Only for the use of a Registered Medical Practitioner or a Hospital or a Laboratory.

Biocon

Tacrolimus Ointment 0.03%w/w / 0.1% w/w

TBIS® 0.03%/0.1% टीबिस ०.०३%/०.१%

Composition:
TBIS®0.03%
Each gram contains
Tacrolimus IP 0.3mg
Ointment base q.s.

TBIS®0.1%
Each gram contains
Tacrolimus IP 1.0mg
Ointment base q.s.

Description: Tacrolimus Ointment is a macrolide immunosuppressant produced by Streptomyces tsukubaensis. It is for topical dermatologic use only.

ATC code: L04AD02

CLINICAL PHARMACOLOGY
Mechanism of Action:
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, IL-5, GM-CSF, and TNF-α, 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 and to down-regulate the expression of Fc£RI on Langerhans cells.

INDICATIONS AND USAGE
Tacrolimus ointment, both 0.03% w/w and 0.1 % w/w for adults, and only 0.03% w/w for children aged 2 to 15 years, is indicated for the short-term and intermittent long-term treatment of moderate to severe atopic dermatitis in adults and children not responding / intolerant to other alternative / conventional therapies.

Dosage Administration:
Apply Tacrolimus ointment to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis. Tacrolimus ointment should not be used with occlusive dressings.

Pediatric: Use Tacrolimus ointment 0.03% w/w - Apply a thin layer of Tacrolimus ointment 0.03% w/w to the affected skin areas twice daily and rub in gently and completely. Treatment should be continued for one week after clearing of signs and symptoms of atopic dermatitis. Tacrolimus ointment 0.03% w/w should not be used with occlusive dressings.

Contraindications:
Tacrolimus ointment is contraindicated in patients with a history of hypersensitivity to Tacrolimus or any other component of the preparation.

WARNINGS
Long-term Safety of Topical Calcineurin Inhibitors Has Not Been Established.
Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including Tacrolimus ointment. Therefore: • Continuous long-term use of topical calcineurin inhibitors, (including Tacrolimus) in any age group should be avoided and application limited to areas of involvement with atopic dermatitis. • Tacrolimus is not indicated for use in children less than 2 years of age. Only Tacrolimus ointment 0.03%w/w is indicated for use in children 2-15 years of age.

Prolonged systemic use of calcineurin inhibitors for sustained immunosuppression in animal studies and transplant patients following systemic administration has been associated with an increased risk of infections, lymphomas, and skin malignancies. These risks are associated with the intensity and duration of immunosuppression. • Tacrolimus should not be used in immunocompromised adults and children. If signs and symptoms of atopic dermatitis do not improve within 6 weeks, patients should be re-examined and their diagnosis should be reconfirmed. • The safety of Tacrolimus has not been established beyond one year of non-continuous use.

PRECAUTIONS
General: Studies have not evaluated the safety and efficacy of Tacrolimus in the treatment of clinically infected atopic dermatitis. In the presence of infections like Kaposi's varicelliform eruption, chicken pox or shingles, herpes simplex virus infection, or eczema herpeticum the balance of risks and benefits associated with Tacrolimus ointment use should be evaluated.

In clinical studies, 33 cases of lymphadenopathy (0.8%) were reported and were usually related to infections (particularly of the skin) and noted to resolve upon appropriate antibiotic therapy. It is prudent for patients to minimize or avoid natural or artificial sunlight exposure. The use of Tacrolimus ointment may cause local symptoms such as skin burning (burning sensation, stinging, soreness) or pruritus. Localized symptoms are most common during the first few days of Tacrolimus ointment application and typically improve as the lesions of atopic dermatitis heal. With Tacrolimus ointment 0.1% w/w, 90% of the skin burning events had duration between 2 minutes and 3 hours (median 15 minutes). 90% of the pruritus events had duration between 3 minutes and 10 hours (median 20 minutes). The use of Tacrolimus in patients with Netherton's Syndrome is not recommended due to the potential for increased systemic absorption of Tacrolimus. The safety of Tacrolimus has not been established in patients with generalized erythroderma.

