# Tacrograf<sup>®</sup>

### Tacrolimus

### FORMS AND PRESENTATION

. nyl methylcellulose maonesium stearate oelatin methyl naraben monyl naraben tartrazine titanium dioxide sodium la

....tc. tograf<sup>ts</sup> 1: Feesh tains Tacrolim

or contai nyl methylcellulose, magnesium stearate, gelatin, bril

mhon brilliont bloo oo

phale. rrograf<sup>10</sup> 5: Each capsule contains Tacrolimus 5mg. onvl methylcellulose maonesium stearate oelatin methyl n

dioxide, sodium lauryl sulphate. PHARMACOLOGICAL PROPERTIE

....record/ERTTE ...armacodynamic properties Therapeutic class: Immunosuppressants. ATC code: L04AD02. At the molecular level, the effects of Tacrolin The FKBP12-Tacrolinnas convolution proputation ATC code: LDADD2. Att molecular local, the effects of Tacrolinnus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compt. The FKBP12-Tacrolinnus complex expectically and competitively binds and inhibits calcinearin, leading to a calcium-dependent inhibition of T-cell signal transduction pathways, the provening transcription of adverts wire of cytosice genes. Tacrolinnus in highly plant immunoappressive agent and has proven activity in bothen in vitos acade in vice organization. Tacrolinnus appresses T-cell activation and T-helpe dependent T-cell proteines, as well as the formation of psyndhoines (tach as interchaines 2-3, and y-interfacion) and the expression of the interchaine? Acceptate

### etic propertie

Pharmacolinatic properties <u>Alcoration</u> In man Tacostimus has been shown to be able to be absorbed throughout the gashointelling tract. Following cell administration of Tacostimus capuales peak concentrations (C Tacostimus arbitocaus) advanced in approximately 1 - 3 hours. In some pairs, Tacostimus appears to be continuously absorbed over a prolonged peaked yielding architery of at ables Afor cell administration (D 3) may (absorb to be abbeed peaked). The pairs of the continuously absorbed over a prolonged peaked yielding architery of at ables Afor cell administration (D 3) may (absorb to be transplay patients, Rushy-date concentrations of Tacostimus were ablesed within 3 days in the majority of grants. The landary abjects Tacostimus D 5 mg. Excostimus (Inged Tacostimus) may capable able when hown to be becognitive, when administered acquired adso. The rest and extert of absorption of Tacostimus (Inged Tacostimus) may capable able becomes to be real-absorption of Tacostimus. A three accentation exclusive between AUC and whole bload tronggli levels at fanday-date: Monitoring of whole bload tronggli levels ago and grants of the approximate of systemic experiments. A three accentation exclusive between AUC and whole bload tronggli levels at fanday-date: Monitoring of whole bload tronggli levels ago and grants of systemic experiments of the spectration experiments of the produced as a specific data and a spectration experiments of the spectration of the spectration of the spectration of the spectration experiments of the spectratin experiments of the

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mately 1300 liters (healthy

data based on whose bood sevenged 4/3 intex. *Biogrammonical formation of the second sevenged 4/3 intervention of the stability of the stabil* 

activity. In systemic circulation only one of the inactive methodolies is present at low concentrations. Therefore, methololis do not contribute to pharmacological activity of Therefinate, Tacorlinna is a low-clearance subfinance. In healthy subject, the average test body clearance (TBC) estimated from whole blod concentrations was 225 hl. In shall liver, kidnes and there transplant patients, values of 4.1 ht, 6.7 ht and 3.91k, respectively, have been observed. Poliatic is not remapsive trajectoristar have a Tale agreement by twice that of a shall hive; transplant patients, relates of 4.1 ht, 6.7 ht and 3.91k, respectively, have been observed. Poliatic is not remapsive trajectoristar have a Tale agreement by twice that of a shall hive; transplant patients, Factors such as low hematocritic and protein its velve, which results in an increase in the surboard faction. Therefore, corticological contension its consequences in the surboard factor in Charorismus, is consequent to the surboard factor in the subset of the surboard factor in the surboard in the subset of the Higher consequences in the surboard factor in Charorismus, security decomposition is also used in the subset of the Higher consequences in the surboard factor in Charorismus is and und poliatric. For ransplant patients, the results in transplant patients, the results and talk blogs that the results and talk blogs trajectorismus have a Tale and the solar thalf-fit descering that in transplant patients, the respectively composition of this 150 km in altrice data in the subset that the laboard trajectorismus is trajectorismus in the solare that the solare trajectorism here are the constraints the the solare that differences in the solare that that the solare that the

recipients. Following introvenus and coll administration of VC-backed Taccolimus, most of the radioactivity was eliminated in the foces. Approximately 2 % of the radioactivity was eliminated the urine. Less than 1 % of unchanged Taccolimus was detected in the urine and foces, indicating that Taccolimus is almost completely metabolized prior to elimination: Bile being the

the urnne. Loss -principal route of elimination. INDICATIONS

rophylaxis of transplant rejection in liver, kidney or heart allograft recipients. nent of allograft rejection resistant to treatment with other immunosuppressive medicinal products It is also indicated in the treat CONTRAINDICATIONS

us or other macrolides.

- Hypersensitivity to any of the excipients PRECAUTIONS - Patients

ted on a single formulation of Tacrolimus with the corresponding daily dosing regimen; alter ant specialist. Following conversion to any alternative formulation, therapeutic drug monito ations in formulation or regimen should only take place under ing must be performed and dose adjustments made to ensure does supervisien of a transplant speciality. Following conversions to any alternative formulation, thempetic, day monitoring must be performed and does adjustments made to meare that supform exposure of the second second mean structure of the second seco nould be man

blood glucose levels, elserboyles (princisally patsainin), liver and real function tests, hemotology parameters, coagulation values, and plasma proton determinant for immunosement damages are sens, adjustmost of the immunosements of the considered. - When sublances with a poteral fair interaction-periodally shong inhibitors of CP3244 (such as latoconazole, veriformacle, interaconale, testifarmey; nor elariflermeyrino ir plasma of CP3244 (such as latoconazole, tellifarmeyrino elariflermeyrino) in plasma - prioda and a subject of the subje

concentrations and the frequencie effect of Theoremisms.
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te necessary in patients with severe liver impairment. lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficie

product. Ability to drive and use machines Tocrolimus may cause visual and n jcal disturbances. This effect may be enhanced if Tacrolimus is administered in assave been performed.

### on the ability to drive and use machine PREGNANCY AND LACTATION

PRECENSION INDUCTORDN Humm data show the Theorims acrosses the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse effects on the course and outcome of programy under Theorims acrosses the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse effects on the course and outcome of programy under Theorims transmost on its one after attransmission and when the precision deterily infish for the placentaria fish to the fasts. In cost of an attransmission of the newborn for the posterial adverse effects of Tacoliums is recommended (in particular the effects on the kidneys). There is a risk for prenature delivey (-37 work) for discase of 66 of 123 https://discase.under.org/index/discases.under.org/index/discases.unde

### s on male fertility in the form of reduced sperm counts and motility was observed in rats

DRUG INTERACTIONS

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netrostwei. – h roch ter förleving utsblacen huve ben skovn to be potential inhibites of Tacrelinus nettoblere: Benereciptus, corsione, dapson, engstamine, geskolere, lakecine, mephenytin, niconazole, miskolane, nibradipue, porehistorus, quindine, turoxiden, tukoratomytin. Corpetini jace in bene noprodet to increase in blood level of Caccimism and houdt hereber be workkel. Lancepared and cyclosporine may potentially inhibit CVP3A4-mediated methodism in circumstee in blood level of Caccimism and houdt hereber be workkel. Lancepared and cyclosporine may potentially inhibit CVP3A4-mediated methodism in circumstee in the structure of Caccimism and houdt hereber be workkel. Lancepared and cyclosporine may potentially inhibit CVP3A4-mediated methodism in circumstee in the structure of Caccimism and houdt hereber be workkel. Lancepared in a fast in the structure of Caccimism and the structure of the structure of

magescame administratively observed with refarming head results. (TPA) at history entries/initially taking to determined Theoremine block/seck/ - strong interactions have been observed with infrançiais, phatysiking et Sk. John's Wort (*Hyperleam performanty*) which may require increased Theoremine block levels. - High does prohinologies or methy operation observed with phenotebulk Maintenance does of corticolderoids have been shown to reduce Theoremine block levels. - High does prohinologies or methy operation of theoremine Theoremine Theoremine Board and the phenotebulk - Market and the structure of the phenotial by doesand Theoremine. - Theoremines is a laware CVEPA4 inhibiter, thus concentrations of Sacching products known to be metabolized by CVEPA44 may affect the metabolism of such medicanal processing and the metabolism

medicinal products. The bulfelist of cyclosporties is prolonged when Taerolinus is given concentinely. In addition, synapsilicioldditive nephrotoxic effects can occur. For these reasons, the combined administration of cyclosportie and Taerolinus is not recommended and care should be taken when administering Taerolinus to patients who have previously received cyclosportie. Tarcolinus has been shown to increase the blood level of phenytoin. As Tarcolinus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure, particular care should be exercised when deciding upon o

owledge of interactions between Tacrolimus and statins is available. Available data suggests that the pharmacokinetics of statins are largely unaltered by the co-ac

ave shown that Tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and phenazone

### Other in intal effects

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### avoided. ADVERSE EFFECTS

