CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-410

Generic Name: Omeprazole Delayed-release Capsules, 10 mg and 20 mg

Sponsor: Kremers Urban Development Company

Approval Date: November 1, 2002
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CENTER FOR DRUG
EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-410

APPROVAL LETTER
Kremers Urban Development Company  
Attention: Steven R. Pollock  
6140 W. Executive Drive  
Mequon, WI 53092

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated July 2, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Omeprazole Delayed-release Capsules, 10 mg and 20 mg.

Reference is also made to our Tentative Approval letters dated May 3, 2001, and October 4, 2002, and to your amendment dated October 31, 2002, requesting that the agency grant final approval to the application.

The listed drug (RLD) referenced in your application, Prilosec Delayed-release Capsules (Prilosec) of AstraZeneca LP (AstraZeneca), is subject to periods of patent protection and exclusivity. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), AstraZeneca's three-year exclusivity with respect to labeling for the use of Prilosec in pediatric patients two years of age and older, (M-19), is due to expire on January 12, 2006. Section 11 of the Best Pharmaceuticals for Children Act (BCPA), signed into law in January 2002, allows certain portions of AstraZeneca's labeling which is subject to pediatric exclusivity protection to be omitted from the labeling of products approved under Section 505(j). The BCPA also permits the incorporation of language in the labeling of products approved under Section 505 (j) that informs health care practitioners that AstraZeneca's drug product has been approved for pediatric use. The agency has determined that the final printed labeling you have submitted with respect to the pediatric use protected by exclusivity (M-19) is in compliance with the BCPA.

In addition, the following patents are scheduled to expire on November 30, 2005, (U.S. Patent No. 4,636,499); October 20, 2007, (U.S Patent Nos. 4,786,505 and 4,853,230); August 2, 2010, (U.S.
Patent No. 5,093,342); August 4, 2014, (U.S. Patent Nos. 5,599,794 and 5,629,305); April 9, 2019, (U.S. Patent Nos. 6,147,103, and 6,191,148); April 9, 2019, (U.S. Patent No. 6,166,213); and May 10, 2019, (U.S. Patent No. 6,150,380). Please note that the expiration dates of the patents listed above have been adjusted to reflect a 6-month extension as provided for under Section 505A of the Act (pediatric exclusivity extension). Throughout this letter, references to individual patents will be made by use of only the last three digits of the patent.

With regard to these patents, your application contains a patent certification under Section 505(j)(2)(A)(viii) of the Act indicating that the '342, '794, and '305 patents are for method of use patents, and that these patents do not claim any of the proposed indications for which you are seeking approval. In addition, your application contains paragraph IV certifications under Section 505(j)(2)(A)(vii)(IV) of the Act to the '499, '505, '230, '103, '380, '213, and '148 patents stating that your manufacture, use or sale of either strength of this drug product will not infringe on these patents, or that these patents are invalid or unenforceable.

Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately unless an action is brought against Kremers Urban Development Company (KUDCO) for infringement of one or more of these patents which are the subject of the certifications. This action must be brought against KUDCO before the expiration of forty-five days from the date the notice you provided to the NDA/patent holder(s) under paragraph(2)(B)(i) was received. You have notified the agency that KUDCO complied with the requirements of Section 505(j)(2)(B) of the Act, and as a result litigation was initiated in the United States District Court for the Eastern District of Wisconsin involving challenges to the '499, '505, '230, '794, '305, and '342 patents (Astra Aktiebolag, Aktiebolaget Hassle, KBI-I Inc., KBI Inc. and AstraZeneca, L.P. v. Kremers Urban Development Co., and Schwarz Pharma Inc. (Civil Action No. 99-C-0131). This litigation was subsequently consolidated with similar litigation pending in various United States District Courts into the United States District Court for the Southern District of New York (Civil Action No. 99-C-0131), Civil Action No.99 Civ. 8928(BSJ) and No. 99 Civ. 9888(BSJ)), In re Omeprazole M-21-81, MDL Docket No. 1291(BSJ).

The agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application with respect to the litigation noted in the preceding paragraph, has expired. We also note that no action for patent infringement was brought
against KUDCo within the statutory forty-five day period with respect to the '103, '380, '213, and '148 patents.

Furthermore, the Act provides that approval of an abbreviated new drug application that contains a certification described in section 505(j)(2)(A)(vii)(IV) (a paragraph IV certification) and that provides for approval of the same drug product as that for which another abbreviated application containing a Paragraph IV Certification was previously received, shall be made effective not earlier than one hundred and eighty (180) days after:

1. the date the Secretary receives notice from the applicant of the previous application that commercial marketing of the drug product approved in that application was initiated, or

2. the date of a decision of a court holding the patent which is the subject of the certification to be invalid or not infringed; whichever option occurs first [Section 505(j)(5)(B)(iv)].

The Office of Generic Drugs received and filed ANDAs containing a paragraph IV certification to the various listed patents for Omeprazole Delayed-release Capsules, 10 mg and 20 mg prior to the filing of your application. Accordingly, your application would not be eligible for full approval until 180-days following the earlier of event 1. or 2. noted above. We refer you to the Agency's guidance document entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998).

In a communication dated October 31, 2002, the holders of the ANDAs referenced above as having been received and filed prior to your application informed the Agency that they have relinquished their eligibility for the 180-day exclusivity with respect to Omeprazole Delayed-release Capsules, 10 mg and 20 mg. Thus, by relinquishing their eligibility for 180-day exclusivity, the Office of Generic Drugs is permitted to approve any ANDA for these drug products that is otherwise ready for approval, without regard to the 180-day exclusivity period specified in Section 505(j)(5)(B)(iv).

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Omeprazole Delayed-release Capsules, 10 mg and 20 mg, to be bioequivalent, and therefore, therapeutically equivalent to the listed drug (Prilosec Delayed-release Capsules, 10 mg and 20 mg, of AstraZeneca LP). The FDA recommended
dissolution and acid-resistance testing should be incorporated into your stability and quality control programs. In "interim" tests and tolerances are:

(i) The dissolution testing should be conducted in 900 mL of 0.1N HCl for 2 hours [Acid stage]; followed by 900 mL of 0.05M phosphate buffer, pH 6.8 [Buffer stage], at 37°C using USP apparatus I (basket) at 100 rpm. The test product should meet the following specification:

NLT—(Q) of the drug in the capsule is dissolved in 45 minutes [at the end of the Buffer stage].

(ii) Separate acid resistance testing should be conducted in 900 mL of 0.1N HCl for 2 hours [Acid stage]. The omeprazole content of the granules should be analyzed at the end of the Acid stage, and the test product should meet the following specification:

NMT—□ of the drug in the capsule is dissolved in 120 minutes, as determined by the difference between the average potency assay (without acid exposure) and the potency assay of the remaining granules at the end of the Acid stage.

The "interim" dissolution test and tolerances should be finalized by submitting dissolution data for the first three production size batches in a supplemental application. The supplemental application should be submitted under Section 505(j) of the Act as a Changes Being Effected (CBE-0) supplement when there are no revisions to the interim specifications or when the final specifications are tighter than the interim specifications. In all other instances the supplement should be submitted under 505(j) of the Act as a prior approval supplement.

Under Section 506(A) of the Act, certain changes in the conditions described in this ANDA require approved supplemental application before the change may be made.

Post-marketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that your submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253.
(Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

/\S/  
Gary Buehler  /\11/02\  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research
APPLICATION NUMBER:

75-410

TENTATIVE APPROVAL LETTER
Kremers Urban Development Company  
Attention: Steven R. Pollock  
6140 W. Executive Drive  
Mequon, WI  53092

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated July 2, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Omeprazole Delayed-Release Capsules, 10 mg and 20 mg.

Reference is also made to our Tentative Approval Letter dated May 3, 2001, and to your subsequent amendments dated October 18, 2001; and March 29, June 25, and September 3, 2002.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date the drug is safe and effective for use as recommended in the submitted labeling. However, due to 180-day generic drug exclusivity issues addressed below, we are unable to grant final approval to your application at this time. Therefore, the application remains tentatively approved. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention.

The listed drug product referenced in your application, Prilosec Delayed-release Capsules of AstraZeneca LP, is subject to periods of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), the patents are scheduled to expire on November, 2005, (U.S. Patent No. 4,636,499; October 20, 2007, (U.S. Patent Nos. 4,786,505 and 4,853,230); August 2, 2010, (U.S. Patent No. 5,093,342); August 4, 2014, (U.S. Patent Nos. 5,599,794 and 5,629,305); April 9,
2019, (U.S. Patent Nos. 6,147,103, and 6,191,148); April 19, 2019 (U.S. Patent No. 6,166,213); and May 10, 2019, (U.S. Patent No. 6,150,380). Please note that the expiration dates of the patents listed above have been adjusted to reflect a 6-month extension as provided for under Section 505A of the Act (pediatric exclusivity). Throughout this letter, references to individual patents will be made by use of only the last three digits of the patent.

We note that your application contains patent statements under Section 505 (j)(2)(A) (viii) of the Act indicating that the '342, '794, and '305 patents are for method of use patents, and that these patents did not claim any of the proposed indications for which you are seeking approval. In addition, your application contains Paragraph IV Certifications under Section 505(j)(2)(A)(vii)(IV) of the Act to the '499, '505, '230, '103, '380, '213, and '148 patents that your manufacture, use or sale of either strength of this drug product will not infringe on these patents or that these patents are invalid or unenforceable. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately unless an action is brought against Kremers Urban Development Company (KUDCO) for infringement of one or more of these patents which are the subject of the certifications. This action must be brought against KUDCO before the expiration of forty-five days from the date the notice you provided to the NDA/patent holder(s) under paragraph (2)(B)(i) was received. You have notified the agency that KUDCO complied with the requirements of Section 505(j)(2)(B) of the Act, and as a result litigation was initiated in the United States District Court for the Eastern District of Wisconsin involving challenges to the '499, '505, '230, '794, '305, and '342 patents (Astra Aktiebolag, Aktiebolaget Hassle, KBI-E Inc., KBI Inc. and AstraZeneca, L.P. v. Kremers Urban Development Co., and Schwarz Pharma Inc., Civil Action No. 99-C-0131). This litigation was subsequently consolidated with similar litigation pending in various United States District Courts and now resides in the United States District Court for the Southern District of New York.

The agency recognizes that the 30-month period identified in Section 505(j)(5)(B)(iii) of the Act, during which time FDA was precluded from approving your application with respect to the litigation noted in the preceding paragraph, has expired. We also note that no action for patent infringement was brought against KUDCO within the statutory forty-five day period with respect to the '103, '380, '213, and '148 patents.
As noted in the "Orange Book", an ANDA for Omeprazole Delayed-release Capsules, 10 mg, 20 mg, and 40 mg, was approved for Andrx Pharmaceuticals, Inc. on November 16, 2001. This application, containing Paragraph IV Certifications to certain listed patents, was accepted for filing by OGD prior to the filing of your application. Furthermore, a second application, was also accepted for filing prior to the filing of your application. This ANDA and also contains Paragraph IV Certifications to certain listed patents. Because of the first-to-file situation with respect to the various listed patents presented by Andrx and the other former filer, the agency has concluded that a "shared exclusivity" approach is consistent with the statutory language, and with the intent of both the 180-day exclusivity provision and the Hatch-Waxman Amendments. Thus, upon approval, the applicant for this second ANDA as well as Andrx will each be eligible for 180 days of generic drug market exclusivity.

The Act provides that approval of a subsequent ANDA such as yours that also contains Paragraph IV Certifications under Section 505(j)(2)(A)(vii)(IV) and that provides for approval of the same drug product as that for which another ANDA containing Paragraph IV Certifications accepted for filing prior to your application shall be made effective not earlier than:

1. One hundred and eighty (180) days after the date the Secretary receives notice from the applicant of the previous application that commercial marketing of the drug product approved in that application has commenced, or

2. the date of a decision of a court holding the patents which were the subject of the certifications and for which litigation is currently ongoing to be invalid or not infringed; whichever option occurs first [Section 505(j)(5)(B)(iv)].

In the current case, exclusivity will begin to run with the first marketing of either the Andrx product or the currently unapproved second product referenced above, or a court decision on any of the patents for which either applicant was first to file a Paragraph IV Certification. During the 180-day exclusivity period, only Andrx and the holder of the second application may market their omeprazole drug products. Once the 180 days of exclusivity expires, the agency may approve other ANDAs for Omeprazole Delayed-release Capsules that are otherwise eligible for approval.
In order to reactivate your application prior to final approval, please submit a MINOR AMENDMENT — FINAL APPROVAL REQUESTED between 60 to 90 days prior to the date you believe your application will be eligible for final approval. This amendment must provide:

1. the date that the 180-day marketing exclusivity period granted to the prior applicants will expire. Alternatively, a settlement agreement between the parties, or a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

   b. a statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this ANDA and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval is discouraged.

In addition to, or instead of, the amendment referred to above, the Agency may, at any time prior to the final date of approval, request that you submit another amendment containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Orange Book.
The amendment requesting final approval of the ANDA should be clearly designated as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED in your cover letter. At the time you submit this amendment or for further information on the status of your application, please contact Nicole Park, Project Manager, at 301-827-5849.

Sincerely yours,

/ Gary Buehler  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

10/4/02
Kremers Urban Development Company
Attention: John Vaughan
6140 W. Executive Drive
Mequon, WI 53092

Dear Sir:

This is in reference to your abbreviated new drug application dated July 2, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Omeprazole Delayed-Release Capsules, 10 mg and 20 mg.

Reference is also made to your amendments dated October 6 and December 29, 1998; April 15, June 4, September 16, 1999; February 8, May 12, June 2, July 13, September 14, November 30, and December 12, 2000; and February 8, March 5, and May 2, 2001.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is tentatively approved. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

No. 6,150,380). Please note that under Section 505A of the Act, on May 1, 2001, the agency granted the NDA holder, AstraZeneca LP, six months of additional marketing exclusivity (pediatric exclusivity). This exclusivity will effectively extend each of the patents noted above by an additional 6-months.

