הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 3102.50)

תאריך ___ December 15, 2014 ___

שם תכשיר באנגלית ומספר הרישום

_ PROGRAF 5 mg/ml Ampoules Concentrate for solution for infusion _

107 71 29160 00

שם בעל הרישום Salomon, Levin & Elstein Ltd, POBox 3696, Petach-Tikva 49133

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות

טקסט חדש	טקסט נוכחי	פרק בעלון
		Indication
		Contraindications
		Posology, dosage & administration
Substances with potential for interaction When substances with a potential for interaction (see section 4.5) - particularly strong inhibitors of CYP3A4 (such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) or inducers of CYP3A4 (such as rifampicin, rifabutin) – are being combined with tacrolimus, tacrolimus blood levels should be monitored to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure. Herbal preparations containing St. John's Wort (Hypericum perforatum) or other herbal preparations should be avoided when taking Prograf due to the risk of interactions that lead to decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus (see section 4.5 ~~Interactions with other medicinal products and other forms of interactions~~). The combined administration of ciclosporin and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see sections 4.2 and 4.5).	When substances with a potential for interaction (see section 4.5) - particularly strong inhibitors of CYP3A4 (such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) or inducers of CYP3A4 (such as rifampicin, rifabutin) – are being combined with tacrolimus, tacrolimus blood levels should be monitored to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure. Herbal preparations containing St. John's Wort (Hypericum perforatum) or other herbal preparations should be avoided when taking Prograf due to the risk of interactions that lead to decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus (see section 4.5 Interactions with other medicinal products and other forms of interactions). The combined administration of ciclosporin and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see sections 4.2 and 4.5).	**Special Warnings and Special Precautions for Use**

High potassium intake or potassium-sparing diuretics should be avoided (see section 4.5). Certain combinations of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see section 4.5). Vaccination Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided. Gastrointestinal disorders Gastrointestinal perforation has been reported in patients treated with tacrolimus. As gastrointestinal perforation is a medically important event that may lead to a life-threatening or serious condition, adequate treatments should be considered immediately after suspected symptoms or signs occur. Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea. ~~The combined administration of ciclosporin and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see sections 4.2 and 4.5).~~ Cardiac disorders Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed on rare occasions. Most cases have been reversible, occurring primarily in children 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, particularly young children and those receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at three months and then at 9-12 months). If abnormalities develop, dose reduction of Prograf therapy, or change of treatment to another immunosuppressive agent should be	Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed on rare occasions. Most cases have been reversible, occurring primarily in children 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, particularly young children and those receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at three months and then at 9-12 months). If abnormalities develop, dose reduction of Prograf therapy, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval but at this time lacks substantial evidence for caus ing Torsades de Pointes. Caution should be exercised in patients in patients diagnosed or suspected Congenital Long QT Syndrome Patients treated with Prograf have been reported to develop EBV-associated lymphoproliferative disorders. Patients switched to Prograf therapy should not receive anti-lymphocyte treatment concomitantly. Very young (< 2 years), EBV-VCA-negative children have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with Prograf. 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. 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 medications associated with PRCA. As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high	

considered. Tacrolimus may prolong the QT interval and may ~~but at this time lacks substantial evidence for~~ cause ~~ing~~ *Torsades 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, bradyarrhythmias and electrolyte abnormalities. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT Syndrome or acquired QT prolongation or patients on concomitant medications known to prolong the QT interval, induce electrolyte abnormalities or known to increase tacrolimus exposure (see section 4.5). Lymphoproliferative disorders and malignancies Patients treated with Prograf have been reported to develop Epstein-Barr-virus (EBV)-associated lymphoproliferative disorders (see section 4.8) . Patients switched to Prograf therapy should not receive anti-lymphocyte treatment concomitantly. Very young (< 2 years), EBV-VCA-negative children have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with Prograf. 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. As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8). Pure Red Cell Aplasia 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 medications associated with PRCA. ~~As with other immunosuppressive agents, owing to the potential risk of malignant skin~~	protection factor. As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8). Prograf 5 mg/ml concentrate for solution for infusion contains polyoxyethylene hydrogenated castor oil, which has been reported to cause anaphylactoid reactions. Caution is therefore necessary in patients who have previously received preparations containing polyoxyethylene castor oil derivatives either by intravenous injection or infusion, and in patients with an allergenic predisposition. The risk of anaphylaxis may be reduced by slow infusion of reconstituted Prograf 5 mg/ml concentrate for solution for infusion or by the prior administration of an antihistamine.	

