DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-881/S-009

KV Pharmaceutical Company
Attention: Herbert G. Luther, Ph.D.
Vice President, Regulatory and Clinical Affairs
2503 South Hanley Road
St. Louis, MO 63144-2555

Dear Dr. Luther:

Please refer to your supplemental new drug application (sNDA) dated May 17, 2002, received May 20, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gynazole·1® (butoconazole nitrate) Vaginal Cream, 2%.

We acknowledge the receipt of your submission dated June 17, 2003.

This supplemental new drug application provides for the following revisions to the package insert (additions are double underlined and deletions are ~~strikethrough~~).

1. **RX Only** was added before the **Description** section.

2. The following revisions were made to the **CLINICAL PHARMACOLOGY, Microbiology** subsection:

   Butoconazole nitrate is an imidazole derivative that has fungicidal activity *in vitro* against *Candida* spp. and ~~is~~ has been demonstrated to be clinically effective against vaginal infections due to *Candida albicans*. *Candida albicans* has been identified as the predominant species responsible for vulvovaginal candidasis.

3. The following revisions were made to the **INDICATIONS AND USAGE** subsection:

   Gynazole-1® (butoconazole nitrate) vaginal cream, 2% is indicated for the local treatment of vulvovaginal candidiasis (infections caused by *Candida)~~albicans.~~* The diagnosis should be confirmed by KOH smears and/or cultures (see **CLINICAL STUDIES**).

   Note: Gynazole-1®is safe and effective in non-pregnant women; however, the safety and effectiveness of this product in pregnant women has not been established. (See **PRECAUTIONS:** Pregnancy)

4. The following **CLINICAL STUDIES** section was added to the package insert:

   Vulvovaginal Candidiasis: Two studies were conducted in the US and one in Sweden. Only two directly compared 2% butoconazole nitrate cream with clotrimazole tablets. There were 322 enrolled patients, 161 received 2.0 % butoconazole vaginal cream and 161 patients inserted the 500-mg clotrimazole vaginal tablet. At the second follow-up visit (30 days post-therapy), 118

patients in the butoconzole group and 116 in the clotrimazole group were evaluable for efficacy analysis, respectively. All of these patients had infection caused by *Candida albicans*.

The efficacy of the study drugs was assessed by evaluating clinical, mycologic and therapeutic cure rates, which are summarized in Table 1.

The therapeutic cure is defined by a complete resolution of signs and symptoms of vaginal candidiasis (clinical cure) along with a negative KOH examination and negative culture for *Candida* spp. (microbiologic eradication) at the long term follow-up. The therapeutic cure rate was 67% in the butoconazole group and 61% in the clotrimazole group.

	2% butoconazole nitrate cream	**500-mg clotrimazole vaginal tablet**
Enrolled	161	161
Evaluable at Late Follow-up	118	116
Clinical Cure	95/118 (81 %)	93/116 (80 %)
Mycologic Eradication *	87/118 (74 %)	77/116 (66 %)
Therapeutic Cure	79/118 (67%)	71/116 (61 %)

*=*C. albicans* in the vaginal culture was proven at admission in all of these patients.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, this application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling (text for package insert submitted June 17, 2003).

Please submit the copies of the final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA* (January 1999*)*. Please submit a Microsoft Word version of the FPL in the same submission with the PDF version. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 19-881/S-009." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Christine Lincoln, RN, MS, MBA, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht

7/24/03 12:56:22 PM