PHARMACOKINETICS
Absorption: The data from three pharmacokinetic studies in 88 adult atopic dermatitis patients indicate that Tacrolimus is minimally absorbed after the topical application of Tacrolimus ointment. Peak Tacrolimus blood concentrations ranged from undetectable to 20 ng/mL after single or multiple doses of Tacrolimus ointment 0.03% w/w and 0.1% w/w, with 85% (75/88) of the patients having peak blood concentrations less than 2 ng/mL. The absolute bioavailability of Tacrolimus ointment in atopic dermatitis patients is approximately 0.5%.

In a pharmacokinetic study of 14 pediatric atopic dermatitis patients, between the ages of 2-5 years, peak blood concentrations of Tacrolimus ranged from undetectable to 14.8 ng/mL after single or multiple doses of Tacrolimus ointment 0.03% w/w , with 86% (12/14) of patients having peak blood concentrations below 2 ng/mL throughout the study. In clinical studies with periodic blood sampling, a similar distribution of Tacrolimus blood levels was also observed, with 98% (509/522) of pediatric patients having a blood concentration below 2 ng/mL.

Distribution: The plasma protein binding of Tacrolimus is approximately 99% and is independent of concentration over a range of 5-50 ng/mL. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. There was no evidence based on blood concentrations that Tacrolimus accumulates systemically upon intermittent topical application for periods of up to 1 year. As with other topical calcineurin inhibitors, it is not known whether Tacrolimus is distributed into the lymphatic system.

Metabolism: Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system (CYP3A).

Excretion: The mean clearance following IV administration of Tacrolimus is 0.040, 0.083 and 0.053 L/hr/kg in healthy volunteers, adult kidney transplant patients and adult liver transplant patients, respectively. In man, less than 1% of the dose administered is excreted unchanged in urine. When administered PO, the mean recovery of the radiolabel was 94.9 ± 30.7%. Fecal elimination accounted for 92.6 ± 30.7%, urinary elimination accounted for 2.3 ± 1.1 % and the elimination half- life based on radioactivity was 31.9 ± 10.5 hours whereas it was 48.4 ± 12.3 hours based on Tacrolimus concentrations.

CLINICAL STUDIES
Three randomized, double-blind, vehicle-controlled, multi-centre, phase 3 studies were conducted to evaluate Tacrolimus ointment for the treatment of patients with moderate to severe atopic dermatitis. One (Pediatric) study included 351 patients 2-15 years of age, and the other two (Adult) studies included a total of 632 patients 15-79 years of age.

In the pediatric study, a significantly greater ($p < 0.001$) percentage of patients achieved at least 90% improvement based on the physician's global evaluation of clinical response the pre-defined primary efficacy end point) in the Tacrolimus ointment 0.03% w/w treatment group compared to the vehicle treatment group, but there was insufficient evidence that Tacrolimus ointment 0.1% w/w provided more efficacy than Tacrolimus ointment 0.03% w/w.

In both adult studies, a significantly greater ($p < 0.001$) percentage of patients achieved at least 90% improvement based on the physician's global evaluation of clinical response in the Tacrolimus ointment 0.03% w/w and Tacrolimus ointment 0.1% w/w treatment groups compared to the vehicle treatment group. There was evidence that Tacrolimus ointment 0.1% w/w may provide more efficacy than Tacrolimus ointment 0.03% w/w. The difference in efficacy between Tacrolimus ointment 0.1% w/w and 0.03% w/w was particularly evident in adult patients with severe disease at baseline, adults with extensive BSA involvement, and black adults. Response rates for each treatment group are shown below by age groups. Because the two adult studies were identically designed, the results from these studies were pooled in this table.

Table 1 - Global Improvement over Baseline at the End-of-Treatment in Three Phase 3 Studies

Physician's Global Evaluation of Clinical Response (% Improvement)	Pediatric Study (2-15 Years of Age)		Adult Studies		
	Vehicle ointment N=116	Tacrolimus ointment 0.03%w/w N=117	Vehicle ointment N=212	Tacrolimus ointment 0.03%w/w N=211	Tacrolimus ointment 0.1%w/w N=209
100%	4 (3%)	14 (12%)	2 (1%)	21(10%)	20 (10%)
≥90%	8 (7%)	42 (36%)	14 (7%)	58 (28%)	77 (37%)
≥75%	18 (16%)	65 (56%)	30 (14%)	97 (46%)	117 (56%)
≥50%	31 (27%)	85 (73%)	42 (20%)	130 (62%)	152 (73%)

A statistically significant difference in the percentage of adult patients with ≥ 90% improvement was achieved by week 1 for those treated with Tacrolimus ointment 0.1% w/w, and by week 3 for those treated with Tacrolimus ointment 0.03% w/w. A statistically significant difference in the percentage of pediatric patients with ≥ 90% improvement was achieved by week 2 for those treated with Tacrolimus ointment 0.03% w/w.