~~changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.~~ ~~As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8).~~ Excipients Prograf 5 mg/ml concentrate for solution for infusion contains polyoxyethylene hydrogenated castor oil, which has been reported to cause anaphylactoid reactions. Caution is therefore necessary in patients who have previously received preparations containing polyoxyethylene castor oil derivatives either by intravenous injection or infusion, and in patients with an allergenic predisposition. The risk of anaphylaxis may be reduced by slow infusion of reconstituted Prograf 5 mg/ml concentrate for solution for infusion or by the prior administration of an antihistamine. Patients should be closely observed during the first 30 minutes of infusion for possible anaphylactoid reaction.		
Metabolic interactions Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. 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. It is therefore strongly recommended to closely monitor tacrolimus blood levels as well as, QT prolongation (with ECG), renal function and other side effects, whenever substances which have the potential to alter CYP3A4 metabolism are used concomitantly and to interrupt or adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4). Other interactions potentially leading to increased tacrolimus blood levels Tacrolimus is extensively bound to plasma proteins. 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 prokinetic agent metoclopramide, cimetidine a	Metabolic interactions Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. 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. It is therefore 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 are used concomitantly and to interrupt or adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4). Protein binding considerations Tacrolimus is extensively bound to plasma proteins. 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).	**Interaction with Other Medicaments and Other Forms of Interaction**

magnesium-aluminium-hydroxide. ~~Protein binding considerations~~ ~~Tacrolimus is extensively bound to plasma proteins. 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).~~		
		Fertility, Pregnancy and Lactation
The kidneys and the pancreas were the primary organs affected in toxicity studies performed in rats and baboons. In rats, tacrolimus caused toxic effects to the nervous system and the eyes. Reversible cardiotoxic effects were observed in rabbits following intravenous administration of tacrolimus. When tacrolimus is administered intravenously as rapid infusion/bolus injection at a dose of 0.1 to 1.0 mg/kg, QTc prolongation has been observed in some animal species. Peak blood concentrations achieved with these doses were above 150 ng/mL which is more than 6-fold higher than mean peak concentrations observed with Prograf in clinical transplantation. Embryofoetal toxicity was observed in rats and rabbits and was limited to doses that caused significant toxicity in maternal animals. In rats, female reproductive function including birth was impaired at toxic dosages and the offspring showed reduced birth weights, viability and growth. A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats.	The kidneys and the pancreas were the primary organs affected in toxicity studies performed in rats and baboons. In rats, tacrolimus caused toxic effects to the nervous system and the eyes. Reversible cardiotoxic effects were observed in rabbits following intravenous administration of tacrolimus. Embryofoetal toxicity was observed in rats and rabbits and was limited to doses that caused significant toxicity in maternal animals. In rats, female reproductive function including birth was impaired at toxic dosages and the offspring showed reduced birth weights, viability and growth. A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats.	**Preclinical Safety Data**
Infections and infestations As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Prograf. Neoplasms benign, malignant and unspecified (incl. cysts and polyps) Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant	Cardiac disorders common: ischaemic coronary artery disorders, tachycardia uncommon: ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, ECG investigations	**Adverse events**

neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment. Blood and lymphatic system disorders common: anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia not known: pure red cell aplasia, agranulocytosis, haemolytic anaemia Immune system disorders Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see section 4.4). Endocrine disorders rare: hirsutism Metabolism and nutrition disorders very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, anorexia, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia Psychiatric disorders very common: insomnia common: anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders uncommon: psychotic disorder	abnormal, heart rate and pulse investigations abnormal rare: pericardial effusion very rare: echocardiogram abnormal,, Blood and lymphatic system disorders common: anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia not known: pure red cell aplasia, agranulocytosis, haemolytic anaemia	

Nervous system disorders very common: tremor, headache common: seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders uncommon: coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia rare: hypertonia very rare: myasthenia	Nervous system disorders very common: tremor, headache common: seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders uncommon: coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia rare: hypertonia very rare: myasthenia	
Eye disorders common: vision blurred, photophobia, eye disorders uncommon: cataract rare: blindness	Eye disorders common: vision blurred, photophobia, eye disorders uncommon: cataract rare: blindness	
	Ear and labyrinth disorders common: tinnitus uncommon: hypoacusis rare: deafness neurosensory very rare: hearing impaired	
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Cardiac disorders common: ischaemic coronary artery disorders, tachycardia uncommon: ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, ECG investigations abnormal, heart rate and pulse investigations abnormal rare: pericardial effusion very rare: echocardiogram abnormal,, electrocardiogram QT prolonged, *Torsades de Pointes*	Vascular disorders very common: hypertension common: haemorrhage, thrombembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders uncommon: infarction, venous thrombosis deep limb, shock Skin and subcutaneous tissue disorders common: pruritus, rash, alopecia, acne, sweating increased uncommon: dermatitis, photosensitivity rare: toxic epidermal necrolysis (Lyell's syndrome) very rare: Stevens Johnson syndrome	
~~Blood and lymphatic system disorders~~ ~~common: anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood~~	Musculoskeletal and connective tissue disorders common: arthralgia, muscle cramps, pain in limb,	

