הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 3102.50)

תאריך ___ December 15, 2014 ___

שם תכשיר באנגלית ומספר הרישום

PROGRAF CAPSULES 0.5 mg, 1 mg, 5 mg

0.5 mg: 122 07 30215 00, 122 07 30215 11,

1 mg: 107 69 29158 00, 107 69 29158 11,

5 mg: 107 70 29159 00, 107 70 29159 11

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
Prograf 0.5 mg hard capsules Each capsule contains 0.5 mg of tacrolimus. Excipient with known effect: 62.85 mg of lactose. The printing ink used to mark the capsule contains trace amounts of soya lecithin (0.48% of total printing ink composition). Prograf 1 mg hard capsules Each capsule contains 1 mg of tacrolimus. Excipient with known effect: 61.35 mg of lactose. The printing ink used to mark the capsule contains trace amounts of soya lecithin (0.48% of total printing ink composition).	Prograf 0.5 mg hard capsules Each capsule contains 0.5 mg of tacrolimus. Excipient with known effect: 62.85 mg of lactose. Prograf 1 mg hard capsules Each capsule contains 1 mg of tacrolimus. Excipient with known effect: 61.35 mg of lactose.	**Qualitative and Quantitative Composition**
		Indication
		Contraindications
		Posology, dosage & administration
Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-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 (see sections 4.2 and 4.8).	Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-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 (see sections 4.2 and 4.8).	**Special Warnings and Special Precautions for Use**

~~Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-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 (see sections 4.2 and 4.8).~~ 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). 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	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). 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	

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 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) .	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 protection factor. As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8). As Prograf capsules contain lactose, special care should be taken in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.	

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 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 As Prograf capsules contain lactose, special care should be taken in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. The printing ink used to mark Prograf capsules 0.5 mg and 1mg contains soya lecithin. In patients who are hypersensitive to peanut or soya, the risk and severity of hypersensitivity should be weighed against the benefit of using Prograf.		
Metabolic interactions Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of	Metabolic interactions Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is	**Interaction with Other Medicaments and Other Forms of Interaction**

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 and 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).~~	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).	
		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	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**

growth. A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats.		
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 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,	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, 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	**Adverse events**

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 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 Cardiac disorders common: ischaemic coronary artery	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 Vascular disorders very common: hypertension	

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*

~~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~~

~~Eye disorders~~
~~common: vision blurred, photophobia, eye disorders~~
~~uncommon: cataract~~
~~rare: blindness~~

~~Ear and labyrinth disorders~~
~~common: tinnitus~~
~~uncommon: hypoacusis~~
~~rare: deafness neurosensory~~

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

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

~~very rare: hearing impaired~~ 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 ~~Skin and subcutaneous tissue disorders~~ ~~common: pruritus, rash, alopecia, acne, sweating increased~~	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.	

~~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~~ ~~Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. A number of associated cases of transplant rejection have been reported (frequency cannot be estimated from available data).~~ ~~Neoplasms benign, malignant and unspecified (including cysts and polyps)~~	<u>Injury, poisoning and procedural complications</u> common: primary graft dysfunction Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. A number of associated cases of transplant rejection have been reported (frequency cannot be estimated from available data).	

~~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.~~	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~~	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~~	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).~~	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~~	Hepatobiliary disorders common: hepatic enzymes and function abnormalities, cholestasis and jaundice,	

~~rare: hepatitic artery thrombosis, venoocclusive liver disease~~ ~~very rare: hepatic failure, bile duct stenosis~~	hepatocellular damage and hepatitis, cholangitis rare: hepatitic artery thrombosis, venoocclusive liver disease very rare: hepatic failure, bile duct stenosis	
~~Reproductive system and breast disorders~~ ~~uncommon: dysmenorrhoea and uterine bleeding~~	Reproductive system and breast disorders uncommon: dysmenorrhoea and uterine bleeding	
~~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~~	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	

הודעה על החמרה (מידע בטיחות) בעלון לצרכן

(מעודכן 3102.50)

