



**TACROZ FORTE OINTMENT**  
**Tacrolimus Ointment 0.1% w/w**

**1. NAME OF THE MEDICINAL PRODUCT**

Tacroz Ointment 0.03% w/w

Tacroz Forte Ointment 0.1% w/w

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Tacrolimus USP 0.1% w/w

Ointment base q.s.

**3. PHARMACEUTICAL FORM**

Ointment

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Tacroz Forte 0.1 % ointment is indicated in adults and adolescents (16 years of age and above).

Flare treatment

*Adults and adolescents (16 years of age and above)*

Treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids.

*Children (2 years of age and above)*

Treatment of moderate to severe atopic dermatitis in children who failed to respond adequately to conventional therapies such as topical corticosteroids.

Maintenance treatment

Treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (i.e. occurring 4 or more times per year) who have had an initial response to a



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maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected).

### **4.2 Posology and Method of Administration**

Tacroz treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis.

Tacroz is available in two strengths, Tacroz 0.03 % and Tacroz Forte 0.1 % ointment.

#### Posology

##### ▪ Flare treatment

Tacrolimus can be used for short-term and intermittent long-term treatment. Treatment should not be continuous on a long-term basis.

Tacrolimus treatment should begin at the first appearance of signs and symptoms. Each affected region of the skin should be treated with Tacrolimus until lesions are cleared, almost cleared or mildly affected. Thereafter, patients are considered suitable for maintenance treatment (see below). At the first signs of recurrence (flares) of the disease symptoms, treatment should be re-initiated.

#### *Adults and adolescents (16 years of age and above)*

Treatment should be started with Tacroz Forte 0.1% twice a day and treatment should be continued until clearance of the lesion. If symptoms recur, twice daily treatment with Tacroz Forte 0.1% should be restarted. An attempt should be made to reduce the frequency of application or to use the lower strength Tacroz 0.03% ointment if the clinical condition allows.

Generally, improvement is seen within one week of starting treatment. If no signs of improvement are seen after two weeks of treatment, further treatment options should be considered.

#### *Older people*

Specific studies have not been conducted in older people. However, the clinical experience available in this patient population has not shown the necessity for any dosage adjustment.

#### *Paediatric population*

Children (2 years of age and above) should use the lower strength Tacroz 0.03% ointment.



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Treatment should be started twice a day for up to three weeks. Afterwards the frequency of application should be reduced to once a day until clearance of the lesion.

Tacroz ointment should not be used in children aged below 2 years until further data are available.

▪ Maintenance treatment

Patients who are responding to up to 6 weeks treatment using tacrolimus ointment twice daily (lesions cleared, almost cleared or mildly affected) are suitable for maintenance treatment.

*Adults and adolescents (16 years of age and above)*

Adult patients (16 years of age and above) should use Tacroz Forte 0.1% ointment. Tacroz Forte ointment should be applied once a day twice weekly (e.g. Monday and Thursday) to areas commonly affected by atopic dermatitis to prevent progression to flares. Between applications there should be 2–3 days without Tacroz Forte treatment.

After 12 months treatment, a review of the patient's condition should be conducted by the physician and a decision taken whether to continue maintenance treatment in the absence of safety data for maintenance treatment beyond 12 months.

If signs of a flare reoccur, twice daily treatment should be re-initiated (see flare treatment section above).

*Older people*

Specific studies have not been conducted in older people (see flare treatment section above).

*Paediatric population*

Children (2 years of age and above) should use the lower strength Tacroz 0.03% ointment. Tacroz ointment should be applied once a day twice weekly (e.g. Monday and Thursday) to areas commonly affected by atopic dermatitis to prevent progression to flares. Between applications there should be 2–3 days without Tacroz treatment.

The review of the child's condition after 12 months treatment should include suspension of treatment to assess the need to continue this regimen and to evaluate the course of the disease.

Tacroz ointment should not be used in children aged below 2 years until further data are available.