cell analyses abnormal uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia not known: pure red cell aplasia, agranulocytosis, haemolytic anaemia Nervous system disorders very common: tremor, headache common: seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders uncommon: coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia rare: hypertonia very rare: myasthenia Eye disorders common: vision blurred, photophobia, eye disorders uncommon: cataract rare: blindness Ear and labyrinth disorders common: tinnitus uncommon: hypoacusis rare: deafness neurosensory very rare: hearing impaired	back pain uncommon: joint disorders Endocrine disorders rare: hirsutism Metabolism and nutrition disorders very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, anorexia, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia Infections and infestations As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Prograf. Neoplasms benign, malignant and unspecified (including cysts and polyps) Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment. Vascular disorders very common: hypertension common: haemorrhage, thromboembolic and	

Vascular disorders very common: hypertension common: haemorrhage, thrombembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders uncommon: infarction, venous thrombosis deep limb, shock Hepatobiliary disorders common: hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis rare: hepatitic artery thrombosis, venoocclusive liver disease very rare: hepatic failure, bile duct stenosis Skin and subcutaneous tissue disorders common: pruritus, rash, alopecias, acne, sweating increased uncommon: dermatitis, photosensitivity rare: toxic epidermal necrolysis (Lyell's syndrome) very rare: Stevens Johnson syndrome Musculoskeletal and connective tissue disorders common: arthralgia, muscle cramps, pain in limb, back pain uncommon: joint disorders Reproductive system and breast disorders uncommon: dysmenorrhoea and uterine bleeding General disorders and administration site conditions common: asthenic conditions, febrile disorders, oedema, pain and discomfort, blood alkaline phosphatase increased, weight increased, body temperature perception disturbed uncommon: multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased, weight decreased rare: thirst, fall, chest tightness, mobility decreased, ulcer very rare: fat tissue increased		ischaemic events, peripheral vascular disorders, vascular hypotensive disorders uncommon: infarction, venous thrombosis deep limb, shock General disorders and administration site conditions common: asthenic conditions, febrile disorders, oedema, pain and discomfort, blood alkaline phosphatase increased, weight increased, body temperature perception disturbed uncommon: multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased, weight decreased rare: thirst, fall, chest tightness, mobility decreased, ulcer very rare: fat tissue increased Immune system disorders Allergic and anaphylactoid reactions have	

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~~Skin and subcutaneous tissue disorders~~ ~~common: pruritus, rash, alopecia, acne, sweating increased~~ ~~uncommon: dermatitis, photosensitivity~~ ~~rare: toxic epidermal necrolysis (Lyell's syndrome)~~ ~~very rare: Stevens Johnson syndrome~~ ~~Musculoskeletal and connective tissue disorders~~ ~~common: arthralgia, muscle cramps, pain in limb, back pain~~ ~~uncommon: joint disorders~~ ~~Endocrine disorders~~ ~~rare: hirsutism~~ ~~Metabolism and nutrition disorders~~ ~~very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia~~ ~~common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, anorexia, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities~~ ~~uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia~~ ~~Infections and infestations~~ ~~As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur.~~ ~~Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Prograf.~~		

Injury, poisoning and procedural complications common: primary graft dysfunction ~~Neoplasms benign, malignant and unspecified (including cysts and polyps)~~ ~~Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment.~~ ~~Vascular disorders~~ ~~very common: hypertension~~ ~~common: haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders~~ ~~uncommon: infarction, venous thrombosis deep limb, shock~~ ~~General disorders and administration site conditions~~ ~~common: asthenic conditions, febrile disorders, oedema, pain and discomfort, blood alkaline phosphatase increased, weight increased, body temperature perception disturbed~~ ~~uncommon: multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased, weight decreased~~ ~~rare: thirst, fall, chest tightness, mobility decreased, ulcer~~ ~~very rare: fat tissue increased~~ ~~Immune system disorders~~ ~~Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see section 4.4).~~ ~~Hepatobiliary disorders~~ ~~common: hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis~~ ~~rare: hepatitic artery~~	Injury, poisoning and procedural complications common: primary graft dysfunction	

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