations.

ODVenta and Vaccinations

Immunosuppressants may affect vaccination. Therefore, during treatment with ODVenta, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to, measles, mumps, rubella, oral polio, BCG, yellow fever and TY 21a typhoid.

Lack of Drug Interaction with ODVenta

At a given mycophenolate mofetil (MMF) dose, mycophenolic acid (MPA) exposure is higher with tacrolimus (immediate release formulation) co-administration than with cyclosporine co-administration due to the inhibitory action of cyclosporine on biliary excretion of MPA-glucuronide by MRP-2 and the resulting reduction in enterohepatic recirculation of MPA. As a result, exposure to MPA when mycophenolate mofetil is given in combination with cyclosporine is approximately 30-40% lower than that observed when given alone or with tacrolimus. No effect on enterohepatic MPA-glucuronide recirculation is exerted by tacrolimus; thus, clinicians should be aware that there is a potential for increased MPA exposure after crossover from cyclosporine to tacrolimus in patients concomitantly receiving MMF or mycophenolate sodium (MPS). Conversely, there is a potential for decreased MPA exposure after crossover from tacrolimus to cyclosporine in patients concomitantly receiving MMF or MPS.

Drug-Food Interactions

Grapefruit juice affects P450 3A-mediated metabolism and should be avoided.

Drug-Herb Interactions

St. John's Wort (Hypericum perforatum) induces CYP3A4 and P-glycoprotein. Since tacrolimus is a substrate for CYP3A4, there is the potential that the use of St. John's Wort in patients receiving ODVenta could result in reduced tacrolimus levels.

Schisandra sphenanthera extracts inhibit CYP3A4 and P-glycoprotein and may increase blood concentrations of tacrolimus.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using sunscreen with a high protection factor

Action and Clinical Pharmacology

Mechanism of action

Tacrolimus is a macrolide lactone immunosuppressant isolated from the fungus Streptomyces tsukubaensis and belongs to the pharmacotherapeutic group of calcineurin inhibitors.

At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compound. The FKBP12-tacrolimus

complex specifically and competitively binds to and inhibits calcineurin (calcium and calmodulin-dependant serine threonine phosphatase), leading to a calcium dependent inhibition of T-cell signal transduction pathways i.e. dephosphorylation and nuclear translocation of various nuclear factors such as cytosolic subunit of nuclear factor of activated T cells (NFAT) and nuclear factor kappa-light-chain-enhancer of activated B-cells (NFκB). Consequently, transcription of a discrete set of lymphokine gene including those encoding IL-2, IL-3, IL-4 IL-5, IFN- γ, GM-CSF, TNF-α and proto-oncogenes such as c-myc and c-rel- is suppressed. The suppression of T-cell activation inhibits the formation of cytotoxic lymphocytes, thereby downregulating processes that are responsible for acute graft rejection. Tacrolimus also inhibits T-helper cell dependant B-cell activation and proliferation."

Pharmacodynamics

Tacrolimus is a potent immunosuppressive agent and has proven activity in both in vitro and in vivo experiments. In particular, tacrolimus inhibits the formation of cytotoxic lymphocytes, which are mainly responsible for graft rejection. Tacrolimus suppresses T-cell activation and T-helper-cell dependent B-cell proliferation, as well as formation of lymphokines (such as interleukins [IL] -2, -3, and gamma-interferon) and the expression of the IL-2 receptor.

Pharmacokinetics

Absorption : Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable.

Distribution : The apparent volume of distribution (based on whole blood concentrations) of tacrolimus is approximately 1.91, 1.41 and 0.85 L/kg in healthy volunteers, kidney and liver transplant patients, respectively

The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5-50 ng/mL. Tacrolimus is bound to proteins, mainly albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration. In a U.S. study in which tacrolimus was administered as IR, the ratio of whole blood concentration to plasma concentration averaged 35 (range 12 to 67).