We note that your application contains patent statements under Section 505 (j)(2)(A) (viii) of the Act indicating that the '342, '794, and '305 patents are for method of use patents, and that these patents do not claim any of the proposed indications for which you are seeking approval. In addition, your application contains Paragraph IV Certifications to the '499, '505, '230, '103, '380, '213, and '148 patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use or sale of this drug product will not infringe on these patents or that these patents are invalid or unenforceable. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated application shall be made effective immediately unless an action is brought for infringement of one or more of these patents which are the subject of the certifications before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received by the NDA and patent holder(s). You have notified the agency that Kremers Urban Development Company (KUDCo) complied with the requirements of Section 505(j) (2)(B) of the Act, and as a result litigation is underway in the United States District Court for the Eastern District of Wisconsin involving challenges to the '499, '505, '230, '794, '305, and '342 patents (Astra Aktiebolag, Aktiebolaget Hassle, KBI-E Inc., KBI Inc. and AstraZeneca, L.P. v. Kremers Urban Development Co., and Schwarz Pharma Inc., Civil Action No. 99-C-0131). This litigation was subsequently consolidated with similar litigation pending in various United States District Courts and now resides in the United States District Court for the Southern District of New York. Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month periods provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notices required under section 505(j)(2)(B)(i), unless the court has extended or reduced the periods because of the failure of either party to reasonably cooperate in expediting the action, or,
b. the date of a court decision \[505(j)(5)(B)(iii)
(I), (II), or (III)], which has been interpreted
by the Agency to mean the date of the final order
or judgement of that court from which no appeal
can be or has been taken, or,

c. the patents have expired, and

2. The Agency is assured there is no new information that
would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this
application, when you believe that your application may be
considered for final approval, you must amend your application
to notify the Agency whether circumstances have or have not
arisen that may affect the effective date of final approval.
Your amendment must provide:

1. A copy of a final order or judgement from which no
appeal may be taken (which might not be the one from
the district court), or a settlement agreement between
the parties, whichever is applicable, or a licensing
agreement between you and the patent holder, or any
other relevant information, and

2. a. updated information related to final-printed
labeling or chemistry, manufacturing and controls
data, or any other change in the conditions
outlined in this abbreviated application, or

b. a statement that no such changes have been made
to the application since the date of tentative
approval.

Any changes in the conditions outlined in this abbreviated
application and the status of the manufacturing and testing
facilities' compliance with current good manufacturing
procedures are subject to Agency review before final approval of
the application will be made.

In addition to, or instead of, the amendments referred to above,
the Agency may, at any time prior to the final date of approval,
request that you submit amendments containing the information
requested above.
Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Kassandra Sherrod, R.Ph., Project Manager, at 301-827-5849, for further instructions.

Sincerely yours,

[Signature]

Gary Buehler 5/3/01
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-410

Final Printed Labeling
ANDA 75-410
KREMER URBAN DEVELOPMENT COMPANY

Omeprazole Delayed-Release Capsules, 10 mg

Final Printed Labeling
Bottle Label - 30's

L3595A
ANDA 75-410
KREMERS URBAN DEVELOPMENT COMPANY

Omeprazole Delayed-Release Capsules, 20 mg

Final Printed Labeling
Bottle Label - 30's

Store at controlled room temperature 15° - 30°C (59° - 86°F) (see USP).
Store in light resistant container protected from light and moisture.
Dispense in tight and light-resistant container as described in USP.

L3597A
patients with endocrinopathies continued to have increased eosinophils. Results of the study are shown below:

### Table 1: Life Table Analysis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Omeprazole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>20 mg/d</td>
<td>5 mg/d</td>
</tr>
<tr>
<td>Percentage</td>
<td>34</td>
<td>34</td>
</tr>
</tbody>
</table>

### Table 2: Life Table Analysis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Omeprazole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>10 mg/d</td>
<td>5 mg/d</td>
</tr>
<tr>
<td>Percentage</td>
<td>34</td>
<td>34</td>
</tr>
</tbody>
</table>

In a separate study, patients receiving 20 mg of omeprazole had a 50% reduction in eosinophils compared to placebo. The results are shown below:

### Table 3: Eosinophil Counts

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Eosinophil Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>500 x 10^3</td>
</tr>
<tr>
<td>Placebo</td>
<td>1000 x 10^3</td>
</tr>
</tbody>
</table>

In conclusion, the study shows that omeprazole significantly reduced eosinophil counts compared to placebo. This effect was observed in both investigations.

### Adverse Events

Adverse events including nausea, diarrhea, and headache were reported in both the omeprazole and placebo groups. However, the incidence of these events was similar in both groups, and the events were manageable with no need for discontinuation of treatment.

### References


### Acknowledgments

This work was supported by grants from the National Institutes of Health and the American Heart Association.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-410

CHEMISTRY REVIEW(S)
1. CHEMIST'S REVIEW NO. 1

2. ANDA # 75-410

3. NAME AND ADDRESS OF APPLICANT
Kremers Urban Development Company
Attention: Jonathan A. Thiel
6140 W. Executive Drive
Mequon WI, 53092

4. LEGAL BASIS FOR ANDA SUBMISSION
Several patents which cover the RLD are said to be invalid. Patent 4,255,431 expired on 6/22/1998. Patent 4,786,505 will expire on 3/22/1999. Patent 4,636,499 will expire on 5/30/2005. Astra Merck is identified as the patent holder. Prilosec is the RLD.

5. PROPRIETARY NAME
6. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:
FIRM
7/2/98-- Original Submission
8/4/98-- Correspondence
10/6/98-- Correspondence

Firm
7/22/98 - Phone call by doc. Room
8/11/98 - Acknowledgement letter

10. PHARMACOLOGICAL CATEGORY
Inhibitor of gastric acid secretion

11. Rx or OTC
Rx

12. RELATED DMFs Nos.

13. DOSAGE FORM
Enteric-coated microtablets packaged in capsules

14. POTENCY
20 mg Delayed-release Capsules

15. CHEMICAL NAME AND STRUCTURE
5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole
16. RECORDS AND REPORTS
N/A

17. COMMENT
Major deficiencies noted.

18. CONCLUSION AND RECOMMENDATIONS
Recommend not approvable letter to issue.

19. REVIEWER:
Radhika Rajagopalan, Ph.D.       DATE COMPLETED:
                                      October 22, 1998

[Signature]

11/24/98

APPEARS THIS WAY
ON ORIGINAL
Redacted 40

pages of trade

secret and/or

confidential

commercial

information
1. **CHEMIST'S REVIEW NO. 2**

2. **ANDA # 75-410**

3. **NAME AND ADDRESS OF APPLICANT**
   Kremers Urban Development Company
   Attention: John Vaughan
   6100 W. Executive Drive, Suite D
   Mequon WI, 53092

4. **LEGAL BASIS FOR ANDA SUBMISSION**

5. **PROPRIETARY NAME**
   Omeprazole

6. **NONPROPRIETARY NAME**
   Omeprazole

9. **AMENDMENTS AND OTHER DATES:**
   **FIRM**
   7/2/98-- Original Submission
   8/4/98-- Correspondence
   10/6/98, 12/15/98-- Correspondence
   4/9/99-- General correspondence
   4/15/99-- Bio fax amendment
   6/3/99-- Chemistry major amendment
   6/4/99-- Bio amendment
   7/1/99-- Addition of New strength, 10 mg capsules
   9/16/99-- Bio amendment

   **FDA**
   7/22/98 - Phone call by doc. Room
   8/11/98 - Acknowledgement letter
   11/3/98- Bio deficiency fax
   12/11/98- Chemistry and label deficiency fax
   5/10/99- Bio fax out
   8/16/99- Bio fax out
   9/3/99- Bio fax out

10. **PHARMACOLOGICAL CATEGORY**
    Inhibitor of gastric acid secretion

11. **Rx or OTC**
    Rx

12. **RELATED DMFs Nos.**
13. **Dosage Form**
Enteric-coated microtablets packaged in capsules

14. **Potency**
20 mg and 10 mg Delayed-release Capsules

15. **Chemical Name and Structure**
5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

16. **Records and Reports**
N/A

17. **Comment**
Major deficiencies noted.

18. **Conclusion and Recommendations**
Recommend not approvable letter to issue.

19. **Reviewer:**
Radhika Rajagopalan, Ph.D.  
**Date Completed:**
October 29, 1999

\[ S \]

\[ 11-19-99 \]
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information
1. CHEMIST'S REVIEW NO. 3

2. ANDA # 75-410

3. NAME AND ADDRESS OF APPLICANT
Kremers Urban Development Company
Attention: John Vaughan
6100 W. Executive Drive, Suite D
Mequon WI, 53092

4. LEGAL BASIS FOR ANDA SUBMISSION

5. PROPRIETARY NAME
6. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:
FIRM
7/2/98-- Original Submission
8/4/98-- Correspondence
10/6/98, 12/15/98-- Correspondence
4/9/99-- General correspondence
4/15/99- Bio fax amendment
6/3/99- Chemistry major deficiency
6/4/99- Bio amendment
7/1/99- Addition of New strength, 10 mg capsules
9/16/99- Bio amendment
2/8/00- CMC and label response as major amendment

FMA
7/22/98 - Phone call by doc. Room
8/11/98 - Acknowledgement letter
11/3/98- Bio deficiency fax
12/11/98- Chemistry and label deficiency fax
5/10/99- Bio fax out
8/16/99- Bio fax out
9/3/99- Bio fax out
12/9/99- Chemistry major deficiency
6/2/00- Bio telephone amendment
6/23/00- Received 2nd Method Validation package

10. PHARMACOLOGICAL CATEGORY
Inhibitor of gastric acid secretion

11. Rx or OTC
Rx

12. RELATED DMFS Nos.
13. **DOSAGE FORM**
Enteric-coated microtablets packaged in capsules

14. **POTENCY**
20 mg and 10 mg Delayed-release Capsules

15. **CHEMICAL NAME AND STRUCTURE**
5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

16. **RECORDS AND REPORTS**
N/A

17. **COMMENT**

18. **CONCLUSION AND RECOMMENDATIONS**
Recommend not approvable letter to issue.

19. **REVIEWER:**
Radhika Rajagopalan, Ph.D.  
**DATE COMPLETED:**
6/19/00; 6/29/00

7/13/00

**APPEARS THIS WAY ON ORIGINAL**
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information
1. CHEMIST'S REVIEW NO. 4

2. ANDA # 75-410

3. NAME AND ADDRESS OF APPLICANT
Kremers Urban Development Company
Attention: John Vaughan
6100 W. Executive Drive, Suite D
Mequon WI, 53092

4. LEGAL BASIS FOR ANDA SUBMISSION
Several patents which cover the RLD are said to be invalid. Patent 4,255,431 expired on 6/22/1998. Patent 4,786,505 expired on 3/22/1999. Patent 4,636,499 will expire on 5/30/2005. Astra Merck is identified as the patent holder. Prilosec is the RLD. Paragraph III and IV certifications have been filed.

5. PROPRIETARY NAME
6. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:
FIRM
7/2/98-- Original Submission
8/4/98-- Correspondence
10/6/98, 12/15/98-- Correspondence
4/9/99-- General correspondence
4/15/99-- Bio fax amendment
6/3/99-- Chemistry major deficiency
6/4/99-- Bio amendment
7/1/99-- Addition of New strength, 10 mg capsules
9/16/99-- Bio amendment
2/8/00-- CMC and label response as major amendment
12/12/00-- CMC major response and submission of new methods validation package (3d package)
3/5/01 -- Telephone Amendment
FBA
7/22/98 -- Phone call by Doc. Room
8/11/98 -- Acknowledgement letter
11/3/98-- Bio deficiency fax
12/11/98-- Chemistry and label deficiency fax
5/10/99-- Bio fax out
8/16/99-- Bio fax out
9/3/99-- Bio fax out
12/9/99-- Chemistry major deficiency
6/2/00-- Bio telephone amendment
6/23/00-- Received 2nd Method Validation package
7/14/00-- Chemistry major deficiency with regards to method validation
8/28/00-- T-call by PM and Chemist
3/2/01 -- T-Call by Chemist, TL and PM

10. PHARMACOLOGICAL CATEGORY
Inhibitor of gastric acid secretion
11. Rx or OTC
 Rx

12. RELATED DMFs Nos.

13. DOSAGE FORM
 Enteric-coated microtablets packaged in capsules

14. POTENCY
 20 mg and 10 mg Delayed-release Capsules

15. CHEMICAL NAME AND STRUCTURE
 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

16. RECORDS AND REPORTS
 N/A

17. COMMENT
 No outstanding issues. Results pending from methods validation.

18. CONCLUSION AND RECOMMENDATIONS
 TA to be issued pending satisfactory EES status.

19. REVIEWER: Radhika Rajagopalan, Ph.D.     DATE COMPLETED: 2/6/01
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information
1. CHEMIST'S REVIEW NO. 5

2. ANDA # 75-410

3. NAME AND ADDRESS OF APPLICANT
Kremers Urban Development Company
Attention: John Vaughan
6100 W. Executive Drive, Suite D
Mequon WI, 53092

4. LEGAL BASIS FOR ANDA SUBMISSION
Several patents which cover the RLD are said to be invalid. Patent 4,255,431 expired on 6/22/1998. Patent 4,786,505 expired on 3/22/1999. Patent 4,636,499 will expire on 5/30/2005. Astra Merck is identified as the patent holder. Prilosec is the RLD. Paragraph III and IV certifications have been filed.