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Method of administration

Tacrolimus ointment should be applied as a thin layer to affected or commonly affected areas of the skin. Tacrolimus ointment may be used on any part of the body, including face, neck and flexure areas, except on mucous membranes. Tacrolimus ointment should not be applied under occlusion because this method of administration has not been studied in patients.

**4.3 Contraindications**

Hypersensitivity to the active substance, macrolides in general, or to any of the excipients.

**4.4 Special Warnings and Precautions for Use**

Exposure of the skin to sunlight should be minimised and the use of ultraviolet (UV) light from a solarium, therapy with UVB or UVA in combination with psoralens (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 a sunscreen product and covering of the skin with appropriate clothing. Tacrolimus ointment should not be applied to lesions that are considered to be potentially malignant or pre-malignant.

The development of any new change different from previous eczema within a treated area should be reviewed by the physician.

The use of tacrolimus ointment is not recommended in patients with a skin barrier defect, such as Netherton's syndrome, lamellar ichthyosis, generalized erythroderma or cutaneous Graft Versus Host Disease. These skin conditions may increase systemic absorption of tacrolimus. Oral use of tacrolimus is also not recommended to treat these skin conditions. Post-marketing cases of increased tacrolimus blood level have been reported in these conditions.

Care should be exercised if applying Tacrolimus to patients with extensive skin involvement over an extended period of time, especially in children.

Patients, particularly paediatric patients should be continuously evaluated during treatment with Tacrolimus with respect to the response to treatment and the continuing need for treatment. After 12 months this evaluation should include suspension of Tacrolimus treatment in paediatric patients.

The potential for local immunosuppression (possibly resulting in infections or cutaneous malignancies) in the long term (i.e. over a period of years) is unknown.



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Tacroz Ointment and Tacroz Forte Ointment contains the active substance tacrolimus, a calcineurin inhibitor. In transplant patients, prolonged systemic exposure to intense immunosuppression following systemic administration of calcineurin inhibitors has been associated with an increased risk of developing lymphomas and skin malignancies. In patients using tacrolimus ointment, cases of malignancies, including cutaneous (i.e. cutaneous T Cell lymphomas) and other types of lymphoma, and skin cancers have been reported. Tacrolimus should not be used in patients with congenital or acquired immunodeficiencies or in patients on therapy that cause immunosuppression.

Patients with atopic dermatitis treated with tacrolimus ointment have not been found to have significant systemic tacrolimus levels.

Lymphadenopathy was uncommonly (0.8%) reported in clinical trials. The majority of these cases were related to infections (skin, respiratory tract, tooth) and resolved with appropriate antibiotic therapy. Transplant patients receiving immunosuppressive regimens (e.g. systemic tacrolimus) are at increased risk for developing lymphoma; therefore patients who receive tacrolimus ointment and who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves. Lymphadenopathy present at initiation of therapy should be investigated and kept under review. In case of persistent lymphadenopathy, the aetiology of the lymphadenopathy should be investigated. In the absence of a clear aetiology for the lymphadenopathy or in the presence of acute infectious mononucleosis, discontinuation of tacrolimus should be considered.

The effect of treatment with tacrolimus ointment on the developing immune system of children aged below 2 years has not been established.

Tacroz Ointment and Tacroz Forte Ointment have not been evaluated for its efficacy and safety in the treatment of clinically infected atopic dermatitis. Before commencing treatment with Tacroz Ointment or Tacroz Forte Ointment, clinical infections at treatment sites should be cleared. Patients with atopic dermatitis are predisposed to superficial skin infections. Treatment with tacrolimus may be associated with an increased risk of folliculitis and herpes viral infections (herpes simplex dermatitis [eczema herpeticum], herpes simplex [cold sores], Kaposi's varicelliform eruption). In the presence of these infections, the balance of risks and benefits associated with tacrolimus use should be evaluated.