Metabolism : Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 enzyme system (CYP3A). A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation in vitro. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In in vitro studies, a 31-demethyl metabolite has been reported to have the same activity as tacrolimus; the 13-demethyl, 15-demethyl and 15- and 31- double-demethylated metabolites were shown to retain an activity of less than 10%.

Excretion : The mean clearance following IV administration of tacrolimus is 0.040, 0.083 and 0.053 L/hr/kg in healthy volunteers, adult kidney transplant patients and adult liver transplant patients respectively. In man, less than 1% of the dose administered is excreted unchanged in urine.

PART II :
SCIENTIFIC INFORMATION

ODVenta and Innovator brand have qualitatively a similar composition.

Both the formulations contain Hypromellose (Hydroxypropyl methyl cellulose; HPMC) and Ethyl cellulose both of which are well known drug release controlling polymers commonly used in pharmaceutical dosage forms for achieving sustained or extended drug release.

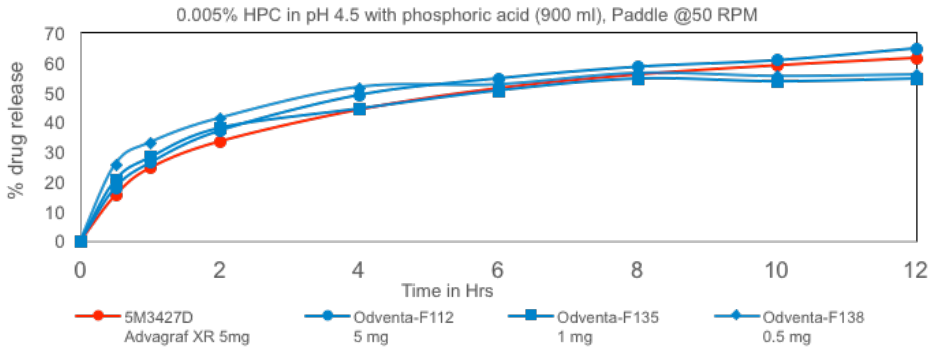
Hypromellose modifies the drug release profile by forming a hydrophilic gel layer, and Ethyl cellulose modifies the release profile by controlling water penetration.

Hence both ODVenta and Innovator brand exhibit a similar in-vitro dissolution profile

ODVenta – In-Vitro Comparison with Innovator brand

Ingredients	Innovator brand® 0.5 mg	ODVenta 0.5 mg	Innovator brand® 1 mg	ODVenta 1 mg
Tacrolimus	√	√	√	√
Ethyl cellulose	√	√	√	√
Hypromellose	√	√	√	√
Lactose monohydrate	51.09 mg	68.80 mg	102.17 mg	68.00 mg
Magnesium Stearate	√	√	√	√
Hard Gelatin Capsules	√	√	√	√
Total Weight	54.5 mg	70.0 mg	109.0 mg	70.0 mg

Comparative In-Vitro Dissolution Profile (OD formulations)



Drug release is well controlled in OD formulation as compared to Immediate Release formulation at 2 hrs. (approx. 35%)

Model Independent Approach Using Similarity Factor for Dissolution profile comparison :

Innovator brand Vs ODVenta	Dissolution Profiles are considered similar if values is between	ODVenta 5mg (F112)	ODVenta 1mg (F135)	ODVenta 0.5mg (F138)
Difference Factor (f_1)	0-15	4.6	2.6	3.1
Similarity Factor (f_2)	50-100	72.7	63.8	67.6

ODVenta – Bioequivalence Study

Study Title :

Single dose oral bioequivalence pilot study of Tacrolimus Extended Release Capsules 5mg and Innovator brand (Tacrolimus) Extended-Release Hard Gelatin Capsules 5mg in healthy adult human subjects under fasting conditions

Clinical & Bioanalytical Centre :

Cliantha Research Limited, Noida

Study Objective :

To compare and evaluate the oral bioavailability of Tacrolimus Extended Release Capsules 5mg with that of Innovator brand (Tacrolimus) Extended-Release Hard Gelatin Capsules 5mg in healthy, adult, human subjects under fasting conditions

To monitor the safety of the subjects

Sample Size :

14 healthy subjects

Study Design :

An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study.