In adult patients who had achieved ≥ 90% improvement at the end of treatment, 35% of those treated with Tacrolimus ointment 0.03% w/w and 41 % of those treated with Tacrolimus ointment 0.1% w/w, regressed from this state of improvement at 2 weeks after end-of-treatment. In pediatric patients who had achieved ≥ 90% improvement, 54% of those treated with Tacrolimus ointment 0.03% w/w regressed from this state of improvement at 2 weeks after end-of-treatment. Because patients were not followed for longer than 2 weeks after end-of-treatment, it is not known how many additional patients regressed at periods longer than 2-weeks after cessation of therapy.
In both Tacrolimus ointment treatment groups in adults and in children, a significantly greater improvement compared to vehicle ($p < 0.001$) was observed in the secondary efficacy endpoints of percent body surface area involved, patient evaluation of pruritus, erythema, edema, excoriation, oozing, scaling, and lichenification.

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A total of 571 patients applied Tacrolimus ointment 0.1% w/w in long-term adult and pediatric safety studies for up to one year. In the adult study, 246 patients were evaluated for at least 6 months and 68 patients for 12 months. In the, pediatric study, 219 patients were evaluated for at least 6 months and 180 patients for 12 months. On average, patients received treatment for 87% of study days. Tacrolimus ointment was found to be safe and effective in adult and pediatric patients with atopic dermatitis for up to 1 year.

ADVERSE REACTIONS
No phototoxicity and no photoallergenicity was detected in clinical studies of 12 and 216 normal volunteers, respectively. One out of 198 normal volunteers showed evidence of sensitization in a contact sensitization study. In three randomized vehicle-controlled studies and two long-term safety studies, 655 and 571 patients respectively, were treated with Tacrolimus ointment. The following table no. 2 depicts the adverse events reported as may be reasonably associated with the use of their drug product. The adverse events were observed in similar percentage in adults and children.

Table 2 – Incidence of Treatment Emergent Adverse Events

	12-Week Randomized, Double-Blind, Phase 3 Studies 12-week Adjusted Incidence Rate (%)					Open-Label Studies (up to 1 year) 0.1% Tacrolimus ointment 0.1%w/w Incidence (%)	
	Adult			Pediatric		Adult	Pediatric
	Vehicle n=212	Tacrolimus ointment 0.03%w/w n=210	Tacrolimus ointment 0.1%w/w n=209	Vehicle n=116	Tacrolimus ointment 0.03%w/w n=118	N=316	N=255
Skin Burning	26	46	58	29	43	47	26
Pruritus	37	46	46	27	41	25	25
Flu-like symptoms	19	23	31	25	28	22	35
Headache	11	20	19	8	5	10	18
Folliculitis	1	6	4	0	2	11	2
Sinusitis	1	4	2	8	3	3	7
Rash	1	5	2	4	2	2	5
Acne	2	4	7	1	0	2	4
Vesiculobullous Rash	3	3	2	0	4	2	2
Lymohadenopathy	2	2	1	0	3	2	3
Skin Tingling	2	3	8	1	2	2	1
Dyspepsia	1	1	4	0	0	1	4
Hyperesthesia	1	3	7	0	0	3	0
Back Pain	0	2	2	1	1	3	1
Varicella Zoster / Herpes Zoster ‡‡	0	1	0	0	5	1	3

‡‡Generally "warts"