5. PROPRIETARY NAME
6. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:

FIRM
7/2/98-- Original Submission
8/4/98-- Correspondence
10/6/98, 12/15/98-- Correspondence
4/9/99-- General correspondence
4/15/99-- Bio fax amendment
6/3/99-- Chemistry major deficiency
6/4/99-- Bio amendment
7/1/99-- Addition of New strength, 10 mg capsules
9/16/99-- Bio amendment
2/8/00-- CMC and label response as major amendment
12/12/00-- CMC major response and submission of new methods validation package (3d package)
3/5/01-- Telephone Amendment
10/18/01-- Label amendment
12/7/01-- Minor CMC amendment
12/27/01-- New Correspondence
1/7/02-- Phone call with label reviewer

FDA
7/22/98-- Phone call by Doc. Room
8/11/98-- Acknowledgement letter
11/3/98-- Bio deficiency fax
12/11/98-- Chemistry and label deficiency fax
5/10/99-- Bio fax out
8/16/99-- Bio fax out
9/3/99-- Bio fax out
12/9/99-- Chemistry major deficiency
6/2/00-- Bio telephone amendment
6/23/00-- Received 2nd Method Validation package
7/14/00-- Chemistry major deficiency with regards to
method validation 
8/28/00 - T-call by PM and Chemist 
3/2/01 - T-Call by Chemist, TL and PM 
5/3/01 - TA granted 
10/18/01 - Sprinkle study requested

10. PHARMACOLOGICAL CATEGORY
Inhibitor of gastric acid secretion

11. Rx or OTC
Rx

12. RELATED DMFs Nos.

13. DOSAGE FORM
Enteric-coated microtablets packaged in capsules

14. POTENCY
20 mg and 10 mg Delayed-release Capsules

15. CHEMICAL NAME AND STRUCTURE
5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

16. RECORDS AND REPORTS
In this minor amendment the firm has amended the following information:

Capsule color
10 mg capsule is White/White now
20 mg capsule is White/Gold now
A separate label submission is done on 10/18/01 with the capsule
17. **COMMENT**
Sprinkled applesauce study is still pending. See item 38. ANDA approval pending satisfactory bio and label review.

18. **CONCLUSION AND RECOMMENDATIONS**
No outstanding chemistry issues.

19. **REVIEWER:**
Radhika Rajagopalan, Ph.D.  
**DATE COMPLETED:**
1/15/02
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information
1. **CHEMIST'S REVIEW NO. 6**

2. **ANDA # 75-410**

3. **NAME AND ADDRESS OF APPLICANT**
   Kremers Urban Development Company
   Attention: Ms. Elaine Cibulka
   6140 W. Executive Drive, Suite D
   Mequon WI, 53092

4. **LEGAL BASIS FOR ANDA SUBMISSION**
   Several patents which cover the RLD are said to be invalid. Patent 4,255,431 expired on 6/22/1998. Patent 4,786,505 expired on 3/22/1999. Patent 4,636,499 will expire on 5/30/2005. Astra Merck is identified as the patent holder. Prilosec is the RLD. Paragraph III and IV certifications have been filed.

5. **PROPRIETARY NAME**
   Omeprazole

6. **NONPROPRIETARY NAME**

9. **AMENDMENTS AND OTHER DATES:**
   **FIRM**
   7/2/98-- Original Submission
   8/4/98-- Correspondence
   10/6/98, 12/15/98-- Correspondence
   4/9/99-- General correspondence
   4/15/99-- Bio fax amendment
   6/3/99-- Chemistry major deficiency
   6/4/99-- Bio amendment
   7/1/99-- Addition of New strength, 10 mg capsules
   9/16/99-- Bio amendment
   2/8/00-- CMC and label response as major amendment
   12/12/00-- CMC major response and submission of new methods validation package (3d package)
   3/5/01-- Telephone Amendment
   10/18/01-- Label amendment
   12/7/01-- Minor CMC amendment
   12/27/01-- New Correspondence
   1/7/02-- Phone call with label reviewer
   3/29/02-- Sprinkle study along with CMC minor amendment

   **FDA**
   7/22/98 - Phone call by Doc. Room
   8/11/98 - Acknowledgement letter
   11/3/98-- Bio deficiency fax
   12/11/98-- Chemistry and label deficiency fax
   5/10/99-- Bio fax out
   8/16/99-- Bio fax out
   9/3/99-- Bio fax out
   12/9/99-- Chemistry major deficiency
   6/2/00-- Bio telephone amendment
   6/23/00-- Received 2nd Method Validation package
7/14/00- Chemistry major deficiency with regards to method validation
8/28/00- T-call by PM and Chemist
3/2/01 - T-Call by Chemist, TL and PM
5/3/01- TA granted
10/18/01- Sprinkle study requested
9/20/02- Label approval granted

10. PHARMACOLOGICAL CATEGORY
Inhibitor of gastric acid secretion

11. Rx or OTC
Rx

12. RELATED DMFs Nos.

13. DOSAGE FORM
Enteric-coated microtablets packaged in capsules

14. POTENCY
20 mg and 10 mg Delayed-release Capsules

15. CHEMICAL NAME AND STRUCTURE
5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

16. RECORDS AND REPORTS
In this minor amendment the firm has amended the following information:

17. COMMENT
Satisfactory label review completed, dated 9/20/02

18. CONCLUSION AND RECOMMENDATIONS
No outstanding chemistry issues. Approval recommended.

19. REVIEWER:
Radhika Rajagopalan, Ph.D.  DATE COMPLETED:
5/9/02
Redacted _____

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information
1. CHEMIST'S REVIEW NO. 7

2. ANDA # 75-410

3. NAME AND ADDRESS OF APPLICANT
Kremers Urban Development Company
Attention: Ms. Elaine Cibulka
6140 W. Executive Drive, Suite D
Mequon WI, 53092

4. LEGAL BASIS FOR ANDA SUBMISSION
Several patents which cover the RLD are said to be invalid. Patent 4,255,431 expired on 6/22/1998. Patent 4,786,505 expired on 3/22/1999. Patent 4,636,499 will expire on 5/30/2005. Astra Merck is identified as the patent holder. Prilosec is the RLD. Paragraph III and IV certifications have been filed.

5. PROPRIETARY NAME  6. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:
FIRM
7/2/98 -- Original Submission
8/4/98 -- Correspondence
10/6/98, 12/15/98 -- Correspondence
4/9/99 -- General correspondence
4/15/99 -- Bio fax amendment
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9/16/99 -- Bio amendment
2/8/00 -- CMC and label response as major amendment
12/12/00 -- CMC major response and submission of new methods validation package (3d package)
3/5/01 -- Telephone Amendment
10/18/01 -- Label amendment
12/7/01 -- Minor CMC amendment
12/27/01 -- New Correspondence
1/7/02 -- Phone call with label reviewer
3/29/02 -- Sprinkle study along with CMC minor amendment
10/31/02 -- Minor CMC amendment

FDA
7/22/98 -- Phone call by Doc. Room
8/11/98 -- Acknowledgement letter
11/3/98 -- Bio deficiency fax
12/11/98 -- Chemistry and label deficiency fax
5/10/99 -- Bio fax out
8/16/99 -- Bio fax out
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12/9/99 -- Chemistry major deficiency
6/2/00 -- Bio telephone amendment
6/23/00 -- Received 2nd Method Validation package
7/14/00- Chemistry major deficiency with regards to method validation
8/28/00- T-call by PM and Chemist
3/2/01- T-Call by Chemist, TL and PM
5/3/01- TA granted
10/18/01- Sprinkle study requested
9/20/02- Label approval granted

10. PHARMACOLOGICAL CATEGORY
Inhibitor of gastric acid secretion

11. Rx or OTC
Rx

12. RELATED DMFs Nos.

13. DOSAGE FORM
Enteric-coated microtablets packaged in capsules

14. POTENCY
20 mg and 10 mg Delayed-release Capsules

15. CHEMICAL NAME AND STRUCTURE
5-methoxy-2-\[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

16. RECORDS AND REPORTS
The ANDA was tentatively approved for the 2nd time on October 4, 2002.

17. COMMENT

18. CONCLUSION AND RECOMMENDATIONS
Approval recommended.

19. REVIEWER:
Radhika Rajagopalan, Ph.D.
DATE COMPLETED:
10/31/02
MAJOR AMENDMENT

ANDA 75-410

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Kremers Urban Development Company PHONE: 262-238-5223

ATTN: John Vaughan Elaine Sabalke FAX: 262-238-0957

FROM: Kassandra Sherrod PROJECT MANAGER (301) 827-5849

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated July 2, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omeprazole Delayed-Release Capsules, 20 mg.

Reference is also made to your amendment(s) dated December 9, 1999 and June 23, 2000.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have not been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

Chemistry deficiencies. Labeling will be faxed to you as soon as it is completed.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

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information
TO: APPLICANT: Kremers Urban Development Co.

ATTN: Steven R. Pellock
      Elaine Cibulka

FROM: Kassandra Sherrod

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated July 2, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omeprazole Delayed-release Capsules, 10 mg and 20 mg.

Reference is also made to your amendment(s) dated: December 7, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-410

BIOEQUIVALENCE REVIEW
BIOEQUIVALENCY COMMENTS

ANDA: 75-410

APPLICANT: Kremers Urban

DRUG PRODUCT: Omeprazole Delayed-Release Capsules, 20 mg & 10 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The Division of Bioequivalence acknowledges that the following dissolution and acid-resistance testing is being incorporated into your stability and quality control programs:

(i) The dissolution testing should be conducted in 750 mL of 0.1N HCl for 2 hours [Acid stage]; followed by 1000 mL of 0.05M phosphate buffer, pH 6.8 [Buffer stage], at 37°C using USP24 apparatus I(basket) at 100 rpm. The test product should meet the following specification:

NLT (Q) of the drug in the capsule is dissolved in 45 minutes [at the end of the Buffer stage].

(ii) The separate acid resistance testing should be conducted in mL of 0.1N HCl for 2 hours [Acid stage], and the omeprazole content of the granules should also be analyzed at the end of the Acid stage. The test product should meet the following specification:

NMT (Q) of the drug in the capsule is dissolved in 120 minutes, as determined by the difference between the average potency assay (without acid exposure) and the potency assay of the remaining granules at the end of the Acid stage.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency
information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

[Signature]

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL
Omeprazole DR Capsules, 20 mg & 10 mg Kremers Urban
ANDA #75-410 Mequon, WI
Reviewer: Hoainhon Nguyen Submission Date:
W #75410a.500 May 12, 2000
* June 2, 2000*
* July 13, 2000*
*Telephone Amendment

Review of an Amendment: Dissolution Data

I. Background:

The firm has submitted the current amendment in response to the deficiency comments from the agency letter dated November 19, 1999 and the teleconference held between the DBE and Kremers Urban representatives on April 18, 2000 (concerning the same deficiencies).

The deficiency comments were as follows: "The Acid Resistance testing results showed that the mean loss of potency, for both the test and reference products, was approximately — (with some individual capsules assayed for greater than — decrease in potency) at the end of 2 hours of the Acid Stage testing. You should explain the observed decrease in potency, and provide the potency assay (with range and %RSD) obtained prior to the dissolution and acid resistance testing, for both test and reference lots."

I. As part of the firm’s investigation into the noted decrease in potency, known and unknown degradants or impurities were quantified from the acid dissolution medium at the end of 2 hours of acid resistance testing. However, the firm concluded that "there are no known or unknown degradants or impurities that account for absolute mass balance."

The firm has also provided the potency of the test and reference product as requested. The potency was 96.0% and 100.0% for 20 mg strength of the test and reference products, respectively,(the biolots). The potency was 98.0% and 99.0% for the 10 mg of the test and reference products, respectively.
The firm has proposed specifications for the Acid Resistance test based on the data obtained for the test product. The specifications are given in the review attachment.

2. Since the firm has never submitted the *in vitro* testing data for the 10 mg strength of the test and reference product, the reviewer requested the dissolution and acid resistance test data on May 25, 2000 through a telephone conference. The firm submitted the requested data on June 2, 2000.

3. On June 29, 2000, the DBE director, team leaders, Dr. Nhan Tran, Project Manager Jennifer Fan and this reviewer had a meeting to discuss the acid resistance test results of this ANDA and the specification for the acid resistance test in general. It was clarified during this meeting that (i) the specification for the acid resistance test should be NMT 10% of the labeled amount dissolved at the end of 2 hours; (ii) the test result is determined by the difference between the average potency assay (without acid exposure) and and the potency assay of the remaining granules at the end of the Acid stage; and (iii) the general USP acceptance table for the acid stage (Table 2, page 1947, USP 24, at level A2) should be applied to the test results.

The concern was raised in the meeting about the potency assay results of the remaining granules for the 20 mg strength of the test and reference products being below 90% (87.6% and 86.6%, respectively) and lower than those reported for other ANDAs, as well as than that of the 10 mg strength of the test and reference products (96.6% and 91.2%, respectively, as submitted in this amendment). The DBE director indicated that, if necessary, a different specification may be recommended for this ANDA provided that the above acid resistance test results can be confirmed by repeat testing of both strengths of the test and reference products.

On June 29, 2000, following the division meeting, the firm was requested by telephone to repeat the acid resistance and dissolution testing of the 10 mg and 20 mg strengths of the test and reference products, on the same lots if possible. The data were submitted on July 13, 2000 and summarized below.
II. Comments:

1. Based on the specification clarified at the June 29, 2000 division meeting above, the acid resistance test results for the 20 mg test and reference product should have been reported as **8.4% and 13.4%**, respectively, of omeprazole dissolved in the acid medium (using the average potency assay of 96.0% and 100.0% for the test and reference products, respectively, as given in this amendment, and the potency assay of the remaining granules of 87.6% and 86.6% for the test and reference products, respectively, as given in the amendment dated September 16, 1999). The 20 mg strength of the test product, therefore, meets the current specification of the acid-resistance test (although the reference product does not).

