# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**75-329**

## Bioequivalence Review(s)

**Miconazole Nitrate Combination Pack**
Cream 2%, Suppositories 200 mg
ANDA # 75-329
Reviewer: Jahnavi S. Kharidia
V:\FIRMSNZ\PERRIGO\LTRS&REV\75329a2.199

**L. Perrigo Company**
117 Water Street
Allegan MI 49010
Submission Date:
January 12, 1999
February 19, 1999
February 26, 1999

## Review of an Amendment

### Background

- The firm has submitted a waiver request for its Miconazole Nitrate Combination Pack 2%, 200 mg. The Division of Bioequivalence completed the review and there were no outstanding bio issues (Attachment A, Review Date: June 23, 1998).

- The Division of Chemistry completed the review and some deficiencies were communicated to the firm (Letter Date: August 4, 1998). One of the chemistry deficiencies (Comment 1) was that the firm should revise their specifications for the finished product and stability for suppositories to include a dissolution test.

- In response, the firm proposed that the product should have a disintegration test rather than a dissolution test (Amendment Date: September 21, 1998). The firm's proposal of using disintegration test as their quality control was not acceptable (Bio Review Date: November 14, 1998)

- The firm then proposed to establish and validate an appropriate dissolution procedure and specification for their Miconazole Nitrate suppositories as a post approval commitment (Amendment Date: January 12, 1999). The Division of Bioequivalence did not accept the firm's proposal and requested that the firm send dissolution data prior to approval (Telephone conversations between OGD and the firm, Dates: February 12, 1999 and February 22, 1999).

- The firm is now responding to the comments received from the Division of Bioequivalence.

### Dissolution:

The dissolution method and data on the test and reference products are summarized in Table 1 and Figure 1.

**Table 1- In Vitro Dissolution Testing**

Drug (Generic Name): Miconazole Nitrate
Dosage Form: Suppositories
Dose Strength: 200 mg

I. Conditions for Dissolution Testing:

Apparatus: 1 (Basket)
Speed: 100 rpm
No. Units: 12
Medium: 0.45% SLS
Volume: 900 mL at 40°C
Sampling Time: 15, 30, 45 and 60 minutes
Tolerance: n 60 minutes

II. Results of In Vitro Dissolution Testing:

| Time (min) | Test Product # Lot # 9A3155V, Exp. 2/01 Mean | Range | % RSD | Reference Product (Monistat 3 Day) # Lot # 27K862, Exp. 8/00 Mean | Range | % RSD |
|---|---|---|---|---|---|---|
| 15 | 33 | | 12.1 | 40 | | 24.0 |
| 30 | 75 | | 5.8 | 77 | | 4.9 |
| 45 | 87 | | 3.5 | 88 | | 5.7 |
| 60 | 90 | 8.7 - 9.5 | 3.0 | 91 | | 2.6 |

| Time (hr) | Test Product # Lot # 9B1086V, Exp. 2/01 Mean | Range | % RSD | Reference Product (Monistat 3 Day) # Lot # 28L410, Exp. 10/01 Mean | Range | % RSD |
|---|---|---|---|---|---|---|
| 15 | 37 | | 7.6 | 28 | | 33.6 |
| 30 | 78 | | 4.5 | 71 | | 13.1 |
| 45 | 92 | | 2.7 | 86 | | 5.1 |
| 60 | 95 | | 1.4 | 92 | | 2.3 |

| Time (min) | Test Product * Lot #.5M0520, Exp. 12/97 Mean | Range | % RSD | Reference Product (Monistat 3 Day) * Lot # 15A156, Exp. 1/98 Mean | Range | % RSD |
|---|---|---|---|---|---|---|
| 15 | 29 | | 21.3 | 14 | | 13.2 |
| 30 | 69 | | 11.9 | 53 | | 14.0 |
| 45 | 86 | | 6.7 | 76 | | 6.0 |
| 60 | 92 | 86 | 2.8 | 85 | | 3.1 |

* Test and Reference batches were used in the bioequivalence study, however, the batches were expired when dissolution was performed.

\# Unexpired batches of test and reference products

## Comment:

The *in vitro* dissolution method and data have been found acceptable.