Emollients should not be applied to the same area within 2 hours of applying tacrolimus ointment. Concomitant use of other topical preparations has not been assessed. There is no experience with concomitant use of systemic steroids or immunosuppressive agents.

Care should be taken to avoid contact with eyes and mucous membranes. If accidentally applied to these areas, the ointment should be thoroughly wiped off and/or rinsed off with water.



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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 intended for treatment.

Tacrolimus is extensively metabolised in the liver and although blood concentrations are low following topical therapy, the ointment should be used with caution in patients with hepatic failure.

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

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

Tacrolimus ointment is not metabolised in human skin, indicating that there is no potential for percutaneous interactions that could affect the metabolism of tacrolimus.

Systemically available tacrolimus is metabolised via the hepatic Cytochrome P450 3A4 (CYP3A4). Systemic exposure from topical application of tacrolimus ointment is low (<1.0 ng/ml) and is unlikely to be affected by concomitant use of substances known to be inhibitors of CYP3A4. However, the possibility of interactions cannot be ruled out and the concomitant systemic administration of known CYP3A4 inhibitors (e.g. erythromycin, itraconazole, ketoconazole and diltiazem) in patients with widespread and/or erythrodermic disease should be done with caution.

##### *Paediatric population*

An interaction study with protein-conjugated vaccine against *Neisseria meningitidis* serogroup C has been investigated in children aged 2-11 years. No effect on immediate response to vaccination, the generation of immune memory, or humoral and cell-mediated immunity has been observed.

#### **4.6 Pregnancy and lactation**

##### Fertility

There are no fertility data available.

##### Pregnancy

There are no adequate data from the use of tacrolimus ointment in pregnant women. Studies in animals have shown reproductive toxicity following systemic administration. The potential risk for humans is unknown.

Tacrolimus ointment should not be used during pregnancy unless clearly necessary.



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Breast-feeding

Human data demonstrate that, after systemic administration, tacrolimus is excreted into breast milk. Although clinical data have shown that systemic exposure from application of tacrolimus ointment is low, breast-feeding during treatment with tacrolimus ointment is not recommended.

**4.7 Effects on ability to drive and use machines**

Tacrolimus ointment has no or negligible influence on the ability to drive or use machines.

**4.8 Undesirable effects**

In clinical studies approximately 50% of patients experienced some type of skin irritation adverse reaction at the site of application. Burning sensation and pruritus were very common, usually mild to moderate in severity and tended to resolve within one week of starting treatment. Erythema was a common skin irritation adverse reaction. Sensation of warmth, pain, paraesthesia and rash at the site of application were also commonly observed. Alcohol intolerance (facial flushing or skin irritation after consumption of an alcoholic beverage) was common.

Patients may be at an increased risk of folliculitis, acne and herpes viral infections.

Adverse reactions with suspected relationship to treatment are listed below by system organ class.

Frequencies are defined as very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ) and uncommon ( $\geq 1/1,000$  to  $< 1/100$ ). Within each defined as very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ) and uncommon ( $\geq 1/1,000$  frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<b>System Organ Class</b>	<b>Very Common <math>\geq 1/10</math></b>	<b>Common <math>\geq 1/100, &lt; 1/10</math></b>	<b>Uncommon <math>\geq 1/1000, &lt; 1/100</math></b>	<b>Not known (cannot be estimated from the available data)</b>
Infections and infestations		Local skin infection regardless of specific aetiology including but not limited to: Eczema herpeticum, Folliculitis, Herpes simplex, Herpes virus infection, Kaposi's		



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		varicelliform eruption*		
Metabolism and nutrition disorders		Alcohol intolerance (facial flushing or skin irritation after consumption of an alcoholic beverage)		
Nervous system disorders		Paraesthesias and dysaesthesias (hyperaesthesia, burning sensation)		
Skin and subcutaneous tissue disorders		Pruritus	Acne*	Rosacea*
General disorders and administration site conditions	Application site burning, Application site pruritus	Application site warmth, Application site erythema, Application site pain, Application site irritation, Application site paraesthesia, Application site rash		Application site oedema*
Investigations				Drug level increased*

\* The adverse reaction has been reported during post-marketing experience

#### Post-marketing

Cases of malignancies, including cutaneous (i.e. cutaneous T Cell lymphomas) and other types of lymphoma, and skin cancers, have been reported in patients using tacrolimus ointment.