AUVELOSE LEPECES
The adverse darg machine profile associated with immunosuppressive agents is often difficult to selabilish owing to the underlying disense and the concurrent use of multiple medications.
Way of the advectory grantensis ikatabelow are revensible and/or respond to dose reduction. The forgunary of advector reactions is difficult to selabilish owing to the underlying disense and the concurrent two of multiple model and/or respond to dose reduction. The forgunary of advector reactions is difficult to selabilish owing to the underlying disense and the concurrent two of multiple model and/or respond to dose respond to advector dose respond to advector dose respondent on the distance database and the resolution of the distance database and distance database and the distance data

b) By mphatic system disorders: Anamia, leucopenia, thrombocytopenia, abnormal leukocytosis red blood cell analyses (common): congulepathics, abnormal congulation and manyses, parcycopenia, caratopenia (uncommot, thrombock thermbocytopenia parcus, hypoprofitornhinemia (mai), system disorders: Endeth.chrome(vvv) common systems, dishubares in onecoassess, parcellassian and parcellassian and system disorders: Endeth.chrome(vvv) common systems, dishubares in onecoassess, parcellassian and parcellassian and system disorders: Endeth.chrome(vvv) common systems, dishubares in onecoassess, parcellassian and anapathies, discrimentation and system disorders: Endeth.chrome(vvv) common systems, dishubares in onecoassess, parcellassian and anapathies, discrimentation and system disorders: The system and anapathies and constructions and anapathies and parcesis, encephalopathy, speech and language abnormalizes, system disorders: The system anapathies and constructions and systems and anapathies and parcesis, encephalopathy, speech and language abnormalizes, system disorders: The system anapathies and constructions and systems and anapathies and parcesis, encephalopathy, speech and language abnormalizes, system disorders: The system anapathies and constructions and parcesis, encephalopathy, speech and language abnormalizes, system disorders: The system anapathies and constructions and systems and syst amon); hypertonia (rare); my asthenia (very rare).

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Endocrine disorders: Hirsutism (rare). Metabolism and nutrition disorders: Hyperglyc woonstremia fluid overload hyperuricemia dec emic conditions, diabetes mellitus, hyperkalemia (very common); hypomagnesemia, hypophosphatemia, hypokalemia, hypor reased appetite, anorexia, metabolic acidosis, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, other electrolyte abno

Indexine disorder: Heating (ms)
 Medvolim and attribution disorder: Hyperglocarric conditions, diabets mellins, hyperkalenii (very common); hypornaguesenii, hyperkalenii, hypoclalenii, avel a melli hypoclalenii, hyp

DOSAGE AND ADMINISTRATION

crograft<sup>48</sup> therapy requires careful monitoring by adequately qualified and equipped personnel. en molicinal product should only be prescribed, and changes in immunosuppressive therapy initiated by physicians experienced in imm replated patients.

## General considerations

STORAGE CONDITIONS Keep in original pack in intact cond Date of revision: November 2012.

Locusiaritizations commanded initial desages presented below are intended to act solely as a guideline. Tacrograff dosing should primarily be based on clinical assessments of rejection and tokenability patient individually aided by bload beet monitoring. If clinical signs of rejection are properties, therefore the immunosappressive regimen should be considered, and dosing any commance only. Fine cases, by a thin individing the contents supported to active viscous signal solution and tokenability her immunosappressive agents in the initial post-operative period. The Tacrograff dose may vary depending upon the immunosappressive regiment chosen.