## Recommendation:

1. The Division of Bioequivalence finds the application submitted by L. Perrigo for Miconazole Nitrate Combination Pack acceptable. Miconazole Nitrate Combination Pack contains an approved product Miconazole Nitrate Vaginal Suppositories, USP 200 mg (ANDA# 75-003) and an approved product Miconazole Nitrate Cream, 2%

(ANDA# 74-760). The Division of Bioequivalence deems Miconazole Nitrate Combination Pack manufactured by L. Perrigo bioequivalent to the reference listed product Monistat® 3 Combination Pack manufactured by Ortho Pharmaceutical Corporation.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.45% SLS using USP 23 Apparatus 1 at 100 rpm at 40° C. The test products should meet the following specifications:

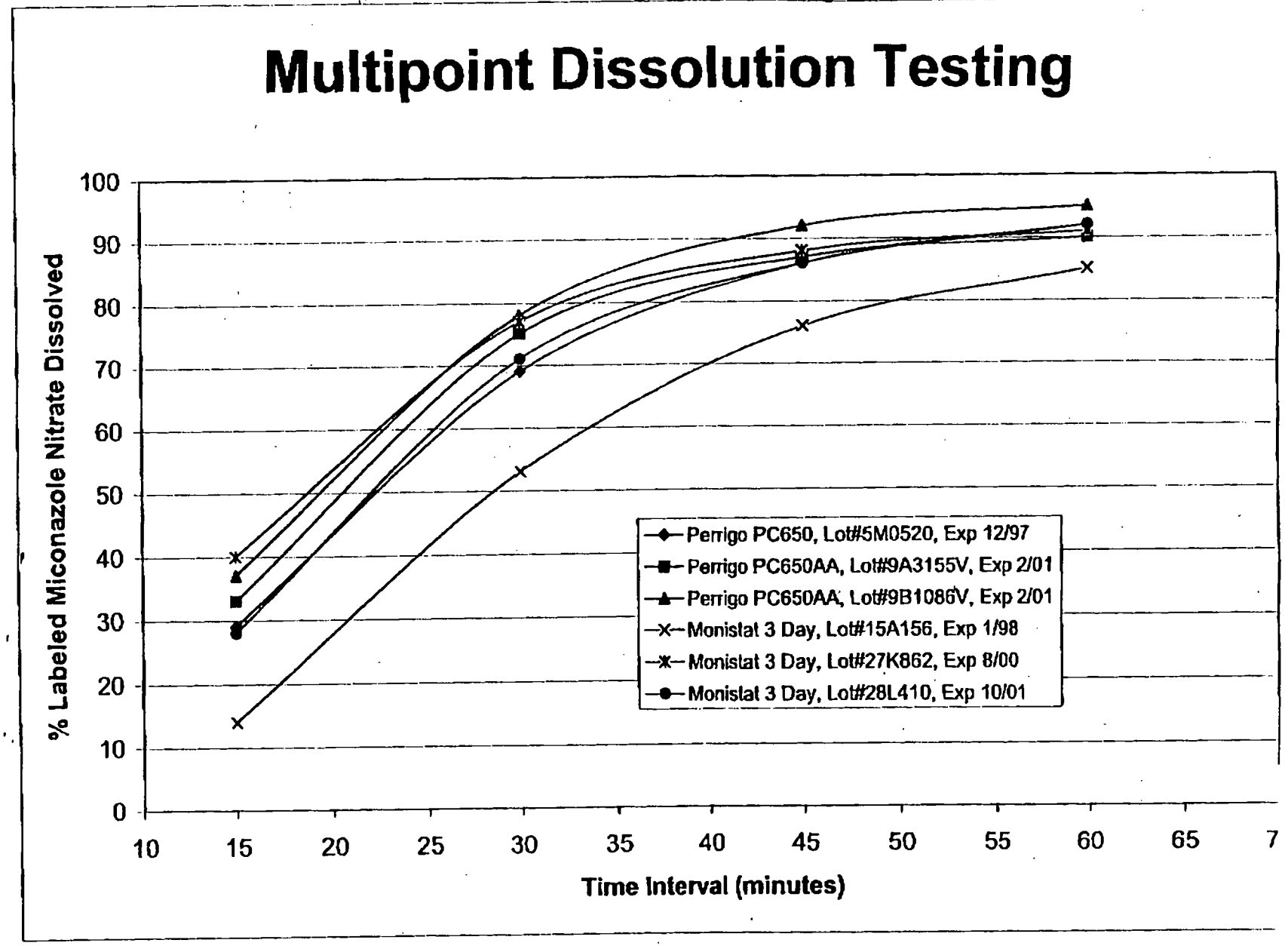
   Not less [illegible] of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