#### Maintenance treatment

In a study of maintenance treatment (twice weekly treatment) in adults and children with moderate and severe atopic dermatitis the following adverse events were noted to occur more frequently than in the control group: application site impetigo (7.7% in children) and application site infections (6.4% in children and 6.3% in adults).

#### *Paediatric population*

Frequency, type and severity of adverse reactions in children are similar to those reported in adults.

#### **4.9 Overdose**

Overdosage following topical administration is unlikely.





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If ingested, general supportive measures may be appropriate. These may include monitoring of vital signs and observation of clinical status. Due to the nature of the ointment vehicle, induction of vomiting or gastric lavage is not recommended.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Other dermatologicals, ATC code: D11AH01

#### Mechanism of action and pharmacodynamic effects

The mechanism of action of tacrolimus in atopic dermatitis is not fully understood. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known.

Via its binding to a specific cytoplasmic immunophilin (FKBP12), tacrolimus inhibits calcium-dependent signal transduction pathways in T cells, thereby preventing the transcription and synthesis of IL-2, IL-3, IL-4, IL-5 and other cytokines such as GM-CSF, TNF- $\alpha$  and IFN- $\gamma$ .

*In vitro*, in Langerhans cells isolated from normal human skin, tacrolimus reduced the stimulatory activity towards T cells. Tacrolimus has also been shown to inhibit the release of inflammatory mediators from skin mast cells, basophils and eosinophils.

In animals, tacrolimus ointment suppressed inflammatory reactions in experimental and spontaneous dermatitis models that resemble human atopic dermatitis. Tacrolimus ointment did not reduce skin thickness and did not cause skin atrophy in animals.

In patients with atopic dermatitis, improvement of skin lesions during treatment with tacrolimus ointment was associated with reduced Fc receptor expression on Langerhans cells and a reduction of their hyperstimulatory activity towards T cells. Tacrolimus ointment does not affect collagen synthesis in humans.

### **5.2 Pharmacokinetic properties**

Clinical data have shown that tacrolimus concentrations in systemic circulation after topical administration are low and, when measurable, transient.



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#### Absorption

Data from healthy human subjects indicate that there is little or no systemic exposure to tacrolimus following single or repeated topical application of tacrolimus ointment.

Most atopic dermatitis patients (adults and children) treated with single or repeated application of tacrolimus ointment (0.03-0.1%), and infants from age of 5 months treated with tacrolimus ointment (0.03%) had blood concentrations < 1.0 ng/ml. When observed, blood concentrations exceeding 1.0 ng/ml were transient. Systemic exposure increases with increasing treatment areas. However, both the extent and the rate of topical absorption of tacrolimus decrease as the skin heals. In both adults and children with an average of 50% body surface area treated, systemic exposure (i.e. AUC) of tacrolimus from tacrolimus ointment is approximately 30-fold less than that seen with oral immunosuppressive doses in kidney and liver transplant patients. The lowest tacrolimus blood concentration at which systemic effects can be observed is not known.

There was no evidence of systemic accumulation of tacrolimus in patients (adults and children) treated for prolonged periods (up to one year) with tacrolimus ointment.

#### Distribution

As systemic exposure is low with tacrolimus ointment, the high binding of tacrolimus (> 98.8%) to plasma proteins is considered not to be clinically relevant.

Following topical application of tacrolimus ointment, tacrolimus is selectively delivered to the skin with minimal diffusion into the systemic circulation.

