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Tacrolimus (Protopic®) ointment

It is recommended that treatment with tacrolimus be initiated only by physicians (including general practitioners) with a special interest and experience in dermatology, and only after careful discussion with the patient about the potential risks and benefits of all appropriate second-line treatment options[4].

Background Information	Tacrolimus ointment is a topical immunomodulator and belongs to the class of immunosuppressant drugs known as calcineurin inhibitors[1]. They work by reducing inflammation through the suppression of T-lymphocyte responses (different mechanism of action from topical corticosteroids)[1,5].
BNF therapeutic class	13.05.03
Indication	**NICE Recommendations** Tacrolimus (Protopic®) ointment is available in strengths of 0.1% for use in adults and adolescents 16 years of age and above[1,2] and 0.03% for adults, adolescents and children 2 years of age and above.[3,5]. Topical tacrolimus is recommended, within its licensed indications, as an option for the second-line treatment of moderate to severe atopic eczema in adults and children aged 2 years and older that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy[4].NICE clarify 'not controlled by topical corticosteroids' as atopic eczema that has not shown a satisfactory clinical response to adequate use of the maximum strength and potency that is appropriate for the patient's age and the area being treated[4].
Administration	**Tacrolimus (Protopic®) ointment** Tacrolimus ointment should be applied as a thin layer to the 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[2,3]. *(Please note: secondary care may advise the application of tacrolimus ointment on mucous membranes (oral/genital e.g. for lichen planus) in exceptional circumstances. This indication is NOT licensed and hence NOT covered by this guidance. For this indication tacrolimus ointment would be classified as a red drug.)* Flare treatment - Tacrolimus ointment can be used for short-term and intermittent long term treatment. Treatment should not be continuous on a long term basis. Treatment should begin at the first appearance of signs and symptoms. Each affected region of the skin should be treated with tacrolimus ointment 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, maintenance treatment should be re-initiated[2,3].

	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 tacrolimus ointment (lesions cleared, almost cleared or mildly affected)[2,3].
Dosage	**Tacrolimus (Protopic®) ointment** Flare treatment **Adults and adolescents (16 years of age and above):** Treatment should be started with tacrolimus 0.1% ointment twice a day and continued until clearance of the lesion. If symptoms recur, twice daily treatment with tacrolimus 0.1% ointment should be restarted. An attempt should be made to reduce the frequency of application or to use the lower strength tacrolimus 0.03% ointment if the clinical condition allows[2]. 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[2]. **Children 2 years of age and above: should use the lower strength tacrolimus 0.03% ointment:** Treatment of moderate to severe atopic dermatitis in children who failed to respond adequately to conventional therapies such as topical corticosteroids. 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[3]. Maintenance treatment **Adults and adolescents (16 years of age and above):** Tacrolimus 0.1% 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 tacrolimus 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)[2] **Children 2 years of age and above:** Tacrolimus 0.03% 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 tacrolimus 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.If signs of a flare reoccur, twice daily treatment should be re-initiated (see flare treatment section above)[3]

Cautions	**Tacrolimus (Protopic®) ointment** Emollients should not be applied to the same area within 2 hours of applying tacrolimus ointment[2,3]. Exposure of the skin to sunlight should be minimised and the use of UV light from solarium therapy with UVB or UVA should be avoided during the 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 (high SPF cream over 30)[1,2,3 5]. Tacrolimus ointment does not contain alcohol but does contain ingredients derived from animals (beeswax) and patients will need advising of this prior to commencing tacrolimus ointment[2,3]. Avoid: application to malignant or potentially malignant skin lesions; application under occlusion; contact with eyes; contact with mucous membranes; infection at treatment site, alcohol consumption (risk of facial flushing and skin irritation), pregnancy and breastfeeding[2,3]. The development of any new change different from previous eczema within a treated area should be reviewed by the physician[2,3]. Tacrolimus ointment is not recommended in patients with a skin barrier defect, such as Netherton's syndrome, lamellar ichthyosis, generalised erythroderma or cutaneous Graft Versus Host Disease. These skin conditions may increase systemic absorption of tacrolimus. [2,3]. Before commencing treatment with tacrolimus ointment, clinical infections at treatment sites should be cleared. Consider swabbing of skin prior to commencing tacrolimus ointment.[2,3] Patients with atopic dermatitis are predisposed to superficial skin infections. Treatment with tacrolimus 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)[2.3]. Tacrolimus ointment should not be used in patients with congenital or acquired immunodeficiencies or in patients on therapy that cause immunosuppression[2,3]. (See MHRA alert June 2012: *https://www.gov.uk/drug-safety-update/tacrolimus-ointment-protopic-possible-risk-of-malignancies-including-lymphomas-and-skin-cancers*)[6]
Contraindications	**Tacrolimus (Protopic®) ointment** Hypersensitivity to tacrolimus, macrolides in general, or to any of the excipients[1,2,3,5].
Adverse Drug Reactions & Interactions	**Tacrolimus (Protopic®) ointment** **Adverse drug Reactions-**application site reactions-skin irritation, stinging sensation (very common on application which may lesson over time), burning sensation, pruritis, erythema; application site infections -folliculitis, acne or herpes simplex infections; application site reactions -warmth, pain, paraesthesia and rash [1,2,3,5].

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	Interactions - Tacrolimus interacts with alcohol - alcohol increases the risk of facial flushing and skin irritation when given with topical tacrolimus[1,2,3,5]. Systemic absorption of tacrolimus can follow topical application hence possibility of interactions may occur. (See full list in the BNF TACROLIMUS | Drug | BNF content published by NICE).
Monitoring	Initiation by specialist dermatology service under which patient should be given a patient specific treatment plan. Review by Primary care 2 weeks after commencing treatment with Tacrolimus ointment and every 12 months. Review should include discussions around: • Use of all treatments (including concomitant emollients). • Considering suspension of treatment to access need to continue treatment • Liaising with dermatology regarding side effects, increase in skin infections or changes in patients' condition which may have an impact on treatment.

Contact names and details

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References

1. *BNF- https://bnf.nice.org.uk/drug/tacrolimus.html*
2. *Summary of Product Characteristics (SmPC)Tacrolimus 0.1%ointment- https://www.medicines.org.uk/emc/product/1608/smpc*
3. *Summary of Product Characteristics (SmPC)Tacrolimus 0.03% ointment- https://www.medicines.org.uk/emc/product/1612/smpc*
4. *NICE- https://www.nice.org.uk/guidance/ta82*
5. *BNF Children - https://bnfc.nice.org.uk/drug/tacrolimus.html*
6. *MHRA alert tacrolimus ointment June2012 - https://www.gov.uk/drug-safety-update/tacrolimus-ointment-protopic-possible-risk-of-malignancies-including-lymphomas-and-skin-cancers*

Development Process

This guidance has been produced following an AMBER-G classification status of Tacrolimus by the Barnsley Area Prescribing Committee. This guideline has been subject to consultation and endorsement by the Area Prescribing Committee on 14th August 2019.