Jahnavi S. Kharidia
Jahnavi S. Kharidia, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED BDAVIT BMD 3/4/99
FT INITIALED BDAVIT Barbara M Davit Date 3/8/99

Concur: [signature] Date 3/9/99
for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

Figure 1


Multipoint Dissolution Testing
% Labeled Miconazole Nitrate Dissolved
Time Interval (minutes)
100
90
80
70
60
50
40
30
20
10
0
10
15
20
25
30
35
40
45
50
55
60
65
Perrigo PC650, Lot#5M0520, Exp 12/97
Perrigo PC650AA, Lot#9A3155V, Exp 2/01
Perrigo PC650AA, Lot#9B1086V, Exp 2/01
Monistat 3 Day, Lot#15A156, Exp 1/98
Monistat 3 Day, Lot#27K862, Exp 8/00
Monistat 3 Day, Lot#28L410, Exp 10/01

**Miconazole Nitrate Combination Pack**
Cream 2%, Suppositories 200 mg
ANDA # 75-329
Reviewer: Jahnavi S. Kharidia
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**L. Perrigo Company**
117 Water Street
Allegan MI 49010
Submission Date:
September 3, 1998

## Review of An Amendment

### Background

The firm has submitted a waiver request for its Miconazole Nitrate Combination Pack 2%, 200 mg. The Division of Bioequivalence completed the review and there were no outstanding bio issues (Attachment A, Review Date: June 23, 1998). The Division of Chemistry completed the review and some deficiencies were communicated to the firm (Letter Date: August 4, 1998). The firm is now responding to the deficiencies in this amendment.

One of the chemistry deficiencies (Comment 1) was that the firm should revise their specifications for the finished product and stability for suppositories to include a dissolution test. In response, the firm is proposing that the product should have a disintegration test rather than a dissolution test. The Division of Chemistry (Chemists: Drs. Schwartz and Nashed) would like to discuss this issue with representatives from Bio, therefore, this amendment was assigned to a bio reviewer (Jahnavi Kharidia).

Sponsor's Response:

Based on the pharmacology of the drug product (please see vol. 2.1, pg. # 3, Attachment 1 for more details), the lack of standardized methodology and the absence of a compendial requirement to perform dissolution testing on non-absorbed dosage forms, we conclude that establishing specifications for a dissolution procedure is not appropriate at this time. However, we propose to include a disintegration test to be performed as directed in EP monograph.

Bio Reviewer's Comments:

1. The miconazole is slightly soluble in water, however, its solubility increases at lower pH (100 mg/1000 mL of 0.1 N HCl)

2. The firm tried to develop a dissolution method for Miconazole Nitrate suppositories. Table 1 summarizes the firm's efforts to develop dissolution method and the results.

**Not to be released through FOI**

**Table 1: Different dissolution methods employed by the firm for their miconazole suppository**

| Experimental Methods | Apparatus | Dissolution Medium | Speed | Results | Conclusion |
|---|---|---|---|---|---|
| | | | | | |

3. In reviewer's opinion, dissolution testing is important for suppositories as a quality control tool. Disintegration test is an official in EP, however, this test is very qualitative and will not serve the purpose of quality control.

4. Dissolution testing is also used as a basis for granting waiver for post approval changes.

5. There is no standard dissolution method currently available, therefore, the firm should be advised to use various solvent systems and generate the acceptable dissolution profile. Some of the examples for solvent system are:

    - Since the pH of the rectal fluid is 7.2 with low buffer capacity, pH 7.2 phosphate may be a good starting point as a dissolution medium

    - The Division of Bioequivalence recommends use of surfactants at low concentrations in cases where the drug substance shows low aqueous solubility. The firm should be advised to add some surfactants to the dissolution medium such as SLS, Tween 80, Triton x-100 or CTAP (Hexadecyl trimethyl ammonium bromide) at 1-2%.

