”杏輝” cGMP 藥品

黴可舒® 乳膏 1%

Mentax® Cream 1% "Sinphar"

—— 抗 黴 菌 劑 ——

鹽酸布蝶吶(Butenafine hydrochloride)為科研製藥中央研究所合成,具有新架構 Benzyl amine 類抗真菌劑,它具備廣泛之抗寄生性黴菌功能,對於表面性感染之黴菌具有優良的藥效。臨床研究顯示,每天使用一次黴可舒®乳膏便有良好的黴菌治癒及完全治癒的功效。

一般名: 鹽酸布蝶吶(Butenafine hydrochloride)。

化學名: N-4-tert-Butylbenzyl-N-methyl-1-naphthalenemethylamine hydrochloride

成份: Each gm contains:

Butenafine HCl.....10mg (1%)

適應症:指(趾)間黴菌病(香港腳)、圓癬(體癬)、股癬等皮膚真菌屬黴菌引起之皮膚感染症。

劑量及用法:

以少量(約半公分長)塗抹於患部及臨近的部位,輕輕摩擦使藥劑被覆薄層於表面。依不同症狀參照下表使用:

香港腳、指(趾)間黴菌病	一天二次一星期或一天一次四星期
身體、雙手、皮膚皺摺部位之真菌感染	一天一次二星期

藥效藥理:

1.抗黴菌作用:

(1)抗黴菌功能評估:

Butenafine 有絕佳的抗黴菌功能,不同黴菌菌株之體外最小抑制濃度(MIC)可以下表表示:

菌株	MIC *(mg/m^3)
Trichophyton rkbrum	0.007(0.0015～0.025)
Trichophyton mentagrophytas	0.012(0.006～0.025)
Microsporum canis	0.024(0.0125～0.06)
Epidarmophyton floccosum	0.016(0.006～0.025)
Malassezia furfur	3.13(1.56～6.25)

*幾何平均(最小濃度～最大濃度)

(2)趾間黴菌病的治癒:

土撥鼠趾間黴菌感染 10 天後,不同成份 1%的乳膏使用 20 天之後, Bufenafine 顯出明顯的治療效果。

治療比較 *	% of negative cultures
1% Butenafine cream	88.5
1% Bifonazole cream	31.3**
1% Clotrimazole cream	27.1**
None	9.4**

*資料來源”Antimicrobial Agents and Chemotherapy”, 1990 Nov,1990 p2250～ 2253

**與 Butenafine 治療組比較顯著水準 P<0.001

2.皮膚維持性:

預先在實驗土撥鼠背部塗抹 1% Butenafine 液,如於 24 及 48 小時前塗抹可防止。黴菌感染直到 17 天。72 小時前的塗抹可防止同期間 60%感染。在土撥鼠試驗中(n=25)施用 2mg 的 Butenafine 後 24、48、72 小時的皮膚濃度超過體外抑制 *T. mentagrophytes* 所需的濃度(0.012μ g/mL)

(資料來源:Antimicrobial Agents and Chemotherapy”, Nov, 1990:2250～2253)

3.作用機制:

Butenafine 抑制 Squalene epoxidase 的合成,因此干擾黴菌細胞膜成份中的 ergosterol 之合成。

體內藥物動態學:

1.吸收試驗:

健康成人的皮膚表面在 500cm^2 面積上施用Butenafine 1%, 5g,血漿濃度在 12 小時內達到最高濃度 C_{max}, 4.0mg/mL,半衰期為 23.4 小時。在重覆投藥試驗中,12 小時的血漿濃度略少於單劑量試驗的濃度。(資料來源:Antimicrobial Agents and Chemotherapy, 1993, Feb:363-5)

2.皮膚穿透試驗:

在土撥鼠試驗中,Butenafine 穿透性以表面塗抹 2mg 劑量,表皮層於 24 小時達到最高濃度(250～500 μ g/g)。

臨床試驗:

1.臨床有效性:

雙盲試驗於皮膚圓癬患者中,42 位受試者接受 Butenafine 1%乳膏與 36 位受試者接受空白試劑比較每日塗抹一次持續二星期的治療。與空白試劑組相較,患者得到 Bufenafine 治療的治癒率在 14 天時已明顯優於空白對照組(31 vs 3%; p<0.01)。Butenafine 治療組第 42 天的治癒率可持續改善到 67%,與空白組患者 14%相較下更有顯著的不同(p<0.0001)。