Other adverse events which occurred at an incidence greater than or equal to 1% in any clinical study include: alopecia, ALT or AST increased, anaphylactoid reaction, angina pectoris, angioedema, anorexia, anxiety, arrhythmia, arthralgia. arthritis, bilirubinemia, breast pain, cellulitis, cerebrovascular accident, cheilitis, chills, constipation, creatinine increased, dehydration, depression, dizziness, dyspnea, ear pain, ecchymosis, edema, epistaxis, exacerbation of untreated area, eye disorder, eye pain, furunculosis, gastritis, hernia, hyperglycemia, hypertension, hypoglycemia, hypoxia, laryngitis, leukocytosis, leukopenia, liver function tests abnormal, lung disorder, malaise, migraine, neck pain, neuritis, palpitations, paresthesia, peripheral vascular disorder, photosensitivity reaction, procedural complication, routine procedure, skin discoloration, sweating, taste perversion, tooth disorder, unintended pregnancy, vaginal moniliasis, vasodilatation, and vertigo. Alcohol intolerance was seen in 3% of cases with Tacrolimus ointment 0.03%w/w in adults and beningn skin neoplasms were reported in 1% of cases with between Tacrolimus ointment 0.03%w/w and 0.1%w/w.

SPECIAL POPULATION
Pregnancy
Teratogenic Effects: Pregnancy Category C
There are no adequate and well-controlled studies of topically administered Tacrolimus in pregnant women.
Nursing Mothers: Although systemic absorption of Tacrolimus following topical applications of Tacrolimus ointment is minimal relative to systemic administration, it is known that Tacrolimus is excreted in human milk. Its usage should be weighed considering risk and benefits to the patients.
Pediatric Use: Tacrolimus ointment 0.03% w/w may be used in pediatric patients 2 years of age and older. Since the safety and efficacy of Tacrolimus have not been established in pediatric patients below 2 years of age, its use in this age group is not recommended.
Geriatric Use: Twenty-five (25) patients ≥ 65 years old received Tacrolimus ointment in phase 3 studies. The adverse event profile for these patients was consistent with that for other adult patients.

Renal Insufficiency: The effect of renal insufficiency on the pharmacokinetics of topically administered Tacrolimus has not been evaluated.

Hepatic Insufficiency: The effect of hepatic insufficiency on the pharmacokinetics of topically administered Tacrolimus has not been evaluated but dose-adjustment is not expected to be needed.

DRUG INTERACTIONS
Formal topical drug interaction studies with Tacrolimus have not been conducted. Based on its minimal extent of absorption, interactions of Tacrolimus with systemically administered drugs are unlikely to occur but cannot be ruled out. The concomitant administration of known CYP3A4 inhibitors in (erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine) patients with widespread and/or erythrodermic disease should be done with caution.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
No evidence of genotoxicity was seen in bacterial (Salmonella and E. coli) or mammalian (Chinese hamster lung-derived cells) in vitro assays of mutagenicity, the in vitro CHO/HGPRT assay of mutagenicity, or in vivo clastogenicity assays performed in mice. Reproductive toxicology studies were not performed with topical Tacrolimus.

OVERDOSAGE
Tacrolimus ointment is not for oral use.
The safety of topical Tacrolimus has not been established beyond one year of non-continous use.
Oral ingestion of Tacrolimus Ointment may lead to adverse effects associated with systemic administration of tacrolimus. If oral ingestion occurs, medical advice should be sought

INFORMATION FOR PATIENTS
Patients using Tacrolimus ointment should receive the following information and instructions:
1. Patients should use Tacrolimus ointment as directed by the physician. Tacrolimus ointment is for external use only. As with any topical medication, patients or caregivers should wash hands after application if hands are not an area for treatment.
2. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Tacrolimus ointment.
3. Patients should not use this medication for any disorder other than that for which it was prescribed.
4. Patients should report any signs of adverse reactions to their physician.
5. Before applying Tacrolimus ointment after a bath or shower, be sure your skin is completely dry.

Shelf life: Please refer carton / tube.

STORAGE
Store at a temperature not exceeding 25°C, away from light and moisture.
Do not freeze.
Keep out of reach of children
Replace the cap tightly after use
For dermatologic use only.
Not for ophthalmic use

PRESENTATION:
Tacrolimus Ointment 0.03%w/w / 0.1% w/w : Available as 5g (PS) 10g & 30g ointment filled in tube, packed in carton along with leaflet.

Marketed by: **Biocon Biologics India Limited**
Biocon House, Semicon Park, Electronics City,
Phase - II, Bengaluru - 560 100, India.

® - Registered trademark

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free No: **1800 102 9465** or e- mail us at **drugsafety@biocon.com**