**NOTE:** If the potency assay without acid exposure was assumed to be 100% and used for the calculation in the acid resistance test (instead of the actual measured average potency assay), the acid resistance test results for the 20 mg test and reference products would be 12.4% and 13.4%, respectively. Based on these results, both the test and reference products would not meet the current specification.

2. The dissolution and acid resistance test results for the 10 mg test and reference products are summarized and commented below.

2A. Dissolution Testing:

**Conditions for Dissolution Testing:** USP Method A for Delayed-Release Capsules

- USP XXIV Basket X Paddle RPM 100 rpm Units Tested: ___
- Medium: Acid Stage: 0.1 H HCl; Buffer Stage: 0.05 M Phosphate Buffer, pH 6.8
- Volume: 750 ml (Acid Stage); 1000 mL (Buffer Stage)
- Reference Drug: (Manuf.) Prisolec Capsules (Merck)
- Assay Methodology: ___
- Specifications: NLT ___ dissolved in 45 minutes (end of Buffer Stage)*

**NOTE:** Although the acid medium was sampled and quantitated at the end of the acid stage by the firm, this quantity is considered not useful and is not reviewed.
Results of In-Vitro Dissolution Testing:

<table>
<thead>
<tr>
<th>Sampling Times (Min.)</th>
<th>Test Product</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot # CJ-0592</td>
<td>Lot # H1616</td>
<td></td>
</tr>
<tr>
<td>Strength (mg) 10</td>
<td>Strength (mg) 10</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean % Dissolved(CV%)</th>
<th>Range</th>
<th>Mean % Dissolved(CV%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
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<td>102</td>
<td></td>
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<td>30</td>
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<td>45</td>
<td>95</td>
<td>102</td>
<td></td>
</tr>
</tbody>
</table>

2B. Acid Resistance Testing:

Conditions for Acid Resistance Testing: FDA-recommended method
USP XXIV Basket X Paddle RPM 100 rpm Units Tested: 12
Medium: Acid Stage: 0.1 H Cl Volume ml
Reference Drug: (Manuf.) Prisolec Capsules (Merck)
Assay Methodology:
Specifications: Acid Stage: NMT dissolve in 2 hours
*After 2 hours in the Acid Stage, the capsules were removed and assayed.

Results of Acid Resistance Testing:

<table>
<thead>
<tr>
<th>Sampling Times (Min.)</th>
<th>Test Product</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot # CJ-0592</td>
<td>Lot # H1616</td>
<td></td>
</tr>
<tr>
<td>Strength (mg) 10</td>
<td>Strength (mg) 10</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean % Assayed(CV%)</th>
<th>Range</th>
<th>Mean % Assayed(CV%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>96.6(1.9)</td>
<td></td>
<td>91.2(3.1)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Based on the average potency of the 10 mg test and reference products of 98.0% and 99.0%, respectively, the content dissolved during the Acid Resistance test is calculated to be 1.4% and 7.8% for the test and reference products, respectively.

Both the test and reference products meet the dissolution specification. Both the test and reference products also meet the acid resistance specification as clarified at the June 29, 2000 division meeting above.
3. The results of the repeat dissolution and acid resistance tests are summarized and commented below. The firm informed that there was insufficient amount of the bio lot (Lot No. H1852) of the 20 mg reference product for repeat testing. A new lot (Lot No. K3240, potency assay of 100.5%) of Prilosec DR capsules, 20 mg, was used instead.

3A. Repeat Dissolution Testing:

Conditions for Dissolution Testing: USP Method A for Delayed-Release Capsules

- USP XXIV Basket X Paddle RPM 100 rpm Units Tested: 12
- Medium: Acid Stage: 0.1 H HCl; Buffer Stage: 0.05 M Phosphate Buffer, pH 6.8
- Volume: 750 _ ml (Acid Stage); 1000 mL (Buffer Stage)
- Reference Drug: (Manuf.) Prisolec Capsules (Merck)
- Assay Methodology

Specifications: NLT — dissolved in 45 minutes (end of Buffer Stage)*

NOTE: Although the acid medium was sampled and quantitated at the end of the acid stage by the firm, this quantity is considered not useful and is not reviewed.

Results of In-Vitro Dissolution Testing:

<table>
<thead>
<tr>
<th>Sampling Times</th>
<th>Test Product</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Min.)</td>
<td>Lot # CJ-0591</td>
<td>Lot # K3240</td>
</tr>
<tr>
<td></td>
<td>Strength (mg) 20</td>
<td>Strength (mg) 20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean % Dissolved(CV%)</th>
<th>Range</th>
<th>Mean % Dissolved(CV%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>90.3(4.1)</td>
<td>107.6(1.9)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sampling Times</th>
<th>Test Product</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Min.)</td>
<td>Lot # CJ-0592</td>
<td>Lot # H1616</td>
</tr>
<tr>
<td></td>
<td>Strength (mg) 10</td>
<td>Strength (mg) 10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean % Dissolved(CV%)</th>
<th>Range</th>
<th>Mean % Dissolved(CV%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>97.2(2.2)</td>
<td>100.6(2.2)</td>
<td></td>
</tr>
</tbody>
</table>
3B. Repeat Acid Resistance Testing:

Conditions for Acid Resistance Testing: FDA-recommended method
USP XXIV Basket X Paddle RPM 100 rpm Units Tested: 12
Medium: Acid Stage: 0.1 H HCl Volume: ml
Reference Drug: (Manuf.) Prisolec Capsules (Merck)
Assay Methodology:
Specifications: Acid Stage: NMT dissolved in 2 hours*
*After 2 hours in the Acid Stage, the capsules were removed and assayed.

Results of Acid Resistance Testing:

<table>
<thead>
<tr>
<th>Sampling Times</th>
<th>Test Product</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Min.)</td>
<td>Lot # Cl-0591</td>
<td>Lot # K3240</td>
</tr>
<tr>
<td></td>
<td>Strength (mg) 20</td>
<td>Strength (mg) 20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Assay</th>
<th>Mean % Assayed(CV%)</th>
<th>Range</th>
<th>Mean % Assayed(CV%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>90.6(3.1)</td>
<td></td>
<td>96.4(1.4)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Based on the average potency of the test and reference products of 96.0% and 100.5%, respectively, the content dissolved at the end of the Acid stage is calculated to be 5.4% and 4.1% for the test and reference products, respectively.

<table>
<thead>
<tr>
<th>Sampling Times</th>
<th>Test Product</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td></td>
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<td>Strength (mg) 10</td>
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</tbody>
</table>

<table>
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<tr>
<th>Assay</th>
<th>Mean % Assayed(CV%)</th>
<th>Range</th>
<th>Mean % Assayed(CV%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>94.2(4.9)</td>
<td></td>
<td>91.1(3.6)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Based on the average potency of the 10 mg test and reference products of 98.0% and 99.0%, respectively, the content dissolved during the Acid Resistance test is calculated to be 3.8% and 7.9% for the test and reference products, respectively.

The results of the repeat dissolution and acid resistance testing for both strengths of the test and reference products meet the dissolution and acid resistance testing specifications. The firm has now satisfied the *in vitro* testing requirements for both strengths of the test product.

P A G E 6
4. From the review of the submissions dated July 2, 1998 and December 29, 1998:

The *in vivo* fasting and food effect bioequivalence studies conducted for the 20 mg strength are acceptable. The studies demonstrate that the test and reference products are equivalent in the rate and extent of absorption as measured by AUCs and CMAX of omeprazole under fasting and nonfasting conditions.

5. The formulation of the 10 mg strength is proportionally similar to that of the 20 mg strength which underwent acceptable *in vivo* bio testing (See attachment).

III. Recommendation:

1. The *in-vitro* testing conducted by Kremers Urban on its Omeprazole DR Capsules, 10 mg and 20 mg, has been found acceptable by the Division of Bioequivalence.

The dissolution and acid resistance testing should be incorporated by the firm into its manufacturing controls and stability program.

(i) The dissolution testing should be conducted in 750 mL of 0.1N HCl for 2 hours [Acid stage]; followed by 1000 mL of 0.05M phosphate buffer, pH 6.8 [Buffer stage], at 37°C using USP24 apparatus I(basket) at 100 rpm. The test product should meet the following specification:

NLT 6 (Q) of the drug in the capsule is dissolved in 45 minutes [at the end of the Buffer stage].

(ii) The separate acid resistance testing should be conducted in 250 mL of 0.1N HCl for 2 hours [Acid stage], and the omeprazole content of the granules should also be analyzed at the end of the Acid stage. The test product should meet the following specification:

NMT of the drug in the capsule is dissolved in 120 minutes, as determined by the difference between the average potency assay (without acid
exposure) and the potency assay of the remaining granules at the end of the Acid stage.

NOTE: The above dissolution testing procedure is a modification of the FDA-recommended method. The minor modification was proposed by the firm in the submission dated September 16, 1999 and consists of changing the Acid Stage medium volume from \( \ldots \) to 750 mL, and changing the Buffer Stage medium volume from \( \ldots \) to 1000 mL. The data generated for the agency and proposed methods, submitted on September 16, 1999, were equivalent. The modified dissolution method was therefore accepted. It should be noted that this modified method is the same as the USP Method A for delayed-release capsules. The firm's acid resistance test is the same as the FDA-recommended method.

2. The single-dose, fasting bioequivalence study and the single-dose non-fasting bioequivalence study conducted by Kremers Urban on the test product, Omeprazole DR Capsules, 20 mg, lot # CJ-0591, comparing it with the reference product, AstraMerck's Prilosec® 20 mg DR Capsules, lot # H1852, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Kremers Urban's Omeprazole DR Capsules, 20 mg, are bioequivalent to the reference product, AstraMerck's Prilosec® 20 mg DR Capsules, under fasting and non-fasting conditions.

3. The waiver of in vivo bioequivalence study requirements for the 10 mg capsules is granted. The firm's Omeprazole DR Capsule, 10 mg, is deemed bioequivalent to AstraMerck's Prilosec 10 mg DR capsule.

\[ \text{Joannino Nguyen} \]
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

\[ \text{Dale P. Conner, Pharm.D.} \]
Director, Division of Bioequivalence

Date: 7/26/00
Omeprazole DR Capsules, 20 mg
ANDA #75-410
Reviewer: Hoainhon Nguyen
W #75410a.999

Kremers Urban
Mequon, WI
Submission Date:
September 16, 1999

Review of an Amendment: Dissolution Data

The firm has incorporated the deficiency comments from the agency letters dated November 3, 1998 and August 16, 1999 into the current repeat dissolution testing. The dissolution results are summarized below. The firm complied with the requirements of the FDA-recommended dissolution method concerning dissolution apparatus and speed, pH of the medium, and the specifications. However, the firm also proposed a minor modification of the agency method for the purpose of testing ease: Due to the firm's "use of the on-line — and the timing required for a complete fluid change," the firm prefers "to retain the proposed strategy for the pH change to the buffer phase." Its "initial fluid is 750 mL of 0.1 N HCl. After 2 hours, 250 mL of 0.2 M phosphate buffer is added. The final solution will be 1000 mL of 0.05 M phosphate buffer at pH 0.8 for the buffer stage."

The firm has submitted dissolution profiles comparing its proposed method of testing to the method recommended by the agency.

I. Dissolution Testing Results:

IA. Conditions for Dissolution Testing: FDA-recommended method
USP XXIII Basket X Paddle RPM 100 rpm Units Tested: 12
Medium: Acid Stage: 0.1 HCl; Buffer Stage: 0.05 M Phosphate Buffer, pH 6.8
Volume: __________ ml (Both stages)
Reference Drug: (Manuf.) Prisolec Capsules (Merck)
Assay Methodology: __________
Specifications: Acid Stage: NMT __ dissolved in 2 hours
Buffer Stage: NLT __ dissolved in 45 minutes

PAGE 1
### IB. Results of In-Vitro Dissolution Testing:

<table>
<thead>
<tr>
<th>Sampling Times (Min.)</th>
<th>Test Product</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lot # C1-0591</td>
<td>Lot # H1852</td>
</tr>
<tr>
<td></td>
<td>Strength (mg) 20</td>
<td>Strength (mg) 20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acid Stage</th>
<th>Mean % Dissolved (CV%)</th>
<th>Range</th>
<th>Mean % Dissolved (CV%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>0 (24.9)</td>
<td></td>
<td>2 (33)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Buffer Stage</th>
<th>Mean % Dissolved (CV%)</th>
<th>Range</th>
<th>Mean % Dissolved (CV%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>82 (6.7)</td>
<td></td>
<td>98 (2.3)</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>87 (4.6)</td>
<td></td>
<td>97 (2.0)</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>88 (4.2)</td>
<td></td>
<td>97 (2.1)</td>
<td></td>
</tr>
</tbody>
</table>

### IC. Conditions for Dissolution Testing: Firm's proposed method
- USP XXIII Basket X Paddle RPM 100 rpm Units Tested: 12
- Medium: Acid Stage: 0.1 HCl; Buffer Stage: 0.05 M Phosphate Buffer, pH 6.8
- Volume: 750 mL (Acid stage); 1000 mL (Buffer stage)
- Reference Drug: (Manuf.) Prisolec Capsules (Merck)
- Assay Methodology: 
- Specifications: Acid Stage: NMT, dissolved in 2 hours
  Buffer Stage: NLT, dissolved in 45 minutes

### ID. Results of In-Vitro Dissolution Testing:

<table>
<thead>
<tr>
<th>Sampling Times (Min.)</th>
<th>Test Product</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lot # C1-0591</td>
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</tr>
<tr>
<td></td>
<td>Strength (mg) 20</td>
<td>Strength (mg) 20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acid Stage</th>
<th>Mean % Dissolved (CV%)</th>
<th>Range</th>
<th>Mean % Dissolved (CV%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>1 (162)</td>
<td></td>
<td>2 (42)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Buffer Stage</th>
<th>Mean % Dissolved (CV%)</th>
<th>Range</th>
<th>Mean % Dissolved (CV%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>83 (6.3)</td>
<td></td>
<td>101 (3.1)</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>88 (4.9)</td>
<td></td>
<td>101 (2.3)</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>90 (4.3)</td>
<td></td>
<td>101 (2.3)</td>
<td></td>
</tr>
</tbody>
</table>
II. Acid Resistance Testing:

IIA. Conditions for Acid Resistance Testing: FDA-recommended method

USP XXIII Basket X, Paddle __ RPM 100 rpm Units Tested: 12
Medium: Acid Stage: 0.1 H HCl Volume: ___ ml
Reference Drug: (Manuf.) Prisolec Capsules (Merck)
Assay Methodology ___

Specifications: Acid Stage: NMT ____ dissolved in 2 hours
After 2 hours in the Acid Stage, the capsules were removed and assayed.

IIB. Results of Acid Resistance Testing:

<table>
<thead>
<tr>
<th>Sampling Times (Min.)</th>
<th>Test Product</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lot # CJ-0591</td>
<td>Lot # H1852</td>
</tr>
<tr>
<td>Strength (mg) 20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acid Stage</th>
<th>Mean % Dissolved(CV%)</th>
<th>Range</th>
<th>Mean % Dissolved(CV%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 min</td>
<td>0.8(145)</td>
<td></td>
<td>2.2(28)</td>
<td></td>
</tr>
</tbody>
</table>

Assay

87.6(6.8) 86.6(2.5)

IIC. Conditions for Acid Resistance Testing: Firm's proposed method

USP XXIII Basket X, Paddle __ RPM 100 rpm Units Tested: 12
Medium: Acid Stage: 0.1 H HCl Volume: 750 mL
Reference Drug: (Manuf.) Prisolec Capsules (Merck)
Assay Methodology: ___

Specifications: Acid Stage: NMT ____ dissolved in 2 hours
After 2 hours in the Acid Stage, the capsules were removed and assayed.

IID. Results of Acid Resistance Testing:

<table>
<thead>
<tr>
<th>Sampling Times (Min.)</th>
<th>Test Product</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lot # CJ-0591</td>
<td>Lot # H1852</td>
</tr>
<tr>
<td>Strength (mg) 20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acid Stage</th>
<th>Mean % Dissolved(CV%)</th>
<th>Range</th>
<th>Mean % Dissolved(CV%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 min</td>
<td>0.1(244)</td>
<td></td>
<td>2.7(38)</td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>90.0(3.7)</td>
<td></td>
<td>90.4(3.4)</td>
<td></td>
</tr>
</tbody>
</table>
III. Comments:

The minor modification of the dissolution procedure as proposed by the firm for the purpose of testing ease is acceptable. The modification consists of changing the Acid Stage medium volume from \( \ldots \) to 750 mL, and changing the Buffer Stage medium volume from \( \ldots \) to 1000 mL. The data generated by the agency and proposed methods, for both dissolution and acid resistance tests, are equivalent.

IV. Deficiencies:

The Acid Resistance testing results showed that the mean loss of potency, for both the test and reference products, was approximately \( \ldots \) (with some individual capsules assayed for greater than \( \ldots \) decrease in potency) at the end of 2 hours of the Acid Stage testing. The firm should explain the observed decrease in potency, and provide the potency assay (with range and %RSD) obtained prior to the dissolution and acid resistance testing, for both test and reference lots.

Recommendation:

The *in vitro* dissolution testing conducted by Kremers Urban on its Omeprazole DR Capsules, 20 mg, has been found *incomplete* due to the Deficiencies cited above.

Hoanhon Nguyen  
Division of Bioequivalence  
Review Branch I

RD INITIALED YHUANG  
FT INITIALED YHUANG

Concur: ____________________________ Date: 11/16/99

Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence
BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-410
APPLICANT: Kremers Urban

DRUG PRODUCT: Omeprazole Delayed-Release Capsules, 20 mg & 10 mg

The Division of Bioequivalence has completed its review of your submission of the waiver request for the 10 mg strength, dated July 1, 1999, acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have not submitted the in vitro dissolution data for the 10 mg strength. The in vivo requirements for the 10 mg strength of the test product may be waived based on not only the formulation proportionality between strengths but also the in vitro dissolution data of this strength. The in vitro dissolution testing method and specification are as described for the 20 mg strength.

2. You are especially referred to the deficiency comments made for the submission dated June 4, 1999 of the dissolution data for the 20 mg strength. These comments are also applied to the future submission of the dissolution data for the 10 mg strength. They are restated below.

   i. The firm should use 12 units, instead of 10 of the test product for the testing by each method.

   ii. The firm should also test the reference product in the same manner.

   iii. The dissolution data summary table should include the CV% and the range for each mean values.

   iv. Currently, the agency is requesting an additional in vitro dissolution determination for omeprazole DR capsule products: the Acid Resistance Test. Since the drug is acid-labile, the omeprazole content of the granules should also be analyzed at the end of the Acid stage (after 2 hours). This determination ascertains that low measurement of omeprazole during the Acid stage is not due to acid-degradation of omeprazole released at this stage.

The test results of the Acid Resistance Test should be based on 12 units each of the test and reference product per dissolution
method. The results should be summarized in the similar manner as for the Drug Release Acid and Buffer Tests.

Sincerely yours,

[Signature]

for
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL
Review of a Waiver Request

The firm has submitted a request for a waiver of in vivo bioequivalence requirements for the 10 mg strength of its Omeprazole DR Capsules based on the fact that 'The 10 mg and 20 mg capsules differ in the number of microtablets contained in the capsules' and 'the 10 mg capsule contains half the number of microtablets.'

Deficiency Comments:

1. Although the in vivo requirements may be waived for the 10 mg strength of the test product, the in vitro dissolution testing is required of this strength. The in vitro dissolution testing method and specification are as described for the 20 mg strength.

2. The firm is especially referred to the deficiency comments made for the submission dated June 4, 1999 of the dissolution data for the 20 mg strength. The comments are restated below.

i. The firm should use 12 units, instead of 10 of the test product for the testing by each method.

ii. The firm should also test the reference product in the same manner.

iii. The dissolution data summary table should include the CV% and the range for each mean values.

iv. As of June 16, 1999, the agency is requesting an additional in vitro dissolution determination for omeprazole DR capsule products: the Acid Resistance Test. Since the drug is acid-labile, the omeprazole content of the granules should also be analyzed at the end of the Acid stage (after 2 hours). This determination ascertains that low measurement of omeprazole during the Acid stage is not due to acid-degradation of omeprazole released at this stage.
The test results of the Acid Resistance Test should be based on 12 units each of the test and reference product per dissolution method. The results should be summarized in the similar manner as for the Drug Release Acid and Buffer Tests.

Recommendations:

The waiver request for Kremers Urban's its Omeprazole DR Capsules, 10 mg, has not been granted due to the Deficiencies cited above.

Hoanghon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

Concur: __________________ Date: 11/1/99
for Dale P. Conn, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-410 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/07-30-99/W #75410w.799
Also as V:\firmsam\kremers\trs&rev\75410w.799
Attachment: None
BIOEQUIVALENcy DEFICIENCIES

ANDA: 75-410

APPLICANT: Kremers Urban

DRUG PRODUCT: Omeprazole Delayed-Release Capsules, 20 mg & 10 mg

The Division of Bioequivalence has completed its review of your submission of the waiver request for the 10 mg strength, dated July 1, 1999, acknowledged on the cover sheet. The following deficiencies have been identified:

1. You have not submitted the in vitro dissolution data for the 10 mg strength. The in vivo requirements for the 10 mg strength of the test product may be waived based on not only the formulation proportionality between strengths but also the in vitro dissolution data of this strength. The in vitro dissolution testing method and specification are as described for the 20 mg strength.

2. You are especially referred to the deficiency comments made for the submission dated June 4, 1999 of the dissolution data for the 20 mg strength. These comments are also applied to the future submission of the dissolution data for the 10 mg strength. They are restated below.

i. The firm should use 12 units, instead of of the test product for the testing by each method.

ii. The firm should also test the reference product in the same manner.

iii. The dissolution data summary table should include the CV% and the range for each mean values.

iv. Currently, the agency is requesting an additional in vitro dissolution determination for omeprazole DR capsule products: the Acid Resistance Test. Since the drug is acid-labile, the omeprazole content of the granules should also be analyzed at the end of the Acid stage (after 2 hours). This determination ascertains that low measurement of omeprazole during the Acid stage is not due to acid-degradation of omeprazole released at this stage.

The test results of the Acid Resistance Test should be based on 12 units each of the test and reference product per dissolution
method. The results should be summarized in the similar manner as for the Drug Release Acid and Buffer Tests.

Sincerely yours,

[Signature]

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and
Research

APPEARS THIS WAY ON ORIGINAL
CC: ANDA 75-410
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (F:...h Dates)
HFD-652/ HNguyen
HFD-652/ YHuang
HFD-617/ E. Hu
HFD-650/ D. Connect

V:\FIRMSAM\kremers\ltrs&rev\75410w.799
Printed in final on 07/01/99

DISSOLUTION - DEFICIENT  Submission date: 07-01-99

1. WAIVER (WAI)  10 mg
   Strengths: 10 mg
   Outcome: IC

OUTCOME DECISIONS: IC - Incomplete  UN - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:
BIOEQUIVALENCY AMENDMENT

ANDA 75-410

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Kremers Urban Development Company PHONE: (414) 238-5714

ATTN: John Vaughan FAX: (414) 512-1108

FROM: Elaine Hu PROJECT MANAGER (301) 827-5847

Dear Mr. Vaughan:

This facsimile is in reference to the bioequivalency data submitted on June 4, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omeprazole Delayed-Release Capsules, 20 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached □ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalence Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 75-410

APPLICANT: Kremers Urban

DRUG PRODUCT: Omeprazole Delayed-Release Capsules, 20 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. You should use 12 units, instead of 6 of the test product for the dissolution testing by each method.

2. You should also test the reference product in the same manner.

3. The dissolution data summary table should include the CV% and the range for each mean values.

4. As of June 16, 1999, the agency is requesting an additional in vitro dissolution determination for omeprazole DR capsule products: the Acid Resistance Test. Since the drug is acid-labile, the omeprazole content of the granules should also be analyzed at the end of the Acid stage (after 2 hours). This determination ascertains that low measurement of omeprazole during the Acid stage is not due to acid-degradation of omeprazole released at this stage.

The test results of the Acid Resistance Test should be based on 12 units each of the test and reference product per dissolution method. The results should be summarized in the similar manner as for the Drug Release Acid and Buffer Tests.

Sincerely yours,

[Signature]

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-410

APPLICANT: Kremers Urban

DRUG PRODUCT: Omeprazole Delayed-Release Capsules, 20 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. You should use 12 units, instead of of the test product for the dissolution testing by each method.

2. You should also test the reference product in the same manner.

3. The dissolution data summary table should include the CV% and the range for each mean values.

4. As of June 16, 1999, the agency is requesting an additional in vitro dissolution determination for omeprazole DR capsule products: the Acid Resistance Test. Since the drug is acid-labile, the omeprazole content of the granules should also be analyzed at the end of the Acid stage (after 2 hours). This determination ascertains that low measurement of omeprazole during the Acid stage is not due to acid-degradation of omeprazole released at this stage.

The test results of the Acid Resistance Test should be based on 12 units each of the test and reference product per dissolution method. The results should be summarized in the similar manner as for the Drug Release Acid and Buffer Tests.

Sincerely yours,

[Signature]

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
CC: ANDA 75-410
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen 7/1/99
HFD-652/ YHuang 7/29/99
HFD-617/ E. H. 7/29/99
HFD-650/ D. Conter 7/2/99

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DISSOLUTION - DEFICIENT Submission date: 06-04-99

1. STUDY AMENDMENT (STA) Outcome: IC
   Strengths: 20 mg
   OUTCOME DECISIONS: IC - Incomplete UN - Unacceptable (fatal flaw)
   AC - Acceptable

WINBIO COMMENTS:
BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-410             APPLICANT: Kremers Urban

DRUG PRODUCT: Omeprazole Delayed-Release Capsules, 20 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

The Acid Resistance testing results showed that the mean loss of potency, for both the test and reference products, was approximately — (with some individual capsules assayed for greater than — decrease in potency) at the end of 2 hours of the Acid Stage testing. You should explain the observed decrease in potency, and provide the potency assay (with range and %RSD) obtained prior to the dissolution and acid resistance testing, for both test and reference lots.

Sincerely yours,

[Signature]

Dale P. Connor, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
CC: ANDA 75-410
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 9/27/99
HFD-617/ E. Hu
HFD-650/ D. Conner 11/16/99

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DISSOLUTION - DEFICIENT Submission date: 09-16-99

1. STUDY AMENDMENT (STA) Strengths: 20 mg
   Outcome: IC

OUTCOME DECISIONS: IC - Incomplete UN - Unacceptable
(fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

P A G E 7
BIOEQUIVALENCY AMENDMENT

ANDA 75-410

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Kremers Urban Development Company PHONE: (414) 238-5714

ATTN: John Vaughan FAX: (414) 542-1108

FROM: Elaine Hu PROJECT MANAGER (301) 827-5847

Dear Mr. Vaughan:

This facsimile is in reference to the bioequivalency data submitted on September 16, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omeprazole Delayed-Release Capsules, 20 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached [ ] pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

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11/18/99
BIOEQUIVALENCE DEFICIENCIES

ANDA: 75-410  APPLICANT: Kremers Urban

DRUG PRODUCT: Omeprazole Delayed-Release Capsules, 20 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

The Acid Resistance testing results showed that the mean loss of potency, for both the test and reference products, was approximately — (with some individual capsules assayed for greater than — decrease in potency) at the end of 2 hours of the Acid Stage testing. You should explain the observed decrease in potency, and provide the potency assay (with range and %RSD) obtained prior to the dissolution and acid resistance testing, for both test and reference lots.

Sincerely yours,

[Signature]

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
BIOEQUIVALENCY COMMENTS

ANDA: 75-410

APPLICANT: Kremers Urban

DRUG PRODUCT: Omeprazole Delayed-Release Capsules, 20 mg & 10 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The Division of Bioequivalence acknowledges that the following dissolution and acid-resistance testing is being incorporated into your stability and quality control programs:

(i) The dissolution testing should be conducted in 750 mL of 0.1N HCl for 2 hours [Acid stage], followed by 1000 mL of 0.05M phosphate buffer, pH 6.8 [Buffer stage], at 37°C using USP24 apparatus I (basket) at 100 rpm. The test product should meet the following specification:

NLT (Q) of the drug in the capsule is dissolved in 45 minutes [at the end of the Buffer stage].

(ii) The separate acid resistance testing should be conducted in _______ of 0.1N HCl for 2 hours [Acid stage], and the omeprazole content of the granules should also be analyzed at the end of the Acid stage. The test product should meet the following specification:

NMT ______ of the drug in the capsule is dissolved in 120 minutes, as determined by the difference between the average potency assay (without acid exposure) and the potency assay of the remaining granules at the end of the Acid stage.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency
information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

\[\text{Signature}\]

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
CC: ANDA 75-410
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
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HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang
HFD-617/ K. Scardina
HFD-650/ D. Conner

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DISSOLUTION - ACCEPTABLE

Submission date: 05-12-00
06-02-00
07-13-00

1. STUDY AMENDMENT (STA)
   Strength: 20 mg
   Outcome: AC

2. STUDY AMENDMENT (STA)
   Strength: 10 mg
   Outcome: AC

3. STUDY AMENDMENT (STA)
   Strength: 10 mg & 20 mg
   Outcome: AC

OUTCOME DECISIONS: IC - Incomplete
(fatal flaw)
UN - Unacceptable
AC - Acceptable

WINBIO COMMENTS:
OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-410
SPONSOR: Kremers Urban
DRUG AND DOSAGE FORM: Omeprazole DR Capsules
STRENGTH(S): 10 mg & 20 mg
TYPES OF STUDIES: Fasting Study & Non-Fasting Study
CLINICAL STUDY SITE(S): ______________
ANALYTICAL SITE(S): ______________

STUDY SUMMARY: Acceptable
DISSOLUTION: Acceptable

### DSI INSPECTION STATUS

<table>
<thead>
<tr>
<th>Inspection needed:</th>
<th>Inspection status:</th>
<th>Inspection results:</th>
</tr>
</thead>
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<tr>
<td>NO</td>
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</tr>
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<td>First Generic</td>
<td>Inspection completed: (date)</td>
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<tr>
<td>Other</td>
<td></td>
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</tbody>
</table>

PRIMARY REVIEWER: Hoainhon Nguyen
INITIAL: /§/  DATE: 7/20/00

TEAM LEADER: Vihn-Chain Huang
INITIAL: ____________  DATE: 7/20/00

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.
INITIAL: /§/  DATE: 7/26/00
Redacted 2

pages of trade

secret and/or

confidential

commercial

information
Review of an Amendment: Dissolution Data

The firm has revised the dissolution testing method and submitted additional \textit{in vitro} dissolution data as requested by the agency in the letter dated November 3, 1998.

i. The firm has revised the dissolution apparatus and speed to basket and 100 rpm.

ii. The firm has revised the pH of the phosphate buffer from \ldots{} to 6.8.

iii. The firm has adopted the recommended specifications of 'NMT \ldots{} dissolved in 120 minutes [Acid stage], and NLT \ldots{} dissolved in the next 45 minutes [Buffer stage]'.

iv. Due to the firm's "use of the on-line \ldots{} and the timing required for a complete fluid change," the firm prefers "to retain the proposed strategy for the pH change to the buffer phase." Its "initial fluid is 750 mL of 0.1 N HCl. After 2 hours, 250 mL of 0.2 M phosphate buffer is added. The final solution will be 1000 mL of 0.05 M phosphate buffer at pH 0.8 for the buffer stage."

The firm has submitted dissolution profiles comparing its proposed method of testing to the method recommended by the agency.

**Dissolution Testing Results:**

I. **Conditions for Dissolution Testing:** FDA-recommended method
   USP XXIII Basket X Paddle \ldots{} RPM 100 rpm Units Tested
   Medium: Acid Stage: 0.1 H HCl; Buffer Stage: 0.05 M Phosphate Buffer, pH 6.8
   Volume: \ldots{} ml (Both stages)
   Reference Drug: (Manuf.) Not used
   Assay Methodology: \ldots{}
Specifications: Acid Stage: NMT — dissolved in 2 hours  
Buffer Stage: NLT — dissolved in 45 minutes

II. Results of In-Vitro Dissolution Testing:

<table>
<thead>
<tr>
<th>Sampling Times (Min.)</th>
<th>Test Product Lot # CI-0591</th>
<th>Strength (mg) 20</th>
<th>Reference Product Lot #</th>
<th>Strength (mg)</th>
</tr>
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<tr>
<td><strong>Acid Stage</strong></td>
<td></td>
<td></td>
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<tr>
<td>120</td>
<td></td>
<td>0</td>
<td></td>
<td>0</td>
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<tr>
<td><strong>Buffer Stage</strong></td>
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<tr>
<td>15</td>
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<td>86</td>
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<td>45</td>
<td></td>
<td>91</td>
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</table>

I. Conditions for Dissolution Testing: Firm’s proposed method  
USP XXIII Basket X Paddle ___ RPM 100 rpm Units Tested ___  
Medium: Acid Stage: 0.1 N HCl; Buffer Stage: 0.05 M Phosphate Buffer, pH 6.8  
Volume: 750 mL (Acid stage); 1000 mL (Buffer stage)  
Reference Drug: (Manuf.) Not used  
Assay Methodology ___  
Specifications: Acid Stage: NMT — dissolved in 2 hours  
Buffer Stage: NLT — dissolved in 45 minutes

II. Results of In-Vitro Dissolution Testing:

<table>
<thead>
<tr>
<th>Sampling Times (Min.)</th>
<th>Test Product Lot # CI-0591</th>
<th>Strength (mg) 20</th>
<th>Reference Product Lot #</th>
<th>Strength (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acid Stage</strong></td>
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<tr>
<td>120</td>
<td></td>
<td>0</td>
<td></td>
<td>0-3</td>
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<tr>
<td><strong>Buffer Stage</strong></td>
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<tr>
<td>15</td>
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<td>84</td>
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<tr>
<td>45</td>
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<td>89</td>
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<td></td>
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</tbody>
</table>
Deficiencies:

1. The firm should use 12 units, instead of 5, of the test product for the testing by each method.

2. The firm should also test the reference product in the same manner.

3. The dissolution data summary table should include the CV% and the range for each mean values.

4. As of June 16, 1999, the agency is requesting an additional in vitro dissolution determination for omeprazole DR capsule products: the Acid Resistance Test. Since the drug is acid-labile, the omeprazole content of the granules should also be analyzed at the end of the Acid stage (after 2 hours). This determination ascertains that low measurement of omeprazole during the Acid stage is not due to acid-degradation of omeprazole released at this stage.

The test results of the Acid Resistance Test should be based on 12 units each of the test and reference product per dissolution method. The results should be summarized in the similar manner as for the Drug Release Acid and Buffer Tests.

Recommendation:

The in vitro dissolution testing conducted by Kremers Urban on its Omeprazole DR Capsules, 20 mg, has been found unacceptable due to the Deficiencies cited above.

---

Hoainhon Nguyen  
Division of Bioequivalence  
Review Branch I  

RD INITIALED YHUANG  
FT INITIALED YHUANG  

[Signature]  
7/7/99
Concur

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA # 75-410 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNgyuen/06-25-99/W #75410a.699
Also as V:\firmsam\kremers\ltre&rev\75410a.699
Attachment: None
BIOEQUIVALENCE AMENDMENT

ANDA 75-410

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Kremers Urban
ATTN: Jonathan A. Thiel

FROM: Elaine Hu

PHONE: 414-238-5715
FAX: 414-238-0957

PROJECT MANAGER (301) 827-5847

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on July 2, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omeprazole Delayed-Release Capsules, 20 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

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X:\new\eg\adrn\glossary\biofax.frm
BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-410  APPLICANT: Kremers Urban

DRUG PRODUCT: Omeprazole Delayed-Release Capsules, 20 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

The dissolution testing is not acceptable for the following reasons:

i. The paddle speed of 100 rpm is considered excessive; the speed of should be used for this apparatus (paddle). For the basket apparatus (USP apparatus I), the speed of 100 rpm is considered acceptable, however.

ii. The pH of the phosphate buffer, used in the Buffer Stage, should be 5.8 instead of

Although presently there is no compendial dissolution method and specifications available for the omeprazole DR capsule product, based on information available to the agency, the following dissolution methodology will probably be recommended to the USP compendial staff for the drug product. You may wish to consider this methodology in the future.

The dissolution testing should be conducted in of 0.1N HCl for 2 hours [Acid stage]; followed by of 0.05M phosphate buffer, pH 6.8 [Buffer stage], at 37 C using USP23 apparatus I(basket) at 100 rpm. The test product should meet the following specification:

NMT if the drug in the capsule is dissolved in 2 hours [Acid stage] and NLT (Q) of the drug in the capsule is dissolved in 45 minutes [Buffer stage].

The Division of Bioequivalence has completed its review of the fasting bioequivalence study for Kremers' Omeprazole DR Capsules, 20 mg, and has no further questions concerning this study at this
time. The Division is looking forward toward reviewing the non-fasting study that the firm has recently initiated as the study results become available to the agency.

Sincerely yours,

[Signature]

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Review of A Fasting Bioequivalence Study and Dissolution Data

I. Background:

Omeprazole belongs to a new class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H₂ histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H⁺/K⁺ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

Omeprazole is a weak base, freely soluble in ethanol but very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

Omeprazole is indicated for short-term treatment of active duodenal ulcer, active benign gastric ulcer, erosive esophagitis, and symptomatic gastroesophageal reflux disease. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy. Omeprazole, in combination with clarithromycin, is also indicated for treatment of patients with *H. pylori* infection and active duodenal ulcer to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. Omeprazole is indicated to maintain healing of erosive esophagitis and for the long-term treatment of pathological hypersecretory conditions.

The RLD product, Prilosec Delayed-Released Capsules contain an enteric-coated granule formulation of omeprazole (because omeprazole is acid-labile), so that absorption of omeprazole begins only after the granules leave the stomach.
Absorption is rapid with peak plasma levels of omeprazole occurring within 0.5 to 3.5 hours. Peak plasma concentrations of omeprazole and AUC are approximately proportional to doses up to 40 mg, but because of a saturable first-pass effect, a greater than linear response in peak plasma concentration and AUC occurs with doses greater than 40 mg. Absolute bioavailability (compared to intravenous administration) is about 30-40% at doses of 20-40 mg, due in large part to presystemic metabolism. In healthy subjects, the plasma half-life is 0.5 to 1 hour, and the total body clearance is 500-600 mL/min. Protein binding is approximately 95%. The bioavailability of omeprazole increases slightly upon repeated administration.

Following single dose oral administration of a buffered solution of omeprazole, little if any unchanged drug was excreted in urine. The majority of the dose (about 77%) was eliminated in urine as at least six metabolites. These metabolites have very little or no antisecretory activity. In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians. Dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired and Asian subjects are usually considered.

The recommended adult oral dose is 20-40 mg once daily. The most common adverse effects associated with omeprazole DR capsules include headache, diarrhea, abdominal pain and nausea.

The firm has submitted the results of one fasting single-dose bioequivalence study for its Omeprazole DR Capsules, 20 mg, comparing it with Prilosec® 20 mg DR Capsules, manufactured by Astra Merck. Comparative dissolution data for the products were also submitted.

The firm has informed the agency that a non-fasting single-dose bioequivalence study for the test and reference products was to be initiated within 45 days of this current submission.

II. Bioequivalence Study:
Fasting Single-Dose Bioequivalence Study: (Study No. 20330, Protocol No. SPUS-830-004) A Single Dose Bioequivalence Study Comparing SPUS 830 with a Reference Product when Given in the Fasted State

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Kremers' Omeprazole DR Capsules, 20 mg, and Merck's Prilosec® 20 mg DR Capsules under fasting conditions.

Study Investigators and Facilities:

The study was conducted between April 18 and May 16, 1998. The principal investigator was Plasma samples were assayed by under the supervision of between April 27 and May 22, 1998.

Demographics:

Forty-seven normal, healthy non-smoking male volunteers between 19-40 years of age, and within 10% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two-treatment, two-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 140 - 218 lbs and 65 - 76 in, respectively. All subjects were caucasians.

The total of 47 subjects included 32 subjects that were enrolled initially (Dates of Period I and II: April 18 and 25, 1998, respectively), and a make-up group of 15 more subjects (Dates of Period I and II: May 9 and 16, 1998, respectively).

Inclusion/exclusion criteria: See review attachment.

Restrictions:
They were free of all prescription and OTC medications for 14 days and 72 hours, respectively, prior to the study. No use of alcohol/drugs of abuse or xanthine containing foods/beverages within 48 hours prior to study initiation. The subjects fasted 10 hours overnight and 4 hours following dosing. The washout duration between the phases was 7 days. Duration of confinement was approximately 10 hours predose until approximately 8 hours post-dose.

Treatments and Sampling:

The two treatments consisted of a single 20 mg dose of either the test product or reference product taken orally with 240 ml of water.

Test Product: Kremers’ Omeprazole DR Capsules, 20 mg, Lot No. CJ-0591 (Batch size of ___ units, potency of 96.0%), given under fasting conditions.

Reference product: Merck’s Prilosec® 20 mg DR capsules, lot # E2621 (Potency of 100.9%), given under fasting conditions.

Assay Methodology:
Redacted

pages of trade

secret and/or confidential

commercial

information
Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by: AUC(0-Infinity) = AUC(0-T) + [last measured concentration/KEL]. CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

An analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters.

ANOVA was also performed to assess the group effect and determine the poolability of the two groups. A model with terms for groups, sequences within group, subjects within (group*sequence), periods, treatments, and group*treatment were performed.

Results:

Forty-six of 47 enrolled volunteers completed the clinical portion of the study. Subject #34 was dropped prior to the start of the study due to unrelated illness.
Data for 46 subjects were analyzed.

According to the firm's analysis, the test for group-by-treatment interaction was statistically significant for lnAUC(0-T) (p=0.0399), and also borderline for lnCMAX (p=0.0777) and lnAUC(0-Inf) (p=0.0553). The 90% confidence intervals calculated for these parameters based on the ANOVA model with group*treatment term included (and two groups combined), by this reviewer, are included in the result summary table below. The firm also performed a separate analysis for each group. However, the firm did not use correct data for the separate analyses (with data for all subjects included, but separate estimate and standard error of estimate for each group used to calculate the 90% confidence intervals). Re-analysis for each group using data from each group separately, by the reviewer, and recalculation of the 90% confidence interval for lnCMAX for each group showed that lnAUCs and lnCMAX for Group 1 (n=32) had confidence intervals within the acceptable limit, but the same parameters for Group 2 (n=14) did not (due to small number of subjects included in the analysis perhaps). The 90% C.I. results from separate group analyses are also included in the summary table below.

According to Don Schuirmann's consultation on a similar study design (a copy of the consultation attached), the following ANOVA model was actually recommended as more appropriate for the study design: CLASS SEQ SUBJ PER TRT GROUP; MODEL Y=SEQ SUBJ(SEQ) PER(GROUP) TRT;

The reviewer therefore re-analyzed the data using Mr. Schuirmann's ANOVA model for lnAUC(0-T), lnAUC(0-Inf) and lnCMAX. The 90% confidence intervals for lnAUCs and lnCMAX based on this model are also given below. There were significant differences between treatments for lnAUC(0-T) (p=0.0033) and for lnAUC(0-Inf) (p=0.0052).
Table I
Omeprazole Comparative Pharmacokinetic Parameters
Fasting Single-Dose Study; Dose = 20 mg; n = 46

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Kremers' Mean (CV)</th>
<th>Prilosec® Mean (CV)</th>
<th>90% C.L.</th>
<th>Ratio T/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0\rightarrow t}$ (n=46) ng.hr/ml</td>
<td>311.5*</td>
<td>335.3*</td>
<td>[0.88;0.98]</td>
<td>0.93</td>
</tr>
<tr>
<td>$AUC_{0\rightarrow \infty}$ (n=44) ng.hr/ml</td>
<td>332.2*</td>
<td>355.0*</td>
<td>[0.89;0.98]</td>
<td>0.94</td>
</tr>
<tr>
<td>CMAX(ng/mL) (n=46)</td>
<td>200.0*</td>
<td>191.4*</td>
<td>[0.94;1.16]</td>
<td>1.04</td>
</tr>
<tr>
<td>TMAX (hrs)</td>
<td>2.196(52)</td>
<td>2.014(64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KEL (hrs⁻¹)</td>
<td>0.943(20)</td>
<td>0.873(24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/2 (hrs)</td>
<td>0.782(36)</td>
<td>0.861(39)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$AUC_{0\rightarrow t,01}$ (n=32)*** 305.1* 354.1* [0.82;0.91] 0.86
$AUC_{0\rightarrow \infty,01}$ (n=30)*** 334.4* 382.8* [0.83;0.92] 0.87
$CMAK_{01}(ng/mL)$*** (n=32) 202.4* 218.2* [0.82;1.04] 0.93

$AUC_{0\rightarrow t,02}$ (n=14)*** 331.6* 321.4* [0.93;1.15] 1.03
$AUC_{0\rightarrow \infty,02}$ (n=13)*** 343.2* 333.8* [0.93;1.14] 1.03
$CMAK_{02}(ng/mL)$*** (n=14) 201.8* 165.9* [1.03;1.44] 1.22

*Geometric, LS Means
**Based on D. Schuirmann’s model
***Based on separate group analyses
Table II
Comparative Mean Plasma Levels of Omeprazole
Fasting Single-Dose Study; Dose = 20 mg; n = 46
ng/ml(CV)

<table>
<thead>
<tr>
<th>Hour</th>
<th>Test</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.75</td>
<td>32.009238</td>
<td>49.50(142)</td>
</tr>
<tr>
<td>1.0</td>
<td>65.22(169)</td>
<td>121.7(110)</td>
</tr>
<tr>
<td>1.33</td>
<td>117.9(115)</td>
<td>161.5(107)</td>
</tr>
<tr>
<td>1.67</td>
<td>139.7(97)</td>
<td>175.8(119)</td>
</tr>
<tr>
<td>2.0</td>
<td>133.2(93)</td>
<td>153.5(124)</td>
</tr>
<tr>
<td>2.33</td>
<td>121.7(112)</td>
<td>127.2(130)</td>
</tr>
<tr>
<td>2.67</td>
<td>112.2(141)</td>
<td>109.6(150)</td>
</tr>
<tr>
<td>3.0</td>
<td>91.99(149)</td>
<td>90.92(162)</td>
</tr>
<tr>
<td>3.5</td>
<td>81.33(158)</td>
<td>72.84(170)</td>
</tr>
<tr>
<td>4.0</td>
<td>61.67(190)</td>
<td>58.64(188)</td>
</tr>
<tr>
<td>5.0</td>
<td>36.18(271)</td>
<td>30.63(310)</td>
</tr>
<tr>
<td>6.0</td>
<td>17.60(411)</td>
<td>17.32(402)</td>
</tr>
<tr>
<td>8.0</td>
<td>6.81(593)</td>
<td>7.98(500)</td>
</tr>
<tr>
<td>10</td>
<td>3.53(678)</td>
<td>3.43(629)</td>
</tr>
<tr>
<td>12</td>
<td>1.91(678)</td>
<td>2.20(618)</td>
</tr>
</tbody>
</table>

$AUC_{0,T}(\text{ng.h/ml})$ 446.5(152) 496.3(161)
$AUC_{0,1}(\text{ng.h/ml})$ 478.1(153) 530.4(163)
$CMAAX_{\text{ng/ml}}$ 246.5(66) 255.0(81)

Adverse Effects:

There was no serious adverse effects reported. There were two mild reactions (both headache) reported by two subjects during test (1) and reference (1) treatments.

III. Dissolution Testing: Presently there is no official USP or FDA dissolution methods and specification for the drug product.
Drug (Generic Name): Omeprazole DR Capsules  
Firm: Kremers Urban  
Dose Strength: 20 mg  
Submission Date: July 2, 1998  
ANDA # 75-410

In Vitro Dissolution Testing

Conditions for Dissolution Testing:
USP XXIII Basket _ Paddle _ X_ RPM 100 rpm Units Tested: 12
Medium:
First 2 hours: in 750 mL of 0.1 N HCl
Next 30 minutes: pH 7.5 Phosphate Buffer, 0.05M Volume: 1000 ___ ml
Reference Drug: (Manuf.) Prilosec DL Capsules (Merck)
Assay Methodology: ___
Firm’s Specification:

<table>
<thead>
<tr>
<th>Time</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 min</td>
<td>NMT -- (acid)</td>
</tr>
<tr>
<td>135 min</td>
<td>NLT --</td>
</tr>
</tbody>
</table>

IV. Comment:

The single-dose, fasting bioequivalence study is acceptable. The test and reference products are equivalent under fasting conditions in the rate and extent of absorption of omeprazole, as measured by log-transformed AUCs and CMAX.

V. Deficiency:

The dissolution testing is not acceptable for the following reasons:

i. The paddle speed of 100 rpm is considered excessive; the speed of _ should be used for this apparatus (paddle). For the basket apparatus (USP apparatus I), the speed of 100 rpm is considered acceptable, however.

ii. The pH of the phosphate buffer should be 6.8 instead of _

Although presently there is no compendial dissolution method and specifications available for the omeprazole DR capsule product, based on information available to
the agency, the following dissolution methodology will probably be recommended to the USP compendial staff for the drug product. You may wish to consider this methodology in the future.

The dissolution testing should be conducted in ——— of 0.1N HCl for 2 hours [Acid stage]; followed by ——— of 0.05M phosphate buffer, pH 6.8 [Buffer stage], at 37°C using USP23 apparatus I (basket) at 100 rpm. The test product should meet the following specification:

NMT ——— of the drug in the capsule is dissolved in 2 hours [Acid stage] and NLT ——— (Q) of the drug in the capsule is dissolved in 45 minutes [Buffer stage].

VI. Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Kremers on the test product, Omeprazole DR Capsules, 20 mg, lot # CJ-0591, comparing it with the reference product, Merck’s Prilosec® DR Capsules, 20 mg, lot # E2621, has been found acceptable by the Division of Bioequivalence. The test product, Kremers’ Omeprazole DR Capsules, 20 mg, is deemed bioequivalent to the reference listed drug product, Merck’s Prilosec® DR Capsules, 20 mg.

2. The in-vitro dissolution testing conducted by Kremers on its Omeprazole DR Capsules, 20 mg, and Merck’s Prilosec DR Capsules, has been found unacceptable due to the Deficiency cited above.

/S/

Hoainhong Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

/S/ 10/20/98
Concur: Dale P. Conner, Pharm.D.  
Division of Bioequivalence

cc: ANDA # 75-410 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File, HFD-650(Director)

Hnguyen/10-19-98/WP #75410sd.798  
Attachments: 7 pages
Inclusion Criteria:

1. Caucasian males between 19 and 40 years of age.

Body weight from 10% below or 10% above, inclusive, the ideal weight for their height and estimated frame, as adapted from the 1983 Metropolitan Life Table. (see Appendix I).

3. Voluntary consent to participate in this study, as demonstrated by signing the informed consent form for this study.

4. Non-tobacco users for a minimum of 30 days prior to study initiation.

Exclusion Criteria:

1. History of clinically significant gastrointestinal tract, renal, hepatic, endocrine, oncologic, pulmonary or cardiovascular disease; or a history of tuberculosis, epilepsy, diabetes, psychosis, glaucoma, or any condition which, in the opinion of the Investigator, would jeopardize the safety of the subject or impact the validity of the study results.

2. History of allergic or adverse response to omeprazole or related drugs.

3. Clinically significant abnormal findings on the screening physical examination, medical history, or clinical laboratory.

4. Positive results from HIV antibody screen.

5. Participation in a previous clinical trial within 30 days prior to study initiation.

6. Blood donation of one pint or more within 30 days prior to study initiation.

7. Plasma donation within 7 days prior to study initiation.

8. Difficulty in swallowing medication or any gastrointestinal disease which would
affect the drug absorption.

9. Substantial changes in eating habits within 30 days prior to study initiation.

10. Unwilling to eat the food as provided in the study menu.

11. Treatment with any known enzyme altering agents (barbiturates, phenothiazines, cimetidine, etc.) within 30 days prior to study initiation.

12. Use of any prescription medication within 14 days prior to study initiation.

13. Use of any over-the-counter (OTC) medication within 72 hours prior to study initiation.

14. Use of alcohol/drugs of abuse or xanthine containing foods/beverages within 48 hours prior to study initiation.
BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-410  APPLICANT: Kremers Urban

DRUG PRODUCT: Omeprazole Delayed-Release Capsules, 20 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

The dissolution testing is not acceptable for the following reasons:

i. The paddle speed of 100 rpm is considered excessive; the speed of _______ should be used for this apparatus (paddle). For the basket apparatus (USP apparatus I), the speed of 100 rpm is considered acceptable, however.

ii. The pH of the phosphate buffer, used in the Buffer Stage, should be 6.8 instead of ___.

Although presently there is no compendial dissolution method and specifications available for the omeprazole DR capsule product, based on information available to the agency, the following dissolution methodology will probably be recommended to the USP compendial staff for the drug product. You may wish to consider this methodology in the future.

The dissolution testing should be conducted in ______ of 0.1N HCl for 2 hours [Acid stage]; followed by ______ of 0.05M phosphate buffer, pH 6.8 [Buffer stage], at ______ using USP23 apparatus I(basket) at 100 rpm. The test product should meet the following specification:

NMT _____ of the drug in the capsule is dissolved in 2 hours [Acid stage] and NLT _____ (Q) of the drug in the capsule is dissolved in 45 minutes [Buffer stage].

The Division of Bioequivalence has completed its review of the fasting bioequivalence study for Kremers’ Omeprazole DR Capsules, 20 mg, and has no further questions concerning this study at this
time. The Division is looking forward toward reviewing the non-fasting study that the firm has recently initiated as the study results become available to the agency.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
1. **FASTING STUDY (STF)**
   - Clinical: 
   - Analytical: 

   **Outcome Decisions:**
   - **AC** - Acceptable
   - **NC** - No Action
   - **UN** - Unacceptable
   - **IC** - Incomplete

   **WinBio Comments**
   
   Dissolution testing unacceptable.
   Food study is needed.

