TACROLIMUS

ROCIMUS

0.03% w/w Topical Ointment
Calcineurin Inhibitor

Formulation:
Each 10 gram contains :
Tacrolimus ..... 0.03% w/w

Inactive ingredients:
Propylene carbonate USP, Hard paraffin BP, Liquid paraffin BP, White bees wax BP, White soft paraffin BP

Description:
White ointment free from any gritty matter.

Tacrolimus ointment 0.03% contains the immunosuppressant agent tacrolimus. It is a macrolide lactone produced by Streptomyces tsukubaensis. It is for topical dermatologic use only.

Mechanism of action:
The mechanism of action of tacrolimus in atopic dermatitis is not known. It has been demonstrated that tacrolimus inhibits T-lymphocyte activation by first binding to an intracellular protein, FKBP-12. A complex of tacrolimus – FKBP – 12, calcium, calmodulin and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited. This effect has been shown to prevent the dephosphorylation and translocation of nuclear factor of activated T- cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as Interleukin – 2, gamma – interferon). Tacrolimus also inhibits the transcription for genes which encode IL-3, IL-4, GM-CSF and TNF –(alpha), all of which are involved in the early stages of T-cell activation. Additionally, tacrolimus has been shown to inhibit the release of pre-formed mediators from skin mast cells and basophils.

Pharmacokinetics:
When applied to intact human skin, invitro studies have demonstrated that tacrolimus is not readily absorbed. However on inflamed or damaged skin, it is absorbed in sufficient amounts to be topically active. The drug is metabolized in the liver by Cytochrome P4503A4 and is eliminated almost completely in the bile.
Clinical data have shown that tacrolimus concentrations in clinical circulation after topical administration are low, and when measurable, transient.
Tacrolimus does not accumulate in tissues following repeated topical application.
After systemic administration of tacrolimus, bile represents the principal pathway of elimination with a total body clearance of 2.25l/h and a systemic elimination half – life of approximately 40 hours. Cytochrome P-450 3A4 isoenzyme is responsible for the metabolism of tacrolimus. Invitro 8 metabolites have been characterized so far 13-O- demethylated metabolite has been shown to dominate invitro. However it reveals a limit pharmacological activity of 6.4% compared with tacrolimus. Invitro studies on viable human skin report no evident cutaneous metabolism of tacrolimus.
Formal topical drug interaction studies with tacrolimus ointment have not been conducted.
Tacrolimus is not metabolized in human skin, indicating that there is no potential for percutaneous interactions that could effect the metabolism of tacrolimus.

Indications:
In addition to its beneficial effects in the management of atopic dermatitis, topical tacrolimus has also been reported to be of benefit in other immunologically mediated skin diseases including hand dermatitis, contact dermatitis, eyelid dermatitis, erosive lichen planus, steroid – induced rosacea, pyoderma gangrenosum and graft – versus - host disease.

Contraindications:
Hypersensitivity to macrolides in general to tacrolimus or to any other ingredient of the preparation.

Warning:
The use of tacrolimus ointment has not been evaluated in children below 2 years.

Precautions:
Exposure of the skin to sunlight should be minimized and the use of ultraviolet (UV) light from a solarium, therapy with UVB or UVA in combination with psolarens (PUVA) should be avoided during use of tacrolimus ointment. Physicians should advise patients on appropriate sun – protection methods, such as minimization.
Of the time in the sun, use of sunscreen product and covering of the skin with appropriate clothing. Emollients should not be applied to the same area within 2 hours of applying tacrolimus ointment. Concomitant use of other topical preparations have not been assessed. There is no experience of concomitant use of systemic steroids or immunosuppressive agents.
Tacrolimus ointment has not been evaluated for its efficacy and safety in the treatment of clinically infected atopic dermatitis. Before commencing treatment, with tacrolimus ointment, clinical infections at treatment sites should be cleared. Patients with atopic dermatitis are predisposed to superficial skin infections. Treatment with Tacrolimus will be associated with an increased risk of herpes viral infections. In the presence of these infections, the balance of risk & benefits associated with tacrolimus use should be evaluated. Beyond 4 years of treatment, the potential for local immunosuppression (possibly resulting in infections or cutaneous malignancies) is unknown. Care should be taken to avoid contact with eyes and mucous membranes. If accidently applied to these areas, the ointment should be thoroughly wiped off and / or rinsed off with water. The use of tacrolimus ointment under occlusion has not been studied in patients. Occlusive dressings are not recommended.
As with any topical medicinal product, patients should wash their hands after application if the hands are not indicated for treatment.
Tacrolimus is extensively metabolized in the liver and although blood concentrations are low following topical therapy the ointment should be used with caution in patients with generalized erythroderma.

