CONTRAINDICATIONS
PANDEL is contraindicated in the following patients.
1. Patients with known hypersensitivity to hydrocortisone butyrate propionate or any other component of the product.
2. Patients with eczematous otitis externa with perforation of the eardrum. [Cure of the perforation site may be delayed and/or infections may occur.]
3. Patients with ulcers (except for Behçet’s disease) and patients with deep burns or frostbite (deep second-degree to fourth-degree). [Regeneration of the skin may be inhibited and cure may be delayed.]

RELATIVE CONTRAINDICATIONS
As a general rule, PANDEL is contraindicated in the following patients. If the use of this product is considered essential, it should be administered with care.
Patients with skin infections caused by bacteria, fungi, spirochetes or viruses and patients with ectoparasitic skin diseases (scabies, pubic lice, etc.). [Pre-existing infections may be aggravated.]

FORMULATIONS

<table>
<thead>
<tr>
<th>Brand name</th>
<th>PANDEL Ointment 0.1%</th>
<th>PANDEL Cream 0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>Hydrocortisone butyrate propionate (1 mg per g ointment [0.1%])</td>
<td>Hydrocortisone butyrate propionate (1 mg per g cream [0.1%])</td>
</tr>
<tr>
<td>Inactive ingredients</td>
<td>Propylene glycol fatty acid ester, Polysorbate 60, Propylene glycol, Paraffin, Liquid paraffin, White petrolatum</td>
<td>Stearyl alcohol, Light liquid paraffin, White petrolatum, Propylene glycol, Polysorbate 60, Sorbitan monostearate, Glycerol monostearate (self-emulsifying), Methyl parahydroxybenzoate, Butyl parahydroxybenzoate, Citric acid</td>
</tr>
</tbody>
</table>

INDICATIONS
Eczema or dermatitis group (including keratodermia tyloides palmaris progressiva, female facial melanosis, lichen Vidal, radiodermatitis, and solar dermatitis), psoriasis, palmoplantar pustulosis, prurigo group (including lichen urticatus, strophulus, and urticaria perstans), insect stings, lichen ruber planus, and chronic discoid lupus erythematosus.

DOSAGE AND ADMINISTRATION
Normally, the appropriate dose is applied to the affected area once to several times a day.

PRECAUTIONS
1. Important Precautions
(1) As a general rule, PANDEL is contraindicated in patients with eczema and dermatitis complicated by skin infections. If its use is unavoidable, treatment with suitable antibacterial and/or antifungal agents should be performed before initiating PANDEL therapy or the concomitant use of the product with these anti-infectives should be considered.
(2) The use of PANDEL in high doses and prolonged use of the product on large skin areas (especially in conjunction with occlusive dressings) may cause adverse systemic corticosteroid effects.
(3) If symptoms do not improve with the use of this product or become exacerbated, discontinue PANDEL therapy.
(4) Upon improvement of symptoms, PANDEL should be withdrawn without delay.

2. Adverse Reactions
Ointment
A total of 92 adverse reactions were encountered in 80 (0.54%) of 14,697 patients treated with PANDEL ointment. The most common adverse reactions included folliculitis in 18 cases, irritation in 16 cases, and steroid acne in 13 cases. [Data submitted for reexamination]
Cream

A total of 54 adverse reactions were encountered in 50 (0.84%) of 5,944 patients treated with PANDEL cream. The most common adverse reactions included folliculitis in 11 cases, irritation in 11 cases, steroid acne in 5 cases, and dry skin in 5 cases. [Data submitted for reexamination]

(1) Clinically significant adverse reactions

Glaucoma, posterior subcapsular cataract: Caution should be exercised when applying PANDEL to the eyelid area, because it may cause increased intraocular pressure or glaucoma. PANDEL can cause an increase in the risk of glaucoma, posterior subcapsular cataract, and other ophthalmic disorders, especially when high doses, prolonged use on large skin areas, or occlusive dressings are involved.

(2) Other adverse reactions

The following adverse reactions may occur. If any abnormalities related to these adverse reactions are observed, appropriate measures, such as withdrawal of PANDEL, should be instituted.

<table>
<thead>
<tr>
<th>Skin infections [Note 1]</th>
<th>Incidence 0.2% ≥ 0.1%</th>
<th>Incidence &lt; 0.1%</th>
<th>Incidence unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial skin infections (contagious impetigo, folliculitis, etc.)</td>
<td>Fungal skin infections (candidiasis, tinea blanca, etc.)</td>
<td>Rosacea-like dermatitis/perioral dermatitis (flushing, papules, pustules, and/or telangiectasia occurring on the cheeks and/or around the mouth), steroid-induced dermatosis (skin atrophy, telangiectasia, purpura, etc.), hypertrichosis, ichthyosiform skin changes</td>
<td></td>
</tr>
<tr>
<td>Other skin symptoms [Note 2]</td>
<td>Steroid acne, skin depigmentation, dry skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyper-sensitivity</td>
<td>Irritation</td>
<td>Rash, pruritus</td>
<td></td>
</tr>
<tr>
<td>Pituitary-adrenal axis</td>
<td>Pituitary-adrenal axis suppression associated with high doses, prolonged use on large skin areas, or use of an occlusive dressing.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* These adverse reactions are more likely to occur with use of an occlusive dressing.