在雙盲試驗中,使用 Butenafine 1% Cream 每日二次的患者(人數 132 人)在第 8 天與空白試劑組的患者(人數 139 人)相較,兩組的趾間足癬患者有明顯的差異性(43 vs 25%; p=0.021),這種狀況在第 42 天時患者間的比較有更顯著的差異(74 vs 22%; p<0.0001)在全部 824 位患者進行的控制式或非控制式臨床比較試驗,對足癬患者有效率為 81.8%、圓癬患者為 89.4%、股癬患者為 86.1%。

(資料來源:Journal of the American Academy of Dermatology, 1997; 36:99-S14
Journal of the American Academy of Dermatology, 1997; 36:S15-19)

2.容許度試驗:

根據日本貼布研究基準,黴可舒乳膏並未造成受試者陽性反應(皮膚刺激性),結果顯示 Butenafine 對皮膚刺激度非常低。

使用禁忌:

黴可舒乳膏(Butenafine HCl Cream) 1%不應使用於對本產品已知或可能有過敏的患者。若已經知道對丙烯胺(Allylamine)抗黴菌藥物過敏者應小心使用黴可舒乳膏,因為可能有交互作用產生。

注意事項:

<u>一般事項:</u>

黴可舒乳膏 1%只能外用,如果使用黴可舒乳膏時會引起過敏反應,須立即停止用藥,並給予適當的治療。適應症應經診斷確認,可將表皮細胞泡製於氫氧化鉀溶液,透過顯微鏡鏡檢或適當的培養基培養。使用黴可舒乳膏應經由醫師處方,並且避免接觸眼睛、鼻子、嘴巴等黏膜組織。

<u>給患者的用藥知識:</u>

患者應該遵循以下說明:

1.使用黴可舒乳膏必須遵循醫師指示。在患部使用乳膏後雙手應予洗淨,避免接觸眼睛、鼻子、嘴巴等處之黏膜。黴可舒乳膏只可外用。

2.假如您希望在洗澡後使用黴可舒乳膏 1%,必須先將患部充份乾燥。

3. 即使徵候已經有明顯改善,必須遵循醫師的治療程序。假如於治療結束後症狀並無改善,甚至症狀有惡化的現象,應立即告知醫師。

4.如果使用期間發生以下症狀應立即告知醫師:刺激、發紅、發癢、發熱、脆化、發腫、滲水。

5.避免使用壓迫性膠帶,除非經由醫師指示。

藥品交互作用: 黴可舒乳膏與其它引起交互作用的藥品資料尚未完全建立。

致癌性、致突變性、致畸胎性:

長期致癌性尚未評估。由兩項體外試驗(Bacterial reverse mutation test 及 Chromosome aberration test)及一項體內試驗(Rat micronucleus bioassay)顯示並無致癌性。繁殖試驗中使用劑量(150gm/m^2/day)為治療指間黴菌病最大劑量(15gm/m^2/day)的 10 倍;或是治療股癬、體癬最大劑量(24gm/m^2/day)的 6 倍,於此劑量下雄性或雌性動物的繁殖能力皆無不良影響。

懷孕期: 於動物試驗中鼠類及兔類器官發生期施用高於治療劑量的 6～10 倍亦未發現胎兒畸形現象,然而動物的繁殖試驗結果並不完全預測人的反應,因此孕婦使用應謹慎。

哺乳婦女:目前尚未得知 Butenafine HCl 是否會排出於母乳中,因為許多藥品會隨母乳排出,因此哺乳婦女使用時應小心。

孩童使用: 12 歲以下孩童的安全性及效用尚未評估。12～16 歲的患者使用黴可舒乳膏 1%與成人無異。

不良反應:

在臨床試驗中,230 位患者中有 3 位(約 1%)使用黴可舒乳膏的皮膚有不良的反應,症狀包括發紅、發癢或情況惡化。在相同試驗中接受空白藥劑組 250 患者有 1 位患者產生嚴重不良反應。一般試驗中不良反應的症狀為接觸性皮膚炎、紅腫、發癢及刺激,發生率在 2%以下。

(資料來源:Drugs, 1998, Mar:55(3):405-412)

儲存:於 25℃下儲存,應置於孩童無法取得之處。

包裝: 1000g 以下管、罐裝。

本藥須由醫師處方使用　　衛署藥製字第 044012 號 G - 7257 號

科研製藥株式會社技術合作

cGMP
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Mentax® Cream 1% "Simplar"

— Topical Antifungal Agent —

Butenafine hydrochloride is a new benzylamine antimycotic agent, which was synthesized by Kaken Pharmaceutical Co.Ltd. It has a wide spectra to pathogenic umycetes and exhibited an excellent result in the treatment of superficial dermatophytoses. Clinically, once daily treatment of Mentax® cream 1%, has excellent mycological and overall cure rate.

General Name:

Butenafine hydrochloride.