תאריך ___ December 15, 2014 ___

שם תכשיר באנגלית ומספר הרישום

PROGRAF CAPSULES 0.5 mg, 1 mg, 5 mg

0.5 mg: 122 07 30215 00, 122 07 30215 11,

1 mg: 107 69 29158 00, 107 69 29158 11,

5 mg: 107 70 29159 00, 107 70 29159 11

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

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות

פרק בעלון	טקסט נוכחי	טקסט חדש
התוויות		
מתי אין להשתמש בתכשיר?		
אזהרות מיוחדות הנוגעות לשימוש בתרופה:		
אין להשתמש בתרופה מבלי להיוועץ ברופא לפני התחלת הטיפול:		- הדיו של הכיתוב המודפס על כמוסות פרוגרף 0.5 מ"ג ו- 1 מ"ג מכיל לציתין של סויה. במידה והינך רגיש לבוטנים או לסויה עליך להודיע לרופא אשר יחליט אם לרשום לך את התרופה. - אם הינך חש כאבי בטן עזים מלווים/לא מלווים בתופעות אחרות כגון צמרמורת, חום, בחילה או הקאה - ה- ECG שלך מצביע על שינוי בהולכה החשמלית הנקרא "הארכת זמן QT" - בחולים המטופלים בפרוגרף דווח על סיכון גובר של ליקוי ביצור רקמות הלימפה (lymphoproliferative disorders). יש להיוועץ ברופא.
תגובות בין תרופתיות:	• אומפרזול, לנסופרזול (נגד אולקוס)	• תרופות לטיפול באולקוס ובדלקת הוושט מזרם חוזר (כגון: אומפרזול, לנסופרזול ~~(נגד אולקוס)~~ • תרופות למניעת בחילות והקאות (כגון מטוכלופרמיד) • שילוב נוגדי חומצה מגנזיום ואלומיניום הידרוקסיד לטיפול בצרבת
הריון והנקה:		
כיצד תשתמש בתרופה:		
תופעות לוואי:	תופעות לוואי חמורות אשר דווחו כוללות תגובות אלרגיות ואנפילקטיות (רגישות יתר). כתוצאה מדיכוי מערכת החיסון,	~~תופעות לוואי חמורות אשר דווחו כוללות תגובות אלרגיות ואנפילקטיות (רגישות יתר). כתוצאה מדיכוי מערכת החיסון, דווחו גם גידולים שפירים וממאירים.~~