** Dry skin has been reported to occur with the use of the cream (not the ointment).

Note 1: If these symptoms develop, appropriate antibacterial or antifungal agents should be administered concomitantly. If a favorable response does not occur promptly, PANDEL should be discontinued.

Note 2: If these symptoms develop, taper off PANDEL slowly and switch to a drug that does not contain any corticosteroids.

3. Geriatric Use

Since adverse reactions are, in general, more likely to occur in elderly patients, caution should be exercised in the administration of this product, especially when high doses, prolonged use on large skin areas, or occlusive dressings are involved.

4. Use during Pregnancy, Delivery, or Lactation

The safety of PANDEL during pregnancy has not been established; accordingly, avoid high doses and prolonged use on large skin areas in women known or suspected to be pregnant.

5. Pediatric Use

The use of PANDEL either in high doses for prolonged periods of time or in conjunction with occlusive dressings may cause developmental disturbances. Parents/caregivers should be warned that diapers or plastic pants may act as occlusive dressings if the product is applied to the diaper area, potentially leading to an increased risk of serious side effects.

6. Precautions concerning Use

PANDEL must not be used for ophthalmologic treatment. (See 2. Adverse Reactions)

7. Other Precautions

PANDEL is a therapeutic agent for skin diseases and is not a cosmetic preparation; therefore, the product should not be used as a makeup base, an after-shaving cream, or the like.

PHARMACOKINETICS

1. Absorption

Animal studies:
When hydrocortisone butyrate propionate dissolved in physiological saline was applied to the skin of male Wistar rats, rapid absorption was observed during the first 30 minutes, with slower absorption occurring thereafter. Intradermal levels reached a peak after 1 hour, and then declined gradually.

2. Distribution

Animal studies:
When 3H-hydrocortisone butyrate propionate ointment was applied to the skin of male Wistar rats under an occlusive dressing, it was rapidly distributed to the stratum corneum, followed by a similar but less rapid distribution to the stratum Malpighi and the dermis. The radioactivity remained in the stratum corneum even after removal of the ointment, but its accumulation was low.

3. Metabolism

Animal studies:
When administered subcutaneously to male rabbits, the drug was present mainly as the unchanged parent compound in the skin. After absorption into the bloodstream, hydrocortisone butyrate propionate was rapidly hydrolyzed by esterases, converted first into hydrocortisone butyrate and then into hydrocortisone, which was identical to the naturally occurring adrenal glucocorticoid hormone.
4. Excretion

Animal studies:
When \(^{3}H\)-hydrocortisone butyrate propionate was administered subcutaneously to male rabbits, 38.4% of the injected radioactivity was excreted in the urine and 9.2% in the feces within 24 hours of administration.

CLINICAL STUDIES
The results of open or double-blind trials are as follows:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Overall efficacy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eczema or dermatitis group</td>
<td>Ointment: 93.2% (287/308)  Cream: 91.9% (272/296)</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Ointment: 93.4% (212/227)  Cream: 84.6% (110/130)</td>
</tr>
<tr>
<td>Palmoplantar pustulosis</td>
<td>Ointment: 82.5% (52/63)  Cream: 82.5% (47/57)</td>
</tr>
<tr>
<td>Prurigo group</td>
<td>Ointment: 100% (52/52)  Cream: 100% (56/56)</td>
</tr>
<tr>
<td>Lichen ruber planus</td>
<td>Ointment: 90.5% (19/21)  Cream: 90.0% (18/20)</td>
</tr>
<tr>
<td>Chronic discoid lupus erythematous</td>
<td>Ointment: 95.7% (22/23)  Cream: 75.0% (24/32)</td>
</tr>
</tbody>
</table>

[Data submitted for approval]

PHARMACOLOGY

1. Vasoconstrictive effect
The vasoconstrictive effects of various corticosteroid preparations were examined in healthy male adults. Each corticosteroid was applied to the skin under an occlusive dressing for 2 hours, and the vasoconstrictive activity was evaluated at 4 hours after removal of each drug. The activity of 0.1% hydrocortisone butyrate propionate (HBP) was higher than that of 0.12% betamethasone 17-valerate (BV) or 0.1% hydrocortisone 17-butyrate (HB), and equal to that of 0.05% clobetasol propionate.

2. Separation between topical anti-inflammatory and systemic effects
When administered topically or locally to male Wistar rats, HBP exerted more potent anti-inflammatory effects than did BV or HB on croton oil-induced dermatitis, croton oil-induced ear edema, carrageenin-induced paw edema, and cotton pellet granuloma. In contrast, HBP exhibited less potent thymolytic activity (a systemic effect) than did BV or HB. These findings suggest that HBP can produce a favorable separation between topical anti-inflammatory and systemic effects.

3. Affinity for inflammatory cells
The affinity of HBP was higher than that of BV or HB for rat polymorphonuclear leukocytes (i.e., inflammatory cells) in vitro.

4. Binding affinity to glucocorticoid receptors
The binding affinity of HBP to cytoplasmic glucocorticoid receptors in the male Wistar rat liver was higher than that of HB or hydrocortisone.

DESCRIPTION

Generic name:
Hydrocortisone butyrate propionate (JAN)
Hydrocortisone probutate (USAN)

Chemical name:
17-Butyroyloxy-11β-hydroxy-21-propionyloxy-4-pregnene-3,20-dione