Chemical Name:

N-4-tert-Butylbenzyl-N-methyl-1-naphthalenemethylamine hydrochloride

Composition:

Each gm contains:

Butenafine HCl……...10mg(1%)

Indications:

Dermatophytoses: interdigital tinea pedis (athlete's foot)、tinea corporis (ring-worm)、tinea cruris (jock itch).

Dosage and Administration:

Apply once daily as required to cover the affected and immediate surrounding area in a thin layer. Duration and frequency follow the table below:

Tinea pedis	1week twice daily or 4week once daily
Tinea cruris and corporis	2week once daily

Pharmacodynamics:

1. Antimycotic activity

(1) Antimycotic eraluation

Butenafine has excellent antimycotic activity, which was defined as the lowest concentration (MIC) that completely inhibited in vitro growth of dermatophytes.

Strain	MIC (mg/m^3)*
Trichophyton rkbrum	0.007(0.0015～0.025)
Trichophyton mentagrophytas	0.012(0.006～0.025)
Microsporum canis	0.024(0.0125～0.06)
Epidarmophyton floccosum	0.016(0.006～0.025)
Malassezia furfur	3.13(1.56～6.25)

* Geometric mean (minimum-maxium)

(2) Interdigital tinea treatment:

In comparative study, 10 days after the planta of the hind paw of guinea-pigs was inoculated with *Trichophyton mentagrophytas*, a variety of antifungal agents (1% cream formulation) were applied once daily for 20 days. Butenafine shows a greater mycological eradiation than comparator agents.

Treatment *	% of negative cultures
1% Butenafine cream	88.5
1% Bifonazole cream	31.3**
1% Clotrimazole cream	27.1**
None	9.4**

* (Data adapted from"Antimicrobial Agents and Chemotherapy", 1990 Nov, P.2250～2253.)

** $p<0.001$ versus butenafine treatment group.

2.Skin retenability:

Topical butenafine 1% solution was applied once 24、48 or 72 hours before fungal inoculation with *T. mentagrophytes* in guinea-pigs (dorsal skin). In experiments of 24 and 48 hours preteatment, mycological infection was prevented for up to 17 days; preteatment 72 hours before inoculation prevented 60% infection of animals over the same period.

In guinea-pigs (n=5) the concentration of butenafine in the skin 24、48、72 hours after application of 2mg of the agent (0.2mL of 1% solution) was over the *in vitro* concentrations required for fungicidal activity against *T. mentagrophytes* (0.012 μg/mL).

3.Mechanisms:

Butenafine inhibits synthesis of squalene epoxidase which interfere with ergosterol synthesis of fungal cell membrane.

Pharmacokinetics:

1. Adsorption:

On healthy adult skin surface, single dose of bufenafine 1% 5g on 500cm^2 surface area, the plasma concentration at 12 hours arrived at maxmum concentration of C_{max} 4.0mg/mL, and the half life was 23.4 hours. In addition, for the 7 days multiple dose, the 12 hours plasma concentration was slightly lower than that of single dose.

(Data adaped from: Animicrobial Agents and Chemotherapy, 1993, Feb, 363-5)

2. Skin permeation:

In guinea-pigs model, skin permeation of butenafine was assessed after topical application of 2mg dosage (24 hours duration), the highest concentration (estimated as 250 to 500 μg/g) was found in the epidermis.

Therapeutic Clinical Trials:

1. Clinical Effectiveness

In a double-blind trial patients with tinea corporis received either butenafine 1% cream (n=42) or cream vehicle (n=36) once daily for 2 weeks. Compared with vehicle recipients, patients receiving bufenafine had a significantly higher overall cure rate by day 14 (31 vs 3%; $p<0.01$) which improved by day 42 (67 vs 14%; $p<0.0001$).

In a double-blind trial, butenafine 1% cream applied twice daily for 7 days (n=132) produced a significantly higher mycological cure rate than vehicle (n=139) as early as day 8 in patients with tinea pedis (43 vs 25%; $p=0.021$). This rate was further increased up to 5 weeks after treatment cessation (day 42) in the bufenafine group, but declined in vehicle recipients (74 vs 22%; $p< 0.0001$).

In total of 824 patients comparative controlled or non-controlled trials, the effective rate for tinea pedis was 81.8%, tinea cruris, 89.4% and tinea corporis 86.1%.

(Data adapted from: 1. Journal of the American Academy of Dermatology, 1997; 36:S9-14)
2. Journal of the American Academy of Dermatology, 1997, 36, S15-19)

2. Tolerability:

A skin patch test, according to the Japan Investigational Group criteria, was carried out in healthy volunteers. The positive patch test (assumed skin irritation) result was not observed in butenafine cream or solution. The data suggest butenafine has a low potential for skin irritation.

