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

Pimecrolimus Cream 1% w/w

PICON® पाइकौन

COMPOSITION
Each gram contains
Pimecrolimus 10 mg
Benzyl alcohol IP 10 mg
(as preservative)
Cream base q.s.

ATC Code: D11AH02

PIMECROLIMUS CREAM
Pimecrolimus Cream 1% w/w is a nonsteroid anti-inflammatory dermatological cream for cutaneous use. The cream is whitish, odourless, non-staining, and easily spreadable.

Pimecrolimus Cream 1% w/w contains the compound Pimecrolimus, the immunosuppressant 33-epi-chloro-derivative of the macrolactam ascomycin.

Chemically, Pimecrolimus is (1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-2-{(1R,3R,4S)-4-chloro-3-methoxycyclohexyl}-1-methylvinyl]-17-ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.04,9]octacos-18-ene-2,3,10,16-tetraone.

The compound has the empirical formula $C_{43}H_{68}ClNO_{11}$ and the molecular weight of 810.47.

INDICATIONS AND USAGE
Pimecrolimus 1% w/w is indicated as second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.

DOSAGE AND ADMINISTRATION
Apply a thin layer of Pimecrolimus Cream 1% w/w to the affected skin twice daily and rub in gently and completely. Pimecrolimus Cream 1% w/w may be used on all skin areas, including the face, head, neck and intertriginous areas.

In the long-term management of atopic dermatitis (eczema), Pimecrolimus Cream 1% w/w treatment should begin at first appearance of signs and symptoms of atopic dermatitis to prevent flares of the disease. Pimecrolimus Cream 1% w/w should be used twice daily until signs and symptoms resolve. If signs and symptoms persist beyond 6 weeks, patients should be re-examined to confirm the diagnosis of atopic dermatitis. If discontinued, treatment should be resumed upon first recurrence of signs and symptoms to prevent flares of the disease. Emollients can be applied immediately after using Pimecrolimus Cream 1% w/w. However, after a bath/shower, emollients should be applied before using Pimecrolimus Cream 1% w/w.

Due to the low level of systemic absorption, there is no restriction either in the total daily dose applied or in the extent of the body surface area treated or in the duration of treatment.

Paediatric patients
PICON® Cream 1% is not indicated for use in children less than 2 years of age. The long-term safety and effects of Pimecrolimus Cream 1% on the developing immune system are unknown.

Elderly Patients
Atopic dermatitis (eczema) is rarely observed in patients aged 65 and over. Clinical studies with Pimecrolimus Cream 1% w/w did not include a sufficient number of these patients.

CONTRAINDICATIONS
Known hypersensitivity to Pimecrolimus or to any related constituents.

WARNING
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 Picon Cream..

Therefore:
- Continuous long-term use of topical calcineurin inhibitors, including PICON® Cream, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis.
- PICON® Cream is not indicated for use in children less than 2 years of age.

SAFETY INFORMATION
Toxicology studies after dermal application
A variety of preclinical safety studies were conducted with the Pimecrolimus cream formulations in several animal species. There was no evidence of irritation, (photo) sensitization, or local or systemic toxicity.

ADVERSE REACTIONS
The safety profile of Pimecrolimus Cream 1% w/w has been established in more than 2000 patients including infants (≥ 3 months), children, adolescents, and adults enrolled inphase 2 and 3 studies. Over 1500 of these patients were treated with Piecrolimus Cream 1% w/w and over 500 were treated with control treatment i.e.either Pimecrolimus vehicle and/or topical corticosteroids.

The most common adverse events were application site reactions which were reported by approximately 19% of the patients treated with Prmecrolimus Cream 1% w/w and 16% of patients in the control group. These reactions generally occurred early in treatment, were mild/moderate in severity and were of short duration.

Table 1 and 2 describes noted adverse reactions with Pimecrolimus in clinical trials and in post marketing experiences.

Table 1 - Skin and subcutaneous tissue disorders

Very common	application site burning
Common	application site reactions (irritation, pruritus and erythema), skin infections (folliculitis)
Uncommon	impetigo, condition aggravated, herpes simplex, herpes simplex dermatitis (eczema herpeticum), molluscum contagiosum, application site disorders such as rash, pain, paraesthesia, desquamation, dryness, oedema, skin papilloma, furuncle

Table 2 - Voluntarily reported reactions during post marketing experience

Immune system disorders	
Very rare	anaphylactic reactions
Metabolism and nutrition disorders	
Rare	alcohol intolerance[1)]
Skin and subcutaneous tissue disorders	
Rare	allergic reactions (e.g. rash, urticaria, angioedema), skin discoloration (e.g. hypo pigmentation, hyperpigmentation)

[1)] In most cases, flushing, rash, burning, itching or swelling occurred shortly after the intake of alcohol.

Rare cases of malignancy, including cutaneous and other types of lymphoma, and skin cancers, have been reported in patients using Pimecrolimus cream, although no causal relationship has been established.

OVERDOSE
There has been no experience of overdose with Pimecrolimus Cream 1% w/w.

DRUG INTERACTIONS
Potential interactions between Pimecrolimus Cream 1% w/w and other drugs have not been systematically evaluated.

A study that included 79 infants treated for up to 2 years showed that treatment with Pimecrolimus Cream 1% w/w did not interfere with the protective immune response to childhood vaccinations. Application of Pimecrolimus Cream 1% w/w to vaccination sites, as long as local reactions persist, was not studied and is therefore not recommended.

PREGNANCY AND LACTATION
Pregnancy
There are no adequate data from the use of Pimecrolimus Cream 1% w/w in pregnant women.
Caution should be exercised when prescribing Pimecrolimus Cream 1% w/w to pregnant women.

Lactation
Animal studies on milk excretion after topical applications were not conducted. It is not known whether Pimecrolimus is excreted in the milk after topical application. Nursing mothers should not apply Pimecrolimus Cream 1% w/w to the breast.

Fertility
There are no clinical data on the effects of Pimecrolimus on male or female fertility.

PHARMACOKINETICS
Data in humans
Absorption in adults
Systemic exposure to Pimecrolimus was investigated in 12 adult patients treated with Pimecrolimus Cream 1% w/w twice daily for 3 weeks. These patients had atopic dermatitis (eczema) lesions affecting 15 to 59% of their body surface area (BSA). 77.5% of Pimecrolimus blood concentrations were below 0.5 ng/mL, the assay limit of quantitation (LoQ), and 99.8% of the total samples were below 1 ng/mL. The highest blood concentration of Pimecrolimus measured in one patient was 1.4 ng/mL.

In 40 adult patients treated for up to 1 year with Pimecrolimus, having 14 to 62% of their BSA affected at baseline, 98% of Pimecrolimus blood concentrations of Pimecrolimus were consistently low, mostly below the LoQ. A maximum blood concentration of 0.8 ng/mL was measured in only 2 patients in week 6 of treatment. There was no increase in blood concentration over time in any patient during the 12 months of treatment. In 8 adult AD patients presenting with at least three quantifiable blood levels per visit day, the $AUC_{(0to12h)}$ values ranged from 2.5 to 11.4 ng x h/mL.

Absorption in children
Systemic exposure to Pimecrolimus was investigated in 58 paediatric patients aged 3 months to 14 years, who had atopic dermatitis (eczema) lesions involving 10 to 92% of the total body surface area. These children were treated with Pimecrolimus Cream 1% w/w twice daily for 3 weeks and five out of them were treated for up to 1 year on a "as needed" basis.

The blood concentrations measured in these paediatric patients were consistently low regardless of the extent of lesions treated or duration of therapy. They were in a range similar to that measured in adult patients treated under the same dosing regimen. 60% of Pimecrolimus blood concentrations were below 0.5 ng/mL (LoQ) and 97% of all samples were below 2 ng/mL.

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Distribution
Consistent with its skin selectivity, after topical application, Pimecrolimus blood levels are very low. Therefore, Pimecrolimus metabolism could not be determined after topical administration.

In vitro plasma protein binding studies have shown that 99.6% of Pimecrolimus in plasma is bound to different lipoproteins.

PHARMACODYNAMICS
Non-clinical pharmacology
Pimecrolimus is an anti-inflammatory ascomycin macrolactam derivative and a selective inhibitor of the production and release of pro-inflammatory cytokines and mediators in T cells and mast cells.

Pimecrolimus binds with high affinity to macrophilin-12 and inhibits the calcium-dependent phosphatase calcineurin. As a consequence, it inhibits T cell proliferation and prevents the transcription and release of both T helper type 1 cell (TH1) and T helper type 2 cell (TH2) inflammatory cytokines such as interleukin-2, interferon-gamma, interleukin-4, interleukin-5, interleukin-10, tumor necrosis factor alpha and granulocyte macrophage colony-stimulating factor. Pimecrolimus and Tacrolimus have similar potencies to inhibit recall antigen responses in human T-helper cell clones, isolated from the skin of an atopic dermatitis patient. Pimecrolimus also prevents the release of cytokines and pro-inflammatory mediators from mast cells in vitro after stimulation by antigen/IgE. Pimecrolimus does not affect the growth of keratinocyte, fibroblast or endothelial cell lines and, in contrast to corticosteroids, does not impair the differentiation, maturation, functions and viability of murine Langserhans cells and human monocytes-derived dendritic cells, thus, underlining its cell-selective mode of action.

In studies using various topical formulations, including the Pimecrolimus cream and corticosteroids, Pimecrolimus penetrates similarly into, but permeates less through skin in vitro than corticosteroids, suggesting a lower systemic exposure to Pimecrolimus after topical application as compared corticosteroids.

Pimecrolimus exhibits high anti-inflammatory activity in animal models of skin inflammation after topical and systemic application. Pimecrolimus is as effective as the high potency corticosteroids like Clobetasol-17-propionate and fluticasone after topical application.

The data show that topical Pimecrolimus has a high and selective anti-inflammatory activity in the skin and minimal percutaneous resorption. It differs from corticosteroids by its selective action on T cells and mast cells, by lack of impairment of Langerhans' cells/dendritic cells, by lack of induction of skin atrophy and by less permeation through skin. It has a lower potential for affecting systemic immune responses.

Clinical data
Short-term (acute) treatment in paediatric patients
Children and adolescents: Two 6-week, vehicle-controlled trials were conducted including a total of 403 paediatric patients aged 2 to 17 years. Patients were treated twice daily with Pimecrolimus Cream 1% w/w. The data of both studies were pooled.
Infants: A similar 6-week study was conducted in 186 patients aged 3 to 23 months.

In these three 6-week studies, the efficacy results at endpoint were as follows:

		Children and adolescents			Infants		
Endpoint	**Criteria**	**Pimecrolimus 1% (N=267)**	**Vehicle (N=136)**	**p-value**	**Pimecrolimus 1% (N=123)**	**Vehicle (N=63)**	**p-value**
IGA*	Clear or almost clear[1]	34.8%	18.4%	<0.001	54.5%	23.8%	< 0.001
IGA*	Improvement[2]	59.9%	33%	not done	68%	40%	Not done
Pruritus	Absent or mild	56.6%	33.8%	< 0.001	72.4%	33.3%	< 0.001
EASI ^	Overall (mean % change)[3]	-43.6	-0.7	< 0.001	-61.8	+ 7.35	<0.001
EASI ^	Head / Neck (mean % change)[3]	- 61.1	+0.6	< 0.001	- 74.0	+ 31.48	<0.001

*Investigators Global Assessment
^ Eczema Area Severity Index (EASI): mean % change in clinical signs (erythema, infiltration, excoriation, lichenification) and body surface area involved
[1] p-value based on CMH test stratified by centre
[2] Improvement=lower IGA than at baseline
[3] p-value based on ANCOVA model of EASI at Day 43 endpoint, with centre and treatment as factors and baseline (Day 1) EASI a covariate

A significant improvement in pruritus was observed within the first week of treatment in 44% of children and adolescents and in 70% of infants.

Long-term treatment in paediatric patients
In two double-blind studies of long-term management of atopic dermatitis in 713 children and adolescents (2 to 17 years) and 251 infants (3 to 23 months), Pimecrolimus Cream 1% w/w was evaluated as first line foundation therapy.

In addition to emollients, the Pimecrolimus group received Pimecrolimus Cream 1% w/w used at first signs of itching and. redness to prevent progression to flares of atopic dermatitis; only in case of flare not controlled by Pimecrolimus Cream 1% w/w, treatment with medium potency topical corticosteroids was initiated.

The control group received a standard treatment consisting of emollient plus medium potency topical corticosteroids to treat flares. Pimecrolimus vehicle was used instead of Pimecrolimus Cream 1% w/w in order to maintain the studies blind.

Both studies showed a reduction in the incidence of flares ($p < 0.001$) in favour of Pimecrolimus Cream 1% w/w first-line treatment; Pimecrolimus Cream 1% w/w first-line treatment showed better efficacy in all secondary assessments (Eczema Area Severity Index, IGA, subject assessment); pruritus was controlled within a week with Pimecrolimus Cream 1% w/w. Significantly more patients on Pimecrolimus Cream 1% w/w completed 6 months; children (61 % Pimecrolimus vs 34% control); infants (70% Pimecrolimus vs 33% control) AND 12 months (children 51 % Pimecrolimus vs 28% control) with no flare. Significantly more patients treated with Pimecrolimus Cream 1% w/w did not use corticosteroids in the first 6 months (children: 65% Pimecrolimus vs 37% control; infants: 70% Pimecrolimus vs 39% control) OR 12 months (children: 57% Pimecrolimus vs 32% control). The efficacy of Pimecrolimus Cream 1% w/w was maintained over time with the ability to prevent disease progression to severe flares.

Special studies
Tolerability studies demonstrated that Pimecrolimus Cream 1% w/w is devoid of any irritation, contact sensitising, phototoxic or photosensitising potential.

The atrophogenic potential of Pimecrolimus Cream 1% w/w in humans was tested in comparison to medium and highly potent topical steroids (betamethasone-17-valerate 0.1 % cream, triamcinolone acetonide 0.1 % cream) and vehicle in sixteen healthy volunteers treated for 4 weeks. Both topical corticosteroids induced a significant reduction in skin thickness measured by echography as compared to Pimecrolimus Cream 1% w/w and vehicle, which did not induce a reduction of skin thickness.

INCOMPATIBILITIES
In the absence of compatibility studies, this medicinal product must not be mixed with other topical medicinal products. Emollients can be applied together with Pimecrolimus Cream 1% w/w.

Shelf Life: Please refer carton/tube.

STORAGE
Store below 30°C. Do not refrigerate or freeze.
Keep out of reach of children
IT IS FOR TOPICAL DERMATOLOGICAL USE ONLY. NOT FOR OPTHALMIC USE.

Information for Patients:
Patients using Pimecrolimus cream should receive the following information and instructions:
- As with any topical medication, patients or caregivers should wash hands after application if hands are not an area for treatment.
- Patients should not use this medication for any disorder other than that for which it was prescribed.
- Patients should report any signs of adverse reactions to their physician.
- The cream should be applied twice daily, once in the morning and once in the evening. Moisturizers (emollients) can be applied immediately after using Pimecrolimus Cream 1% w/w. However, after a bath/shower, moisturizers (emollients) should be applied before using Pimecrolimus Cream 1% w/w.
- If there are no signs of improvement after 6 weeks of treatment, consult your doctor. Sometimes other skin diseases can look like eczema.
  Any unused product or waste material should be disposed of in accordance with local requirements. Once opened, the contents of the tube should be used within 1 year.

PRESENTATION
PICON ® is available in 5g (PS), 10g & 30g (Sales) lami tube with screw cap.

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

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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.**

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