Housing :

At least 11 hours prior to dosing until at least 24 hours post dose in each period.

Dosing Interval :

At least 21 days

Sampling Time Points

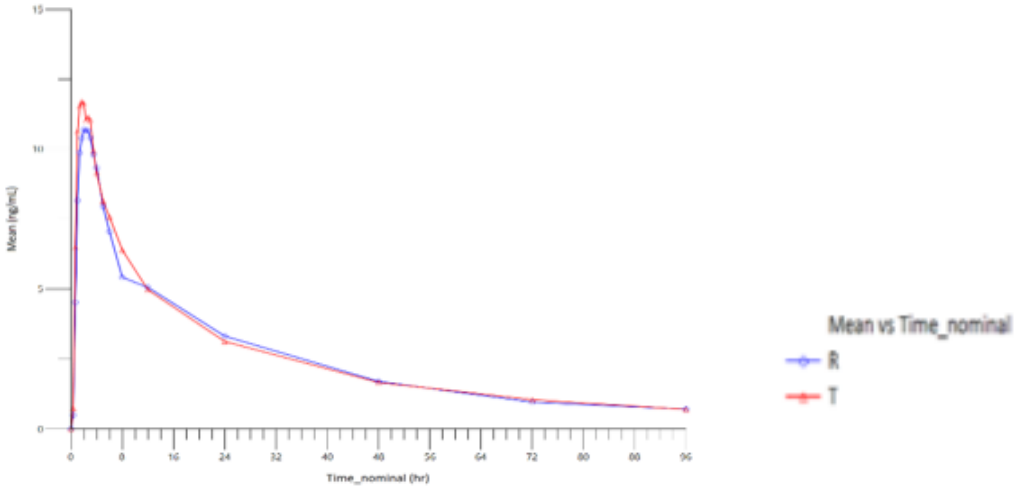
In each period, total 20 venous blood samples (04 mL each) were collected at pre-dose (0.0 hour) and at 0.333, 0.667, 1.0, 1.333, 1.667, 2.0, 2.333, 2.667, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, 48.0, 72.0 and 96.0 hrs

Results :

Innovator brand vs. ODVenta						
Dependent	**Units**	**Reference geometric least square mean**	**Test geometric least square mean**	**Ratio (% T/R)**	**90 % Lower Limit**	**90 % Upper Limit**
Ln (Cmax)	ng/mL	10.940	12.168	111.23	97.06	122.46
Ln (AUC last)	hr*ng/mL	213.591	223.883	104.82	91.38	120.23
Ln (AUCINF_obs)	hr*ng/mL	243.862	254.690	104.44	91.02	119.83
Tmax	hrs	2	1.667	Not applicable		

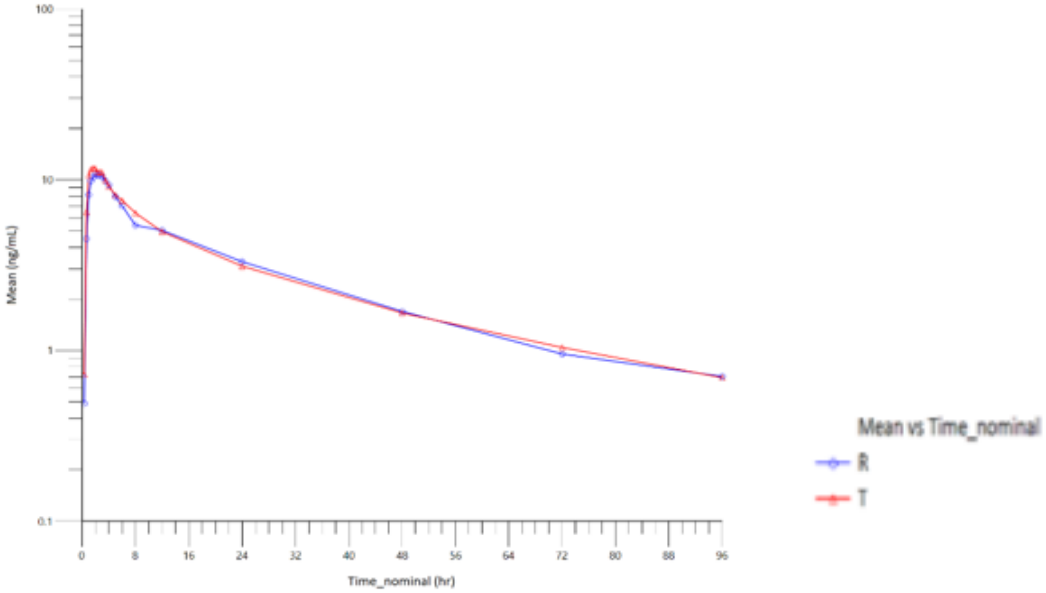
Results :

Linear Plot of Mean Plasma Concentrations versus Time Curves of Tacrolimus in healthy, adult, male, human subjects under fasting condition



Results :

Semi-log Plot of Mean Plasma Concentrations versus Time Curves of Tacrolimus in healthy, adult, male, human subjects under fasting condition



Safety :

- None of the subjects had any Serious Adverse Event during the study
- Adverse events were reported by 4 subjects during the conduct of the study :
  - One subject had increase in heart rate
  - One subject had rash
  - One subject had increase in Alanine Amino transferase
  - One subject had increase in Aspartate Amino transferase
- All the events were mild in severity, expected and resolved completely

Pharmacokinetics of ODVenta

Summary of Pilot Biostudy : Innovator Brand vs Odventa Capsules

Dependent	Units	Reference geometric least square mean	Test geometric least square mean	Ratio (% T/R)	90 % Lower Limit	90 % Upper Limit
Ln(Cmax)	ng/mL	10.940	12.168	111.23	97.06	122.46
Ln(AUC last)	hr*ng/mL	213.591	223.883	104.82	91.38	120.23
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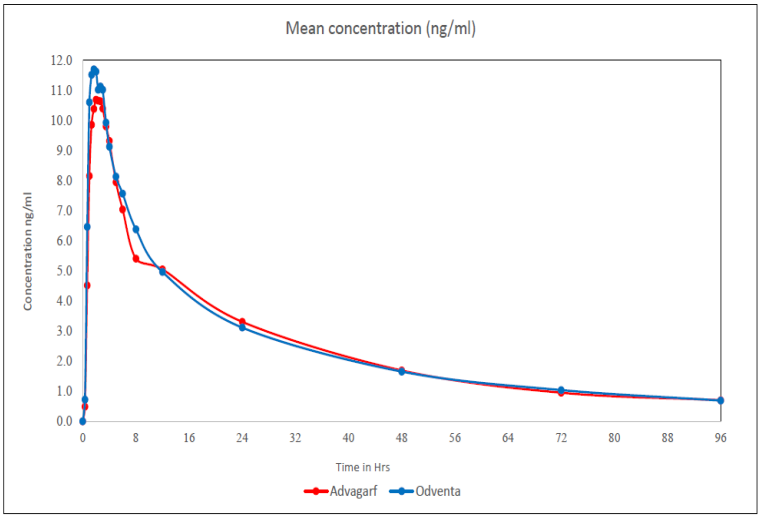
Tmax	Hrs	2	1.667	Not applicable		



Conclusion :

- Based on the in-vitro and the in-vivo comparisons with Innovator brand, it can be concluded that ODVenta is similar to the internationally approved product
- This once daily formulation will be useful especially in cases where non-adherence is major reason of poor drug efficacy.

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