**Recommendation**

The Division of Chemistry should be informed about the reviewer's comments # 1-5.

Jahnavi S. Kharidia
Jahnavi S. Kharidia, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED BDAVIT BMD 11/13/98
FT INITIALED BDAVIT Barbara M Davit 11/13/98

Concur Dale P. Conner Date: 11/14/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Attachment - A

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**Miconazole Nitrate Combination Pack**
Cream 2%, Suppositories 200 mg
ANDA # 75-329
Reviewer: Jahnavi S. Khandia
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**L. Perrigo Company**
117 Water Street
Allegan MI 49010
Submission Date:
January 30, 1998

## Review of a Waiver Request

### Introduction:

Miconazole is used in the treatment of vaginal yeast infections and relief from irritation associated with yeast infection.

### Objective:

The firm has submitted a waiver for Miconazole Nitrate Combination Pack 2%, 200 mg. The Combination Pack includes three Miconazole Nitrate vaginal suppositories, 200 mg, and one tube of Miconazole Nitrate vaginal cream, 2% (9 gm). The reference listed product is Monistat® 3 combination Pack manufactured by Ortho Pharmaceutical Corporation.

### Comments:

1. The firm currently holds ANDA # 74-760 (approved 5/15/97) for Miconazole Nitrate Cream, 2%. The proposed Combination Package includes one tube of the Miconazole Nitrate Cream 2% of the same formulation as described in that approved ANDA # 74-760 (Table 1).

2. The firm is referring to ANDA# 75-003 Miconazole Nitrate Vaginal Suppositories, 200 mg submitted by L. Perrigo on November 12, 1996, and subsequently withdrawn on January 30, 1998.

3. The ANDA# 75-003 was reviewed by the Division of Special Pathogens and Immunologic Drug Products (HFD-590) and by Mary Fanning (Associate Director for Medical Affairs, OGD). It was concluded that L. Perrigo's Miconazole Nitrate 200 mg vaginal suppositories and the reference product (Monistat® 3 Vaginal Suppositories) were equivalent for efficacy and safety in the treatment of vulvovaginal candidiasis. Subsequently the ANDA# 75-003 was withdrawn. However, the firm was informed by OGD Regulatory Support that the information submitted in that application would be transferred to current ANDA 75-329.

4. Composition of suppositories and vaginal cream is shown in Table 1.

**Recommendation:**

The Division of Bioequivalence finds the application submitted by L. Perrigo for Miconazole Nitrate Combination Pack acceptable. Miconazole Nitrate Combination Pack contains an approved product Miconazole Nitrate Vaginal Suppositories, USP 200 mg (ANDA# 75-003) and an approved product Miconazole Nitrate Cream, 2% (ANDA# 74-760). The Division of Bioequivalence deems Miconazole Nitrate Combination Pack manufactured by L. Perrigo bioequivalent to the reference listed product Monistat® 3 Combination Pack manufactured by Ortho Pharmaceutical Corporation.

Jahnavi S. Kharidia

Jahnavi S. Kharidia, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED BDAVIT 6.2.98
FT INITIALED BDAVIT Barbara M. Davit Date 6/6/98
Barbara M. Davit, Ph.D.
Team Leader, Branch III
Division of Bioequivalence

Concur: Dale P. Conner Date 6/23/98
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

**Miconazole Nitrate Combination Pack**
Cream 2%, Suppositories 200 mg
ANDA # 75-329
Reviewer: Jahnavi S. Kharidia
X:\NEW\FIRMSNZ\PERRIGO\LTRS&REV\75329w.198

**L. Perrigo Company**
117 Water Street
Allegan MI 49010
Submission Date:
January 30, 1998

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### Comments:

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Jahnavi S. Kharidia

Jahnavi S. Kharidia, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED BDAVIT 6/12/98
FT INITIALED BDAVIT Barbara M. Davit Date 6/16/98
Barbara M. Davit, Ph.D.
Team Leader, Branch III
Division of Bioequivalence

Concur: Dale P. Conner Date 6/23/98
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence