1.6 Product Information

1.6.1 PRESCRIBING INFORMATION (SUMMARY OF PRODUCTS CHARACTERISTICS)

(SPC, CONTAINER LABELING & PATIENT INFORMATION LEAFLET, MOCK-UPS AND SPECIMENS)

SPC – Summary of the Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

TACROVATE FORTE OINTMENT (Tacrolimus Ointment 0.1% w/w)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g contains:

Tacrolimus USP	1.0 mg
In an Ointment base	q.s.

For full list of Excipients refer 6.1.

3. PHARMACEUTICAL FORM

Topical Ointment. A white to off white ointment, free from grittiness.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tacrolimus forte Ointment is indicated in adults, adolescents and children from the age of 2 years.

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 maximum of 6 weeks treatment of twice daily TACROVATE FORTE OINTMENT (lesions cleared, almost cleared or mildly affected).

4.2 Posology and method of administration

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

TACROVATE FORTE OINTMENT treatment should begin at the first appearance of signs and symptoms. Each affected region of the skin should be treated with TACROVATE FORTE OINTMENT until lesions are cleared, almost cleared or mildly affected. Thereafter, patients are considered suitable for maintenance treatment. 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 TACROVATE FORTE OINTMENT twice a day and treatment should be continued until clearance of the lesion. If symptoms recur, twice daily treatment with TACROVATE FORTE OINTMENT should be restarted. An attempt should be made to reduce the frequency of application or to use the lower strength TACROVATE FORTE 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.

Elderly patients

Specific studies have not been conducted in elderly patients. 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 TACROVATE FORTE OINTMENT.

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.

TACROVATE FORTE 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 TACROVATE FORTE 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 should use TACROVATE FORTE OINTMENT.

TACROVATE FORTE OINTMENT should be applied once a day twice weekly to areas commonly affected by atopic dermatitis to prevent progression to flares. Between applications there should be 2–3 days without TACROVATE FORTE OINTMENT 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.

Elderly patients

Specific studies have not been conducted in elderly patients (see flare treatment section above).

Paediatric population

Children (2 years of age and above) should use the lower strength TACROVATE FORTE OINTMENT.

TACROVATE FORTE OINTMENT should be applied once a day twice weekly to areas commonly affected by atopic dermatitis to prevent progression to flares. Between applications there should be 2–3 days without TACROVATE FORTE OINTMENT 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.
Tacrolimus forte Ointment should not be used in children aged below 2 years until further data are available.

Method of administration

TACROVATE FORTE 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. TACROVATE FORTE 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 minimisation of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing. TACROVATE FORTE 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 TACROVATE FORTE 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 TACROVATE FORTE OINTMENT 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 TACROVATE FORTE OINTMENT with respect to the response to treatment and the continuing need for treatment. After 12 months this evaluation should include suspension of TACROVATE FORTE OINTMENT 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.
TACROVATE 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 forte Ointment

should not be used in patients with congenital or acquired immune deficiencies or in patients on therapy that cause immunosuppression.
Patients with atopic dermatitis treated with TACROVATE FORTE 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, and 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 TACROVATE FORTE 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 TACROVATE FORTE OINTMENT should be considered.
The effect of treatment with TACROVATE FORTE OINTMENT on the developing immune system of children aged below 2 years has not been established.
TACROVATE FORTE 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 TACROVATE FORTE OINTMENT 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 TACROVATE FORTE OINTMENT 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.
The use of TACROVATE FORTE 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

No interaction studies have been performed.

4.6 Pregnancy and lactation

Fertility
There are no fertility data available.
Pregnancy
There are no adequate data from the use of TACROVATE FORTE OINTMENT in pregnant women. Studies in animals have shown reproductive toxicity following systemic administration. The potential risk for humans is unknown.

TACROVATE FORTE OINTMENT should not be used during pregnancy unless clearly necessary.
Breastfeeding
Human data demonstrate that, after systemic administration, tacrolimus is excreted into breast milk. Although clinical data have shown that systemic exposure from application of TACROVATE FORTE OINTMENT is low, breast-feeding during treatment with TACROVATE FORTE OINTMENT is not recommended.

4.7 Effects on ability to drive and use machines
TACROVATE FORTE OINTMENT has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
Skin burning. Pruritus. Skin erythema (approximately 50% in trials though there is a marked decrease within several days with continued use) Skin tingling. Folliculitis. Herpes simplex (herpes, cold sores, eczemaherpeticum [Kaposi's varicelliform eruption]). Hyperaesthesia (increased skin sensitivity, especially to hot and cold).Alcohol intolerance (facial flushing or skin irritation after consumption of alcohol). Acne. Rosacea. Lymphadenopathy has been reported rarely Pimecrolimus Application site reactions - irritation, pruritus and erythema. Skin infections - folliculitis.Alcohol intolerance (facial flushing or skin irritation after consumption of alcohol). Furuncle. Impetigo.Herpes simplex, herpes zoster, herpes simplex dermatitis (eczema herpeticum). Molluscum contagiosum. Skin papilloma. Application site disorders (rash, pain, paraesthesia, desquamation, dryness, oedema, aggravated eczema)

4.9 Overdose
Overdosage following topical administration is unlikely.
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 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.

5.2 Pharmacokinetic properties:

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

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 TACROVATE FORTE OINTMENT (0.03-0.1%), and infants from age of 5 months treated with TACROVATE FORTE 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 Protopic 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.

5.3 Preclinical safety data

Not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sr. No.	Ingredients	Specification
1.	Cetostearyl Alcohol	BP
2.	Cetomacrogol 1000	BP
3.	Light liquid paraffin	BP
4.	Butylated Hydroxytoluene	BP
5.	White soft paraffin	BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30^0 C. Protect from Light.

6.5 Nature and contents of container

10 g tube

6.6 Special precautions for disposal

Do not use the medicine without the prescription of Registered Medical Practitioner.

7. MARKETING AUTHORISATION HOLDER

Ochoa Laboratories
430, Mzz. F, Gundecha Indl. Complex
Akurli Road, kandivali (E).
Mumbai – 400101. India.
E-mail: support@aurochemgroup.com

8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT