Revised: November 2022 (1st version)

Standard Commodity Classification No. of Japan
872646

Topical Synthetic Corticosteroid

Betamethasone Valerate Ointment

BECTMIRAN OINTMENT 0.12%

Storage: Store at room temperature.
Shelf Life: 3 years

Approval No.	22900AMX00122
Date of Initial Marketing in Japan	June 1984

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)

2.1 Bacterial, fungal, spirochetal, and viral skin infections, and animal dermatosis (scabies, crab louse, etc.) [These diseases may be aggravated.]

2.2 Patients with a history of hypersensitivity to any of the ingredients of the product

2.3 Eczematous external otitis with perforation of ear drum [Healing of perforated site may be delayed and infected.]

2.4 Ulcer (excluding Behcet's disease) or deep dermal burn or severer burn/chilblain [Regeneration of skin may be inhibited, and healing may be delayed.]

3. COMPOSITION AND PRODUCT DESCRIPTION

3.1 Composition

Active ingredient per gram	JP Betamethasone Valerate····· 1.2 mg
Excipients	White petrolatum, liquid paraffin

3.2 Product Description

Description/Dosage form	White to pale yellow translucent ointment

4. INDICATIONS

Eczema or dermatitis group (including keratodermia tylodes palmaris progressiva, female facial melanosis, lichen Vidal, radiodermatitis and photosensitive rash), pruritus, prurigo group (including lichen urticatus, strophulus and urticaria perstans), insect sting, psoriasis, palmoplantar pustulosis, lichen planus, lichen nitidus, pityriasis rubra pilaris, Girbert's pityriasis rosea, erythema group (including erythema multiforme, erythema nodosum and erythema annulare centrifugum (Darier)), erythroderma (including erythroderma due to malignant tumor), chronic discoid lupus erythematosus, drug eruption or toxicoderma, alopecia areata (including malignant), burns (including scar and keloid), chilblain, pemphigus group, dermatitis herpetiformis Duhring (including pemphigoid), hemorrhoids, surgical wound of tympanoplasty, fenestration and radical mastoidectomy

5. PRECAUTIONS CONCERNING INDICATIONS

As a rule, this drug should not be used for eczema/dermatitis with skin infection, but if this drug should be used by necessity, treatment with appropriate antibacterial agent (systemic), antifungal agent, or a combination use of these agents should be considered beforehand.

6. DOSAGE AND ADMINISTRATION

The usual adequate dose should be applied on the lesions once to several times daily.

The dosage may be adjusted according to the patient's symptoms.

8. IMPORTANT PRECAUTIONS

8.1 When a large amount or long-term use of this drug in a wide area occlusive dressing technique (ODT) etc. is applied, symptoms similar to those occur with systemic administration of adrenal corticosteroid may develop. [See 9.5, 9.7, 9.8, and 11.1.1]

8.2 If symptoms do not improve or are aggravated with this drug, treatment with this drug should be discontinued.

8.3 After improvement was observed, the use of this drug should be discontinued as soon as possible.

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

9.5 Pregnant Women

A large amount or long-term use of this drug in a wide area must be avoided in pregnant women or women who may possibly be pregnant. [See 8.1]

9.7 Pediatric Use

Studies have reported that long-term/large amount use of this drug or occlusive dressing technique (ODT) caused developmental disorder [1]. In addition, care should be exercised because diapers have the similar effects as that of the occlusive dressing technique (ODT). [See 8.1]

9.8 Geriatric Use

When a large amount or long-term use of this drug in a wide area occlusive dressing technique (ODT) etc. is applied, particular care should be exercised. In general, adverse reactions are likely to occur. [See 8.1]

11. ADVERSE REACTIONS

Since the following adverse reactions may occur, patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuing administration should be taken.

11.1 Clinically Significant Adverse Reactions

11.1.1 Ocular hypertonia, glaucoma, posterior subcapsular cataract (incidence unknown)

When this drug is used on the eyelid skin, ocular hypertonia and glaucoma[2] may develop. When a large amount or long-term use of this drug in a wide area occlusive dressing technique (ODT) is applied, glaucoma, posterior subcapsular cataract, and other symptoms may develop. [See 8.1]

11.2 Other Adverse Reactions

Type/Incidence	0.1% to less than 5% Note 1	Incidence unknown
Hypersensitivity		Skin irritation, dermatitis contact, rash
Eye		Central serous chorioretinopathy
Skin infections Note 2		Bacterial infections (contagious impetigo, folliculitis, furuncle, etc.), mycosis (candidiasis, tinea, etc.), viral infections
Other cutaneous symptoms Note 3	Ichthyosis-like skin lesions, purpura, hypertrichosis , depigmentation	Steroid acne (similar to acne vulgaris but tends to develop multiple whiteheads), steroid rosacea/perioral dermatitis (erythema, papule, capillarectasia, scab, or scales around the mouth and all over the face), steroid skin (skin atrophy, capillarectasia)
Pituitary/adrenocortical		Suppression of

system		pituitary/adrenocortical system functions Note 4

Note 1) Including reevaluation results

Note 2) If such symptoms are found, appropriate antibacterial or antifungal agents should be coadministered, and if symptoms do not improve promptly, the use of this drug should be discontinued. They are more likely to develop in the case of occlusive dressing technique (ODT)

Note 3) If such symptoms occur due to long-term continuous use, the use of this drug should be gradually withdrawn, and treatment drug should be switched to agents containing no adrenal corticoid.

Note 4) Events developed by using this drug extensively in a large amount or over a long period of time and by occlusive dressing technique (ODT). Treatment discontinuation may cause adrenocortical insufficiency acute. When treatment with this drug should be discontinued, the dosage should be gradually reduced according to the patient's condition.

14. PRECAUTIONS CONCERNING USE

14.1 Precautions Concerning the Dispensing of the Drug

Patients should be instructed to pay attention to the following points.

14.1.1 Application

Attention should be paid not to use this drug under makeup or after shaving.

14.1.2 Application site

This drug should not be used as an ophthalmic remedy.

16. PHARMACOKINETICS

16.2 Absorption

After applying 0.15% ^{3}H-labeled betamethasone valerate cream to normal human axillary skins for 30 minutes, 1 hour, 2 hours, 4 hours, and 8 hours by an occlusive dressing technique (ODT), the drug was removed, and transepidermal absorption and absorption through skin appendages were examined by the autoradiography method. As a result, absorption for both was favorable. [3]

Table 16-1 Transepidermal absorption and absorption through skin appendages

Site\Occlusive dressing technique (ODT) time	30 minutes	1 hour	2 hours	4 hours	8 hours
Stratum corneum	-	+	+	-	+
Malpighian layer	-	+	+	++	+
Hair follicle wall (outer)	+	+	++	++	++
Hair follicle wall (inner)	-	+	+	++	++
Sebaceous glands	?	+	+	++	++
Apocrine gland cells	+	+	+	++	++
Apocrine glandular cavity	-	-	-	++	-

Criteria (? : Presence unknown, -: Not observed, +: Observed, ++: Markedly observed)

16.5 Excretion

When 0.1% ^{3}H-labeled betamethasone valerate ointment was applied by occlusive dressing technique (ODT) to 2 patients with psoriasis and 1 patient with pemphigus, the 7-day urinary recovery rates were 2.0 to 18.5% of the applied dose (non-Japanese data). [4]

Table 16-2 Urinary recovery rate

Disease name	Application area	Daily application dose (ODT)Note	Number of days of application	7-day urinary recovery rate (total)
Psoriasis	50% of body surface	20 mg	1 day	2.0%
Psoriasis	50% of body surface	25 mg	2 days	8.7%
Pemphigus	20% of body surface	10 mg	3 days	18.5%

Note: Betamethasone equivalent dose

17. CLINICAL STUDIES

17.1 Clinical Studies for Efficacy and Safety

17.1.1 Japanese clinical study

In a double-blind, controlled study for approval of 0.064% betamethasone dipropionate ointment/cream, 0.12% betamethasone valerate ointment/cream were used as comparators. The efficacy of 0.12% betamethasone valerate ointment was assessed in 131 cases, and the efficacy rate was 85.5% (112 cases). [5]

Table 17-1 Clinical studies

Disease name	Dosage form	Method of use	Duration of use	Number of effective cases/ Number of cases assessed for efficacy	Efficacy rate (%)
Eczema/ dermatitis group (wet type)	Ointment	2 to 3 times/day simple application	1 week	42/44	95.5
Psoriasis	Ointment	2 to 3 times/day simple application	2 weeks	28/43	65.1
	Ointment	1 time/day occlusive dressing technique (ODT)	2 weeks	42/44	95.5

18. PHARMACOLOGY

18.1 Mechanism of action

It is considered that steroids exert its pharmacological action after binding to steroid receptors which form a complex with heat-shock proteins and inhibitory proteins present in the cytoplasm, entering into the nucleus, and activating steroid-responsive genes. In addition, it is known that steroids have actions involved in stability of membranes that inhibit damages to cell membranes of vascular endothelial cells and lymphocytes and actions to suppress the function of important enzymes that induce various inflammatory-inducing substances such as leukotrienes and prostaglandins from cell membrane phospholipids known as phospholipase A_2.

The mechanism of action is considered to be as follows: when a monomeric steroid and its receptor form a complex, the function of intracellular transcription factors known as NFκB or AP-1 regulating induction of cytokine production, the expression of cell adhesion molecules, etc. is inhibited. When it binds to a dimeric receptor, inflammation is controlled through induction of lipocortin, etc. With regard to immunosuppressive effects, it is considered to be due to direct functional suppression on lymphocytes and induction of apoptosis. [6]

18.2 Pharmacological action

18.2.1 Cutaneous vasoconstriction studies

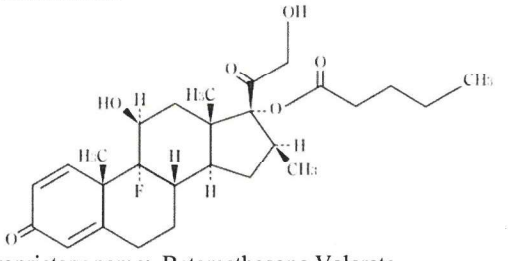
In a cutaneous vasoconstriction study of 20 healthy adults, betamethasone valerate showed cutaneous vasoconstriction potency which was 3.6-fold higher than that of fluocinolone acetonide (non-Japanese data). [7]

18.3 Pharmacodynamic studies

Anti-inflammatory action: A study has examined the anti-inflammatory action of this drug in male Wistar rats (n=45) with footpad edema inhibitory method and capillary permeability method, and the results demonstrated no significant difference between BECTMIRAN OINTMENT 0.12% and RINDERON-V Ointment 0.12%. [8]

19. PHYSICOCHEMICAL PROPERTIES

Structural formula:



Nonproprietary name: Betamethasone Valerate

Chemical name: 9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-pentanoate

Molecular formula: $C_{27}H_{37}FO_6$

Molecular weight: 476.58

Description: Betamethasone Valerate occurs as a white crystalline powder. It is odorless. It is freely soluble in chloroform, soluble in ethanol (95), sparingly soluble in methanol,

	slightly soluble in diethyl ether, and practically insoluble in water.
Melting point:	Approximately 190°C (with decomposition)

20. PRECAUTIONS FOR HANDLING

This drug should be stored in light-proof conditions.

22. PACKAGING

5 g × 10 [tubes]
5 g × 50 [tubes]
100 g [bottle]

23. REFERENCES

1) Vermeer, B.J.et al.:Dermatologica. 1974;149:299-304
2) Zugerman, C.et al.:Arch.Dermatol. 1976;112:1326
3) Atsushi Kukita et al.: The Nishinihon Journal of Dermatology, 1971; 33 : 129-137
4) Butler, J.et al.: Br. J. Dermatol. 1966;78:665-668
5) Toshiaki Yasuda, et al.: Clinical Evaluation. 1974; 2: 271-297
6) Ichiro Katayama: Allergy, 2006; 55 : 1279-1283
7) McKenzie, A. W. et al.:Arch. Dermatol. 1964;89:741-746
8) Internal data: Pharmacodynamic studies

26. MARKETING AUTHORIZATION HOLDER, etc.

26.1 Marketing Authorization Holder

TOWA PHARMACEUTICAL CO., LTD.
2-11, Shinbashi-cho, Kadoma, Osaka 571-8580 Japan