#### Metabolism

Metabolism of tacrolimus by human skin was not detectable. Systemically available tacrolimus is extensively metabolised in the liver via CYP3A4.

#### Elimination

When administered intravenously, tacrolimus has been shown to have a low clearance rate. The average total body clearance is approximately 2.25 l/h. The hepatic clearance of systemically available tacrolimus could be reduced in subjects with severe hepatic impairment, or in subjects who are co-treated with drugs that are potent inhibitors of CYP3A4.

Following repeated topical application of the ointment the average half-life of tacrolimus was estimated to be 75 hours for adults and 65 hours for children.

#### *Paediatric population*

The pharmacokinetics of tacrolimus after topical application are similar to those reported in adults, with minimal systemic exposure and no evidence of accumulation.



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### **5.3 Preclinical safety data**

#### Repeated dose toxicity and local tolerance

Repeated topical administration of tacrolimus ointment or the ointment vehicle to rats, rabbits and micropigs was associated with slight dermal changes such as erythema, oedema and papules.

Long-term topical treatment of rats with tacrolimus led to systemic toxicity including alterations of kidneys, pancreas, eyes and nervous system. The changes were caused by high systemic exposure of rodents resulting from high transdermal absorption of tacrolimus. Slightly lower body weight gain in females was the only systemic change observed in micropigs at high ointment concentrations (3%).

Rabbits were shown to be especially sensitive to intravenous administration of tacrolimus, reversible cardiotoxic effects being observed.

#### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

##### Mutagenicity

In vitro and in vivo tests did not indicate a genotoxic potential of tacrolimus.

##### Carcinogenicity

Systemic carcinogenicity studies in mice (18 months) and rats (24 months) revealed no carcinogenic potential of tacrolimus.

In a 24-month dermal carcinogenicity study performed in mice with 0.1% ointment, no skin tumours were observed. In the same study an increased incidence of lymphoma was detected in association with high systemic exposure.

In a photocarcinogenicity study, albino hairless mice were chronically treated with tacrolimus ointment and UV radiation. Animals treated with tacrolimus ointment showed a statistically significant reduction in time to skin tumour (squamous cell carcinoma) development and an increase in the number of tumours. It is unclear whether the effect of tacrolimus is due to systemic immunosuppression or a local effect. The risk for humans cannot be completely ruled out as the potential for local immunosuppression with the long-term use of tacrolimus ointment is unknown.

##### Reproduction toxicity

Embryo/foetal toxicity was observed in rats and rabbits, but only at doses that caused significant toxicity in maternal animals. Reduced sperm function was noted in male rats at high subcutaneous doses of Tacrolimus.



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**6 Pharmaceutical particulars**

**6.1 List of excipients**

White soft paraffin  
Liquid Paraffin  
White Bees Wax  
Hard Paraffin  
Propylene Carbonate

**6.2 Incompatibilities**

None

**6.3 Shelf life**

24 months

**6.4 Special precautions for storage**

Store below 25°C. Do not freeze.

**6.5 Nature and contents of container**

Tube of 10 gm

**7. Registrant**

**Registered office**

Glenmark Pharmaceuticals Limited,  
B/2, Mahalaxmi Chambers,  
22, Bhulabhai Desai road,  
Mumbai – 400 026

**Address for Correspondence**

Glenmark House,  
HDO-Corporate Building,  
Wing – A, B, D. Sawant Marg, Chakala,  
Off western express highway,  
Andheri (East), Mumbai – 400 099  
TEL NO.: +91-22-40189999 FAX NO.: +91-22-40189990



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**8. Manufacturer**

Glenmark Pharmaceuticals Limited  
Plot No. E -37,39, 'D' Road,  
M.I.D.C Industrial Estate, Satpur  
Nashik - 422007.

**9. Date of revision of the text**

SPC not yet approved

**10. DOSIMETRY (IF APPLICABLE)**

Not applicable

**11. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

Not Applicable.