

11.2022

רופא/ה רוקח/ת נכבד/ה,  
ברצוננו להודיעך על עדכון בעלון לרופא של

## PROGRAF ampoules 5mg/ml

חומר פעיל:

Tacrolimus 5mg/ml

**להלן עדכונים בעלון לרופא (טקסט מסומן ירוק משמעותו עדכון, טקסט מסומן בצהוב משמעותו החמרה, טקסט מסומן באדום משמעותו מחיקה):**

[...]

### 4.4 Special warnings and precautions for use

[...]

#### ***P-glycoprotein***

Caution should be observed when co-administering tacrolimus with drugs that inhibit P-glycoprotein, as an increase in tacrolimus levels may occur. Tacrolimus whole blood levels and the clinical condition of the patient should be monitored closely. An adjustment of the tacrolimus dose may be required (see section 4.5).

[...]

#### Posterior reversible encephalopathy syndrome (PRES)

Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g., MRI) should be performed. If PRES is diagnosed, adequate blood pressure **and seizure** control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

[...]

#### **Thrombotic microangiopathy (TMA) (including haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP))**

The diagnosis of TMA, including thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS), sometimes leading to renal failure or a fatal outcome, should be considered in patients presenting with haemolytic anaemia, thrombocytopenia, fatigue, fluctuating neurological manifestation, renal impairment, and fever. If TMA is diagnosed, prompt treatment is required, and discontinuation of tacrolimus should be considered at the discretion of the treating physician.

The concomitant administration of tacrolimus with a mammalian target of rapamycin (mTOR) inhibitor (e.g., sirolimus, everolimus) may increase the risk of thrombotic microangiopathy (including haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura).

#### 4.5 Interaction with other medicinal products and other forms of interaction

[...]

Medicinal products which have effects on tacrolimus

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
Caspofungin	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection. Mechanism of interaction has not been confirmed.	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed [see section 4.2]. Monitor graft function closely.
Cannabidiol (P-gp inhibitor)	There have been reports of increased tacrolimus blood levels during concomitant use of tacrolimus with cannabidiol. This may be due to inhibition of intestinal P-glycoprotein, leading to increased bioavailability of tacrolimus.	Tacrolimus and cannabidiol should be co-administered with caution, closely monitoring for side effects. Monitor tacrolimus whole blood trough concentrations and adjust the tacrolimus dose if needed [see sections 4.2 and 4.4].

Concomitant administration of tacrolimus with a mammalian target of rapamycin (mTOR) inhibitor (e.g., sirolimus, everolimus) may increase the risk of thrombotic microangiopathy (including haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura) (see section 4.4).

[...]

#### 4.8 Undesirable effects

[...]

##### Blood and lymphatic system disorders

- common: anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal
- uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia, thrombotic microangiopathy
- rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia, thrombotic microangiopathy
- not known: pure red cell aplasia, agranulocytosis, haemolytic anaemia, febrile neutropenia

[...]

##### Investigations

- very common: liver function tests abnormal
- common: ~~hepatic enzymes and function abnormalities~~, blood alkaline phosphatase increased, weight increased

[...]

#### Metabolism and biotransformation

Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450-3A4 (CYP3A4) and the cytochrome P450-3A5 (CYP3A5). Tacrolimus is also considerably metabolised in the intestinal wall. There are several metabolites identified. Only one of these has been shown *in vitro* to have immunosuppressive activity similar to that of tacrolimus. The other metabolites have only weak or no immunosuppressive activity. In systemic circulation only one of the inactive metabolites is present at low concentrations. Therefore, metabolites do not contribute to pharmacological activity of tacrolimus.

[...]

העלון לרופא נשלחו למאגר התרופות שבאתר משרד הבריאות [www.health.gov.il](http://www.health.gov.il) לצורך העלאתם לאתר וניתן לקבלם מודפסים על ידי פניה לבעל הרישום אסטלס פארמה אינטרנשונל ביו.י., ראש העין, מספר טלפון: 03-7501166.

בברכה  
גל פרידמן  
רוקח ממונה