

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-408**

**CHEMISTRY REVIEW(S)**



**NDA 21-408**

**Mentax –TC (butenafine HCl) Cream, 1%**

**Bertek Pharmaceuticals, Inc.**

**Ernest G. Pappas**  
**Division of Dermatological and Dental Drug Products**

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# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

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# Chemistry Review Data Sheet

1. NDA 21-408
2. REVIEW # 1
3. REVIEW DATE: 4/4/02
4. REVIEWER: Ernest G. Pappas
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

14-Dec-2001

Amendment (BZ)

20-Feb-2002

Amendment (BC)

27-Feb-2002

Amendment (BC)

18-Apr-2002

Amendment (BC)

09-May-2002

Amendment (BL)

30-Aug-2002

Amendment (BZ)

06-Sept-2002

Amendment (BC)

09-Sept-2002

Amendment (BC)

26-Sept-2002

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## Chemistry Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Bertek Pharmaceuticals Inc.  
Address: P.O. Box. 14149  
Research Triangle Park, NC 27709-4149  
Representative: Sherron P. Wiechert, RAC  
Director of Regulatory Affairs  
Telephone: (919) 993-5910

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Mentax -TC
- b) Non-Proprietary Name (USAN): butenafine HCl
- c) Code Name/# (ONDC only): KP-363
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 4
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION:

## 10. PHARMACOL. CATEGORY:

Anti-fungal Agent

## 11. DOSAGE FORM:

Cream

## 12. STRENGTH/POTENCY:

1%

## 13. ROUTE OF ADMINISTRATION:

Topical

14. Rx/OTC DISPENSED:   x   Rx             OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

       SPOTS product – Form Completed

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## Chemistry Review Data Sheet

  X   Not a SPOTS product

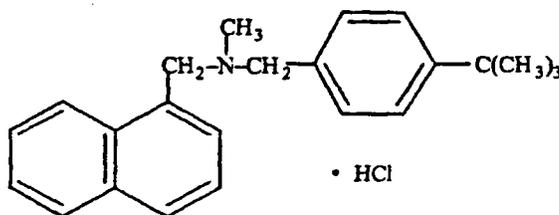
**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Chemical Name: N-4-tert-Butylbenzyl-N-methyl-1-naphthalenemethylamine Hydrochloride

Molecular Formula:  $C_{23}H_{27}N \cdot HCl$

Molecular Weight: 353.93

Chemical Structure:


**17. RELATED/SUPPORTING DOCUMENTS:**
**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED | COMMENTS |
|-------|------|--------|-----------------|-------------------|---------------------|-----------------------|----------|
| —     | II   | —      | —               | 1                 | Reviewed            |                       |          |
| —     | I    | —      | —               | 2                 | No Review           |                       |          |
| —     | III  | —      | —               | 1                 | No Review           |                       |          |

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

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# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION   |
|----------|--------------------|---|
| IND      | 42,762             | Butenafine HCl Cream 1% for Tinea Pedis; Tinea Corporis; Tinea Cruris |
| IND      | 60,471             | Butenafine HCl Cream 1% for Tinea Versicolor                          |
| NDA      | 20,524             | Butenafine HCl Cream 1% for Tinea Pedis                               |
| NDA      | 20,663             | Butenafine HCl Cream 1% for Tinea Corporis; Tinea Cruris              |

### 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|----------------|------|----------|
| EES                           |                |      |          |
| Methods Validation            |                |      | Pappas   |
| ODS                           |                |      | Mahmud   |
| Microbiology                  |                |      | Riley    |

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# The Chemistry Review for NDA 21-408

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA as amended is found acceptable from a chemistry standpoint. An approval letter may be issued pending an acceptable EER

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if approvable

Pharm/Tox should review the additional degradation products for the new formulation for qualification when data become available at a later date.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Substance(s) and Drug Product(s)

##### Drug Substance:

Butenafine HCl is the subject for DMF \_\_\_\_\_ It is important to know the physicochemical characteristic of this drug substance from the standpoint of solubility because of the \_\_\_\_\_ for the finished product. For example, butenafine HCl is very soluble in \_\_\_\_\_ freely soluble in methanol, ethanol, \_\_\_\_\_ but only slightly soluble in \_\_\_\_\_, water \_\_\_\_\_ Butenafine HCl \_\_\_\_\_ is determined by analytical data. There is no chiral center in this drug substance.

The impurity profile was established for butenafine HCl and is consistent throughout its manufacturing. Three known \_\_\_\_\_ have been determined \_\_\_\_\_

\_\_\_\_\_ The acceptance criteria for the \_\_\_\_\_ have been tightened to reflect the manufacturing capability. The specifications specify these limits for the \_\_\_\_\_ impurities in order to assure consistent quality from batch to batch. These impurities were consistent throughout product development.

Based on the evaluation of the primary stability data, the proposed retest date of \_\_\_\_\_ was deemed acceptable.

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## Executive Summary Section

**Drug Product:**

The drug product, Mentax-TC (butenafine HCl) is a 1% topical cream, which is packaged in \_\_\_\_\_ tubes with a white, \_\_\_\_\_ crew cap. The active pharmaceutical ingredient, butenafine HCl, was the first of its class to be approved in this country in April, 1995 for the treatment of tinea pedis, tinea cruris, and tinea corporis (refer to NDA 20-524). Mentax-TC (butenafine HCl) cream, 1% is different from the marketed product, Mentax (butenafine HCl) cream, 1% in that it contains certain new excipients, e.g., trolamine, propylene glycol and polyolprepolymer-2. Polyolprepolymer-2 is a novel excipient in the Mentax-TC formulation. The indication of this NDA is for the treatment of tinea versicolor.

A critical manufacturing parameter for Mentax-TC (butenafine HCl) 1% cream occurs during the \_\_\_\_\_

\_\_\_\_\_, In-process controls (i.e., \_\_\_\_\_), are performed to give adequate assurance that \_\_\_\_\_ occurs at this step, and that no \_\_\_\_\_ is observed. In addition, the release specifications give added assurance of the identity, strength, quality and purity for the finished product.

Another critical parameter that may influence drug product quality is the process impurities and/or degradation products. It was observed that the specifications were found to be higher for the degradation products as the result of the new formulation than those reported in the release specifications for Mentax Cream (NDA 20-524). In this regard, the acceptance criterion for the total degradation products was proposed at \_\_\_\_\_ of butenafine HCl. The acceptance criteria for the individual degradation products were proposed at \_\_\_\_\_ of butenafine HCl for \_\_\_\_\_ respectively. In addition, \_\_\_\_\_ new degradation products were reported for the Mentax-TC Cream. They are \_\_\_\_\_. Acceptance criteria for the individual degradation products were proposed at \_\_\_\_\_ of butenafine HCl, respectively.

The sponsor proposed a \_\_\_\_\_ expiration date for the product to be marketed in \_\_\_\_\_ 15 g, and 30 g, tubes. However, acceptable stability data were only submitted for \_\_\_\_\_ Therefore, a \_\_\_\_\_ expiry date should be granted for this drug product on the data submitted.

It should be noted that if the applicant cannot submitted supporting data from the Pharm/Tox studies performed on \_\_\_\_\_ new degradation products, \_\_\_\_\_ and \_\_\_\_\_, the Division may want to propose a \_\_\_\_\_ expiration period. Since degradation of the finished product occurred after \_\_\_\_\_ the \_\_\_\_\_ expiration period should be imposed until the new degradants are qualified.

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Executive Summary Section

Because Pharm/Tox data are not available at this time to support the — new degradation products, the applicant has lowered the proposed expiration date from — to — as requested.

**B. Description of How the Drug Product is Intended to be Used**

The drug product is to be administered topically as an antifungal agent in the treatment of tinea versicolor.

**C. Basis for Approvability or Not-Approval Recommendation**

The manufacturing and controls identified above are sufficient to assure the consistent identity, strength, quality and purity of the drug product pending the resolution of the CMC deficiencies and Pharm/Tox review approval of the additional degradation products.

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

**C. CC Block**

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39 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

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this page is the manifestation of the electronic signature.**  
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/s/

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Ernest G. Pappas  
10/15/02 02:47:11 PM  
CHEMIST  
Chem. Review is ready for signature.

Wilson H. DeCamp  
10/15/02 05:32:35 PM  
CHEMIST  
concur with review; see Team Leader's addendum for additional  
information