Contraindications:

Mentax® (butenafine HCl cream) cream 1%, is contraindicated in individuals who have known or suspected sensitivity to Mentax® Cream, 1%, or any of its components. Patients who are known to be sensitive to allylamine antifungals

should use Mentax® (butenafine HCl cream) cream, 1%, with caution, since cross-reactivity may occur.

Precautions:

General:

Mentax® Cream, 1%, is for external use only. If irritation or sensitivity develops with the use of Mentax® Cream, 1%, treatment should be discontinued and appropriate therapy instituted. Diagnosis of the disease should be confirmed either by direct microscopic examination of infected superficial epidermal tissue in a solution of potassium hydroxide or by culture on appropriate medium. Use Mentax® Cream, 1%, as directed by the physician, and avoid contact with the eyes, nose and mouth, and other mucous membranes.

Information for Patients:

The patient should be instructed to:

1. Use Mentax® Cream, 1%, as directed by the physician. The hands should be washed after applying the medication to the affected area(s). Avoid contact with the eyes, nose, mouth, and other mucous membranes. Mentax® Cream, 1%, is for external use only.

2. Dry the affected area(s) thoroughly before application, if you wish to apply Mentax® Cream, 1%, after bathing.

3. Use the medication for the full treatment time recommended by the physician, even though symptoms may have improved. Notify the physician if there is no improvement after the end of the prescribed treatment period, or sooner, if the condition worsen(see below).

4. Inform the physician if the area of application shows signs of increased irritation, redness, itching, burning, blistering, swelling, or oozing.

5. Avoid the use of occlusive dressings unless otherwise directed by the physician.

6. Do not use this medication for any disorder other than that for which it was prescribed.

Drug interactions:

Potential drug interactions between Mentax® (butenafine HCl cream) Cream, 1%, and other drugs have not been systematically evaluated.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term studies to evaluate the carcinogenic potential of Mentax® Cream, 1%, have not been conducted. Two *in vitro* assays (bacterial reverse mutation test and chromosome aberration test in Chinese hamster lymphocytes) and one *in vivo* study (rat micronucleus bioassay) revealed no mutagenic or clastogenic potential for butenafin. Reproductive studies were conducted in which approximately 150mg/m^2/day (25mg/kg/day) of butenafine was administered subcutaneously, which is 10 times higher than the miximum recommended human topical dose (15mg/m^2/day) for the treatment of tinea pedis, and six times higher than the anticipated maximum human topical dose (24mg/m^2/day) for the treatment of tinea corporis or tinea cruris. At this dose in animals no adverse effects on male or female ferility were demonstrated.

Pregnancy:

Teratogenic Effects: Pregnancy Category B

Subcutaneous or topical doses of butenafine at 150 to 300 mg/m^2/day (25 to 50 mg/kg/day) levels (equivalent to 10 to 20 times the maximum potential exposure at the recommended human topical dose for the treatment of tinea

pedis, or 6 to 12 times the anticipated maximum exposure at the human topical dose for the treatment of tinea corporis or tinea cruris) during organogenesis in rats and rabbits were not teratogenic. There are, however, no adequate and well-controlled studies that have been conducted of topically-applied butenafine in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:

It is not known if butenafine HCl excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised in prescribing Mentax® Cream 1%, to a nursing woman.

Pediatric Use:

Safety and efficacy in pediatric patients below the age of 12 years have not been studied. Use of Mentax® Cream, 1%, in pediatric patients 12 to 16 years of age is supported by evidence from adequate and well-controlled studies of Mentax® Cream, 1%, in adults.

Adverse Reactions:

In controlled clinical trials, 3 (approximately 1%) of 230 patients treated with Mentax® Cream, 1%, reported adverse events related to the skin. These included burning/ stinging and worsening of the condition. No patient treated with Mentax® Cream, 1%, discontinued treatment due to an adverse event. In the vehicle-treated patients, one of 205 patients discontinued because of severe burning/stinging and itching at the site of application. In uncontrolled clinical trials, the most frequently reported adverse events in patients treated with Mentax® Cream, 1%, were: contact dermatitis, erythema, irritation, and itching, each occurring in less than 2% of patients.

(Data adaped from "Drugs", 1998, Mar:55(3): 405-412)

Storage:

Store between 25℃, keep all drugs out of reach of children.

How supplied:

Mentax® (butenafine HCl cream) Cream, 1%, is supplied in tubes or jars in less than 1000g.

Technology Coopration Kaken Pharmaceutical Co., LTD.

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