	דווחו גם גידולים שפירים וממאירים. **תופעות לוואי שכיחות (עלולות להשפיע עד ל-1 מתוך 10 מטופלים)** • ירידה בספירת תאי הדם (טסיות, תאי דם אדומים או לבנים), עליה בספירת תאי הדם הלבנים, שינויים בספירת תאי הדם האדומים. • ליקוים בתיפקוד האיבר המושתל. **תופעות לוואי נדירות (עלולות להשפיע עד ל-1 מתוך 1,000 מטופלים)** • מחלה חמורה עם שלפוחיות בעור, בפה, בעיניים ואיברי המין, שעירות יתר. דווחו מקרים של ירידה חדה בספירת כדוריות הדם האדומות (pure cell aplasia), ירידה חדה בכדוריות הדם הלבנות (agranulocytosis), וירידה במספר כדוריות הדם האדומות כתוצאה מפירוקם הלא תקין (haemolytic anaemia)	• תופעות לוואי חמורות עלולות להתרחש, מתוכם התופעות המופיעות מטה. במידה והינך חש או חושש מאחת התופעות הבאות עליך לפנות מיד לרופא: • זיהומים מזדמנים (על רקע בקטריאלי, פטרייתי, נגיפים, או חיידקים חד-תאים {protozoal}) • דווחו מקרים של גידולים שפירים וממאירים כתוצאה מטיפולי דחיית שתל • ירידה בטסיות הדם ותרומבוציטים (thrombotic thrombocytic purpura) – זהו מצב המתבטא בחום וחבלות תת-עוריות המופיעות כנקודות אדומות, יחד עם או בלי עייפות מוגברת וחריגה, בלבול, עור או עיניים צהובים (צהבת), ותופעות של אי ספיקה כליתית (מיעוט או עצירת שתן) • ירידה חדה בספירת כדוריות הדם האדומות (red cell aplasia) ואנמיה הימוליטית (פירוק חריג של כדוריות הדם האדומות מלווה בעייפות). בד בבד עם חומרת המחלה עלולות להופיע תופעות כגון: עייפות, תשישות, אדישות, חיוורון חריג של העור, קוצר נשימה, סחרחורות, כאבי ראש, כאבי חזה, ותחושת קור בידיים וברגליים). ירידה חדה במספר כדוריות הדם הלבנות מלוות בפצעים בפה, חום וזיהומים (agranulocytosis). יתכן ולא יופיעו סימנים או לחלופין הינך עלול לחוש באופן פתאומי בחום, צמרמורת, וכאב גרון. • תגובות אלרגיות ואנפילקטיות המתבטאות בתופעות הבאות: פריחה מגרדת פתאומית (חרלת), נפיחות בידיים, ברגליים, בקרסוליים, בפנים, בשפתיים, בפה או בגרון (העלולות לגרום לקשיי בליעה או נשימה) עם הרגשת עילפון. • תיסמונת Posterior Reversible Encephalopathy Syndrome,(PRES) : המתבטאת בכאבי ראש, שינוי מצב נפשי, פרכוסים, וטישטוש ראייה • רפרופים בלב מסוג Torsades de Pointes: זהו שינוי בקצב דופק הלב העלולים להיות מלווה בתופעות כגון כאבים בחזה (תעוקת חזה), עילפון, ורטיגו או בחילה , פעימות לב חזקות ומהירות, וקשיי נשימה. • ניקוב במערכת העיכול- מתבטא בכאבי בטן עזים העלולים להיות מלווים בתופעות אחרות כגון צמרמורת, חום, בחילה או הקאה. • תיסמונת Stevens-Johnson: כאב מתפשט וחריג בעור, נפיחות בפנים, מחלה חמורה עם שלפוחיות בעור, בפה, בעיניים ואיברי המין, גירוי חזק (חרלת), נפיחות בלשון, התפשטות של פריחת עור אדומה או סגולה, השלת עור. • תיסמונת Toxic epidermal necrolysis: שלפוחיות וגבשושיות בעור או ברקמה הרכה, עור אדום ונפוח העלול להיתלש מחלקים גדולים בגוף • תיסמונת המוליטית אורמית Hemolytic uremic syndrome: מתבטאת בתופעות הבאות: ירידה או עצירת שתן (אי ספיקת

		כליה), עייפות מוגברת, עור ועיניים צהובות (צהבת), וחבלות חריגות או דימום וסימני זיהומים. • ליקויים בתיפקוד האיבר המושתל. תופעות לוואי הבאות עלולות גם להתרחש לאחר השימוש בפרוגרף **תופעות לוואי שכיחות (עלולות להשפיע עד ל-1 מתוך 10 מטופלים)** • ~~ירידה בספירת תאי הדם (טסיות, תאי דם אדומים או לבנים), עליה בספירת תאי הדם הלבנים, שינויים בספירת תאי הדם האדומים.~~ • ~~ליקויים בתיפקוד האיבר המושתל.~~ **תופעות לוואי נדירות (עלולות להשפיע עד ל-1 מתוך 1,000 מטופלים)** • ~~מחלה חמורה עם שלפוחיות בעור, בפה, בעיניים ואיברי המין~~, שעירות יתר. ~~דווחו מקרים של ירידה חדה בספירת כדוריות הדם האדומות (pure cell aplasia), ירידה חדה בכדוריות הדם הלבנות (agranulocytosis), וירידה במספר כדוריות הדם האדומות כתוצאה מפירוקם הלא תקין (haemolytic anaemia)~~