with doer immunosupressive agents in the initial pol-operative period. The Tacogart" does may vary depending upon the immunosupressive egitters sciences. Medical data initiation in the oral shift does be administered in two divided does (e.g. morning and evening). Capateles should be taken immediately following removal from the bibits: The equales should be staded with the full effectively water). Capateles should assessible addivided with a full effectively water. Capateles should assessible addivided taken in the state of the should be taken in muchinely following removal from the bibits: The equales should assessible addivided taken in the state of the should be taken in muchinely following removal from the bibits: The equales should assessible addivided taken in the state of the should be taken in the should be taken in muchinely following removal from the bibits: To appress gard rejection, immunosuppression mulb the maintained, consequently, to limit to the duration of coal the target can be given. Design commendation: Letter tangetatime 12 bases after the coalfield of sugget gard wheat the administered in two divided doses (e.g. morning and evening). Administration should commence approximately 12 bases after the completion of suggets. Design administration should commence approximately to low and the duration of constraints and the polytameter and the should be administered in two divided doses (e.g. morning and evening). Administration should commence approximately 12 bases after the completion of suggets. Design administration should be administered in two advided doses (e.g. morning and evening). Design administration should be administered in two advided doses (e.g. morning and evening). Design administration should be administered in the administered in two advided doses (e.g. morning and evening). Design administration should be administered in the administered in two advided doses (e.g. morning and evening). Design administration should be administered in the administered in two adv Doe adjustent using poss-supervise heary, loading to Tacogal<sup>an</sup> monochargis, Pol-tanoplant improvement in the condition of the patient may alter the pharmacokanetics or taceogar<sup>a</sup> and concentrative immunospectrosite the applicability of Tacogal<sup>an</sup> monochargis, Pol-tanoplant improvement in the condition of the patient may alter the pharmacokanetics or taceogar<sup>a</sup> and the magnetic pharmacokanetic pharmacokanetics or taceogar<sup>a</sup> and the magnetic pharmacokanetics or taceogar<sup>a</sup> and the magnetic pharmacokanetic pharmacokanetics or taceogar<sup>a</sup> and the magnetic pharmacokanetic pharmacokanetics or taceogar<sup>a</sup> and the magnetic pharmacokanetics or taceogar<sup>a</sup> and the magnetic pharmacokanetic pharmacokanetics or taceogar<sup>a</sup> and the magnetic pharmacokanetics or taceogar<sup>a</sup> and the magnetic pharmacokanetic pharmacokanetics or taceogar<sup>a</sup> and the magnetic pharmacokanetics or taceogar<sup>a</sup> and the magnetic pharmacokanetics or taceogar<sup>a</sup> and the magnetic pharmacokanetic pharmacokanetics or taceogar<sup>a</sup> and the magnetic pharmacokanetic pharmacokanetic pharmacokanetic pharmacokanetics or taceogar<sup>a</sup> and the magnetic pharmacokanetic pharmacokanetin magneti pharmacokanetic pharmacokaneti pharmacokaneti pharm

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e concessarious. of transplant rejection – children: Following antibody induction, if Tacrograf<sup>®</sup> therapy is initiated orally, the recommended starting dose is 0.10 - 0.30 mg/kg/day administered

- Prophytical of tamophater rejection - dashner. Following antibody induction, if Tacorgat<sup>40</sup> theory is initiated only, the recommended thating does is 0.10 - 0.30 mg/kg/ky adminished as two forked does (e.g. moming and coursing).
 - Does adjubanted aring pool tamophater provid in adults and diablem. Tacorgat<sup>40</sup> theores are usually reduced in the pool-tamophater provide. To be adjusted to the provide state in the does does are usually reduced in the pool-tamophater provides and theory is a state of the provides and the provides and the provides and theory. Tachika and diablem: Tacorgat<sup>40</sup> does, argulterated to concolorised theory, and introduction of the tracers of theory - adults and editablem: Increased Tacorgat<sup>40</sup> does, argulterated to concolorised theory, and introduction of the tracers of theory - adults and editablem: Increased Tacorgat<sup>40</sup> does, argulterated to concolorised theory, and introduction of the tracers of theory - adults and editablem: Increased Tacorgat<sup>40</sup>, and initial of adult on the does and the administered in two double does (e.g. morning and evening). In polarities morehout the Tacorgat<sup>40</sup> and initial of adult of the administered in two double does (e.g. morning and evening). The does not construct the Tacorgat<sup>40</sup> and initial of adult of the administered in two double does (from the administered in the double does (from the administered in the double does of the administered in the double does (from the administered in the double does (from the administered in the administered in the double does (from the administered in the double does the administered in the double does (from the administered in the does (from the administered in the does (from the administered in the does (from the adminintered in the does (from the administered in the does (from

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Thereports drug meatering: Doing should primely be based on clinical measurement of rejection and blenshility in each individual patient aded by whote blood tacongart 'trongmesse membraine. As an aid to optimize doing, several immunosopy are available for determining Tacongard' constraints in whole blood including a semi-automated introparticle compare immunosopy (MLA). Comparison of concentrations from the philadel literature to individual values in clinical practice should be assored with care and knowledge of the asso-method employed. In current clinical partice, whole blood levels are monitored assign munocosoy methods. Blood works blood for transport from the philadel literature to individual values in clinical practice, should be down appointed by the practice of the asso-pare transport of the strength of should be method on the philadel literature to individual values in clinical practice, wheel blood method by the strength of the strength of should be down appointed to the philadel by the philadel by the strength of the strength

ERDORAGE structure with over doage is limited. Several cases of accidental overdoage have been reported, symptoms have included terms; headache, masses and vorning, infections, urficaria, any and increases in blood men atingen, some contains and increase in administ minimum frame. It is a structure denously the conducted of a in high molecule of the structure of the structur

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- A medicament is a product which affects your health, and its consumption contrary to instructions is diagnosing for your health and of uses, and the instructions of the plannical its everythering and the shortfish and risks - The doctor and the pharmical its everyther is medicines, the boundfish and risks - Do not by youndfishing the period for the instrument presented for yous - Do not trypt and fishing the period for the instrument presented for you - Do not pry usual fishing the period for the instrument presented for you - Do not pry usual fishing the period for the instrument presented for your doctor - Medicinement know of reach of childents

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