Drug Interactions:
Formal topical drug interaction studies with tacrolimus ointment have not been conducted.

Tacrolimus is not metabolized in human skin, indicating that there is no potential for percutaneous interactions that could affect the metabolism of tacrolimus.
A potential interaction between vaccination and application of tacrolimus ointment has not been investigated because of the potential risk of vaccination failure.
Vaccination should be administered prior to commencement of treatment, or during a treatment free interval with a period of 14 days between the last application of tacrolimus and the vaccination. In case of attenuated vaccination this period should be extended to 28 days or the use of alternative vaccines should be considered.

Pregnancy & Lactation:
There are no adequate and well-controlled studies of topically administered tacrolimus in pregnant women. The experience with tacrolimus ointment when used by pregnant women is limited. .
Tacrolimus is transferred across the placenta. Tacrolimus is also secreted in milk.
Although clinical data have shown that systemic exposure from application of tacrolimus ointment is minimal relative to systemic administration, Tacrolimus Ointment should be used during pregnancy and in nursing mothers only if the potential benefit to the mother justifies a potential risk to the fetus.

Geriatric use:
Twenty five patients >65 years old received Tacrolimus ointment in phase III studies. The adverse event profile for these patients was consistent with that of adult patients.

Adverse reactions:
Adverse reactions with suspected relationship to treatment are listed below by system organ class. Frequencies are defined as very common (> 1/10), common (> 1/100, < 1/10) and uncommon (> 1/1,000, < 1/100).

General disorders and administration site conditions
Very common: Application site burning, application site pruritus
Common: Application site warmth, application site erythema, application site pain, application site irritation, application site paresthesia, application site rash
Infections and infestations
Common: Herpes viral infections (herpes simplex dermatitis [eczema herpeticum], herpes simplex [cold sores], Kaposi's varicelliform eruption)
Skin and subcutaneous tissue disorders
Common: Folliculitis, pruritus
Uncommon: Acne
Nervous system disorders
Common: Paresthesias and dysesthesias (hyperesthesia, burning sensation)
Metabolism and nutrition disorders
Common: Alcohol intolerance (facial flushing or skin irritation after consumption of an alcoholic beverage)

Overdose:
Overdosage following topical administration is unlikely.
If ingested, general supportive measures may be appropriate. These may include monitoring of vital signs & observation of clinical studies.

Dosage & administration:
Adults:
Tacrolimus ointment 0.03%
A thin layer of tacrolimus ointment 0.03% should be applied to the affected skin areas twice daily and rubbed in gently and completely. Treatment should be continued for one week after clearing of signs & symptoms of atopic dermatitis.
Tacrolimus ointment may be used on any part of the body, including face, neck & flexure areas, except on mucous membrane.
The safety of Tacrolimus ointment under occlusion which may promote systemic exposure has not been evaluated. Tacrolimus ointment 0.03% should not be used with occlusive dressings.

Pediatrics:
Tacrolimus ointment 0.03%
Apply a thin layer of Tacrolimus ointment to the affected skin area daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis. The safety of tacrolimus ointment under occlusion, which may promote systemic exposure, has not been evaluated. Tacrolimus ointment 0.03% should not be used with occlusive dressings.

Storage condition:
Store at temperatures not exceeding 30°C.
Protect from light and moisture.
Keep out of reach of children.

Availability :
10g lami tube (Box of 1's)

Caution :
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:
THE MADRAS PHARMACEUTICALS
137-B, Old Mahabalipuram Road,
Karapakkam, Chennai: 600 096. India.

For : **MEGA LIFESCIENCES (AUSTRALIA) PTY LTD**
Victoria 3810, Australia.

MEGA
We care

Imported & Distributed by: **METRO DRUG, INC.**
Mañalac Avenue, Bagumbayan,
Taguig City, Philippines

MPI/MLS/Rod/PI-15/A
I-R801-M25-00-00