הודעה על החמרה (מידע בטיחות) בעלון לרופא
(מעודכן 3102.50)

תאריך ___October 23, 2013___

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
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.		**Special Warnings and Special Precautions for Use**
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). Inhibitors of metabolism Clinically the following substances have been shown to increase tacrolimus blood levels:	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 recommended to monitor tacrolimus blood levels, whenever substances which have the potential to alter CYP3A4 metabolism are used concomitantly and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4). Inhibitors of metabolism Clinically the following substances have been shown to increase	**Interaction with Other Medicaments and Other Forms of Interaction**

Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin, ~~or~~ HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir) or HCV protease inhibitors (e.g. telaprevir, boceprevir).. Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients. Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, amiodarone, danazol, ethinylestradiol, omeprazole and nefazodone. In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen, troleandomycin. Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided.	tacrolimus blood levels: Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin, or HIV protease inhibitors (e.g. ritonavir, Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients. Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, danazol, ethinylestradiol, omeprazole and nefazodone. In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen, troleandomycin. Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided.	
Fertility A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats (see section 5.3).		**Fertility, Pregnancy and Lactation**
Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.		**Adverse events**

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