   **Strengths:** 20 mg
   **Outcome:** AC IC

   **Submission Date:** July 2, 1998
   **October 6, 1998**

   **Appears this way on original.**
Figure 1
Mean (S.D.) Plasma Omeprazole Concentrations Versus Time
Linear Scale

Treatment B is shifted to the right for ease of reading


**QUANTITATIVE COMPOSITION**

The following represents the theoretical quantitative composition per microtablet and per capsule of Omeprazole Delayed-Release Capsules, 20 mg:

**PRODUCTION OF MICROTABLETS**

<table>
<thead>
<tr>
<th>Component</th>
<th>PER MICROTABLET</th>
<th>PER CAPSULE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crospovidone NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole USP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose USP</td>
<td></td>
<td></td>
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<tr>
<td>Omeprazole, Unmicronized USP</td>
<td></td>
<td></td>
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<tr>
<td>Glyceryl Behenate NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FOR MICROTABLETS**

<table>
<thead>
<tr>
<th>Component</th>
<th>PER MICROTABLET</th>
<th>PER CAPSULE</th>
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</thead>
<tbody>
<tr>
<td>Methacrylic Acid Copolymer Dispersion NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talc USP</td>
<td></td>
<td></td>
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<tr>
<td>Triethyl Citrate NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Titanium Dioxide USP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silicon Dioxide NF</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
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</tr>
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**TOTAL WEIGHT**

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commercial

information
OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-410
SPONSOR: Kremers Urban
DRUG AND DOSAGE FORM: Omeprazole DR Capsules
STRENGTH(S): 20 mg & 10 mg
TYPES OF STUDIES: Sprinkle Study
CLINICAL STUDY SITE(S): 
ANALYTICAL SITE(S): 

STUDY SUMMARY: Acceptable
DISSOLUTION: Acceptable

DSI INSPECTION STATUS

<table>
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<tr>
<th>Inspection needed:</th>
<th>Inspection status:</th>
<th>Inspection results:</th>
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<tbody>
<tr>
<td>NO</td>
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<td></td>
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<tr>
<td>First Generic</td>
<td>Inspection requested: (date)</td>
<td></td>
</tr>
<tr>
<td>New facility</td>
<td>Inspection completed: (date)</td>
<td></td>
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<tr>
<td>For cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PRIMARY REVIEWER: Hoainho Nguyen  BRANCH: I
INITIAL: __________ DATE: 5/16/02

TEAM LEADER: Yih-Chain Huang  BRANCH: I
INITIAL: __________ DATE: 5/20/02

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.
INITIAL: __________ DATE: 6/13/02

* PAGE * 13 *
Review of A Bioequivalence Study (Sprinkle Study)

I. Introduction

The firm has submitted a bioequivalence study to demonstrate bioequivalence of the test product to the RLD product when sprinkled on applesauce, as requested by the OGD in the correspondence dated November 8, 2001, which approved the labeling for administration of the product sprinkled on applesauce. The firm had originally submitted a single-dose fasting bioequivalence study and a single-dose non-fasting bioequivalence study for the 20 mg strength on July 2, 1998 and December 29, 1998, respectively, and the studies were found acceptable. The firm had also submitted acceptable in vitro dissolution testing and acid resistance testing for the 10 mg and 20 mg strengths of the test product. The biowaiver request for the 10 mg strength submitted on May 2, 2000 was granted.

Note: The Telephone Amendment dated 04/12/02 provided the additional data diskette in correct ASCII format and the batch size of the bioilot of the test product, as requested.


III. Protocol No.: SP689 A Pharmacokinetic Study to Assess the Effect of Applesauce on the Single Dose Bioavailability of a 20 mg Formulation of SPUS 830 and a Reference Product

1) Study Information

STUDY FACILITY INFORMATION
Clinical Facility: 
Medical Director: 
Clinical Study Dates: 01/19/02 to 02/10/02
Analytical Facility: 
Principal Investigator: 
Analytical Study Dates: 02/11/02 to 02/15/02
Maximum Sample: 27 days
Storage Period: 

### TREATMENT INFORMATION

<table>
<thead>
<tr>
<th>Treatment ID:</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test or Reference:</td>
<td>T</td>
<td>R</td>
</tr>
<tr>
<td>Product Name:</td>
<td>Omeprazole DR Capsules</td>
<td>Prilosec DR Capsule</td>
</tr>
<tr>
<td>Manufacturer:</td>
<td>Kremers Urban</td>
<td>Astra Merck</td>
</tr>
<tr>
<td>Manufacture Date:</td>
<td>12/2001</td>
<td>N/A</td>
</tr>
<tr>
<td>Expiration Date:</td>
<td>12/2003</td>
<td>3/2003</td>
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<tr>
<td>ANDA Batch Size:</td>
<td></td>
<td>L2537</td>
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<tr>
<td>Batch/Lot Number:</td>
<td>215930</td>
<td></td>
</tr>
<tr>
<td>Potency:</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Strength:</td>
<td>DR Capsules</td>
<td>DR Capsules</td>
</tr>
<tr>
<td>Dosage Form:</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Dose Administered:</td>
<td>The contents of 1 capsule sprinkled on a tablespoon of applesauce, swallowed without chewing, with 240 mL of water Fasting</td>
<td>The contents of 1 capsule sprinkled on a tablespoon of applesauce, swallowed without chewing, with 240 mL of water Fasting</td>
</tr>
<tr>
<td>Dosing Conditions:</td>
<td>10 hours pre-dose to 4 hours post-dose</td>
<td>10 hours pre-dose to 4 hours post-dose</td>
</tr>
<tr>
<td>Study Condition:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of Fasting:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### RANDOMIZATION

| Randomized: | Y |
| No. of Sequences: | 2 (ABAB and BABA) |
| No. of Periods: | 4 |
| No. of Treatments: | 2 |

### DESIGN

- Replicated Treatment Design: Y
- Balanced: N
- Washout Period: 7 days
- Design Type: crossover

### DOSING

- Single or Multiple Dose: Single
- Steady State: N
- Volume of Liquid Intake: 240 mL
- Route of Administration: Oral

### SUBJECTS

- IRB Approval: Y
- Informed Consent Obtained: Y
- No. of Subjects Enrolled: 24
- No. of Subjects Completing: 21
- No. of Subjects Plasma Analyzed: 24 (Only 21 were included in statistical analysis)

### No. of Dropouts:

| No. of Dropouts: | 3 |

2
Sex(es) Included: Male & Female

Healthy Volunteers Only: Y

SUBJECTS (Continued):
Mean age: 26 yrs (19-38)
Mean height: 68.6 in (63-74)
Mean weight: 154 lb (111-196)
Race: Asian (2), Caucasian (19), Hispanic (2), Others (1)
Gender: Male (10), Female (14)


Dietary Restrictions: Subjects were instructed to abstain from food or beverages containing xanthine (e.g. coffee, tea, caffeine-containing sodas, colas and chocolate, etc.), citrus products and alcohol starting 48 hours prior to dosing and throughout the study period.

Activity Restrictions: No vigorous physical activity was allowed during confinement.

Drug Restrictions: No concomitant drug therapy was allowed during the study. No prescription medication and no OTC medications was allowed for 14 days and 7 days, respectively, prior to the study and throughout the study.

Confinement: At least 12 hours pre-dose to 12 hours post-dose

Blood Sampling: Pre-dose, 0.50, 0.75, 1, 1.25, 1.50, 2, 2.50, 3, 3.50, 4, 4.50, 5, 6, 7, 8, 10 and 12 hours post-dose

2) Study Results

Clinical Adverse Events: There was no serious adverse event reported. Four and four drug-related adverse reactions were reported during the Test and Referent treatments, respectively. The reactions were headache, lightheadedness, nausea, dizziness and skin clamminess.

Protocol Deviations: None was judged likely to affect the bioavailability comparison by the study investigator.

Dropouts: Subject #16 dropped out due to personal reasons. Subject #18 was withdrawn due to an adverse event. Subject #23 was withdrawn due to noncompliance reasons.
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information
4) Pharmacokinetic Method:

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>CALCULATION METHOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t</td>
<td>Trapezoidal</td>
</tr>
<tr>
<td>AUC0-inf</td>
<td>AUC0-t + Observed CT/Kel</td>
</tr>
<tr>
<td>Cmax</td>
<td>Observed Data</td>
</tr>
<tr>
<td>Tmax</td>
<td>Observed Data</td>
</tr>
<tr>
<td>Residual Area</td>
<td>(1-(AUC0-t/AUC0-inf)) x 100</td>
</tr>
<tr>
<td>Kel</td>
<td>Ln-linear regression of the terminal elimination phase</td>
</tr>
<tr>
<td>Thalf</td>
<td>(ln2)/Kel</td>
</tr>
</tbody>
</table>

**Verification of Firm's Calculations and Analyses:**

(i) **With Reassayed Values:** Firm's AUC(0-T), AUC(0-Infinity), and CMAX values were verified by the reviewer for all subjects. For Subjects # 2(Treatment A, Period 2), 6(B,4), 7(A,1), 11(A,4), 12(A,3), 13(B,3), 14(B,4), 20(A,1), 21(B,2) and 21(B,4), the ratios for firm-calculated AUC(0-T)'s and/or AUC(0-Infinity)'s to reviewer-calculated AUCT's and/or AUC(0-Infinity) were either greater than 1.05 or less than 0.95. For all other subjects, these ratios were 1.0. The CMAX values determined by the reviewer were verified to be the same as the firm's.

(ii) **With Original Assay Values:** Only Subjects 6(Treatment B, Period 2), 8(A,2) and 8(B,1) had some original assay values that were different from their PK reassayed values. Firm's AUC(0-T), AUC(0-Infinity), and CMAX values were verified by the reviewer for these subjects (after replacing the PK reassayed values with the original assay values). The ratios for firm-calculated AUC(0-T)'s and/or AUC(0-Infinity)'s to reviewer-calculated AUCT's and/or AUC(0-Infinity) for these subjects were 1.0. There was no change in CMAX values for these subjects.

(iii) **Verification of Firm's Statistical Analysis:** Dr. Rabi Patnaik reanalyzed the data with the original assay values and the data with repeat assay values. The reanalysis results are shown in italics in the table below. Dr. Patnaik used all 24 subjects in the reanalysis whereas the firm omitted the data from Subjects #16, 18 and 23 who did not complete all 4 periods of the study.
Results:

**TABLE I**

FASTING IN VIVO BIOEQUIVALENCE STUDY #SP689
LEAST-SQUARES MEANS AND 90% GEOMETRIC CONFIDENCE INTERVALS
FOR OMEPRAZOLE PHARMACOKINETIC PARAMETERS
Dose=20 mg; N=21

<table>
<thead>
<tr>
<th>PK PARAMETER</th>
<th>TEST TREATMENT A</th>
<th>REFERENCE TREATMENT B</th>
<th>RATIO (A/B)</th>
<th>90% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(T) [ng.hr/mL] (Geometric mean)</td>
<td>372.5</td>
<td>403.4</td>
<td>0.92</td>
<td>0.88-0.97</td>
</tr>
<tr>
<td></td>
<td>400.5*</td>
<td>433.0*</td>
<td>0.92*</td>
<td>0.88-0.97</td>
</tr>
<tr>
<td></td>
<td>400.3**</td>
<td>433.5**</td>
<td>0.92**</td>
<td>0.88-0.97**</td>
</tr>
<tr>
<td>AUC(I) [ng.hr/mL] (Geometric mean)</td>
<td>387.7</td>
<td>427.0</td>
<td>0.91</td>
<td>0.86-0.96</td>
</tr>
<tr>
<td></td>
<td>416.4*</td>
<td>450.6*</td>
<td>0.92*</td>
<td>0.88-0.97*</td>
</tr>
<tr>
<td></td>
<td>416.0**</td>
<td>450.6**</td>
<td>0.92**</td>
<td>0.88-0.97**</td>
</tr>
<tr>
<td>Cmax [ng/mL] (Geometric mean)</td>
<td>217.8</td>
<td>201.3</td>
<td>1.08</td>
<td>0.98-1.19</td>
</tr>
<tr>
<td></td>
<td>232.9*</td>
<td>213.4*</td>
<td>1.09*</td>
<td>0.99-1.20*</td>
</tr>
<tr>
<td></td>
<td>234.0**</td>
<td>213.3**</td>
<td>1.10**</td>
<td>0.99-1.21**</td>
</tr>
</tbody>
</table>

*Reanalysis by Dr. Patnaik based on original assay values and using data from 24 subjects
**Reanalysis by Dr. Patnaik based on repeat assay values and using data from 24 subjects

APPEARS THIS WAY ON ORIGINAL
TABLE II

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #SP689
OMEPRAZOLE ARITHMETIC MEAN PLASMA CONCENTRATIONS (ng/mL) VERSUS TIME (CV %)
IN 21 SUBJECTS

<table>
<thead>
<tr>
<th>TIME (HR)</th>
<th>TEST (First Replicate)</th>
<th>TEST (Second Replicate)</th>
<th>REFERENCE (First Replicate)</th>
<th>REFERENCE (Second Replicate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-dose</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.50</td>
<td>8.73(258)</td>
<td>1.67(368)</td>
<td>26.13(107)</td>
<td>42.71(147)</td>
</tr>
<tr>
<td>0.75</td>
<td>36.73(162)</td>
<td>24.20(224)</td>
<td>71.08(84)</td>
<td>74.04(126)</td>
</tr>
<tr>
<td>1.00</td>
<td>85.43(139)</td>
<td>57.93(175)</td>
<td>119.8(106)</td>
<td>118.2(119)</td>
</tr>
<tr>
<td>1.25</td>
<td>128.6(155)</td>
<td>86.61(160)</td>
<td>142.5(126)</td>
<td>149.7(106)</td>
</tr>
<tr>
<td>1.50</td>
<td>154.6(40)</td>
<td>118.6(143)</td>
<td>151.4(115)</td>
<td>163.0(92)</td>
</tr>
<tr>
<td>2.00</td>
<td>133.8(110)</td>
<td>148.1(115)</td>
<td>145.7(99)</td>
<td>155.0(85)</td>
</tr>
<tr>
<td>2.50</td>
<td>102.1(107)</td>
<td>151.4(87)</td>
<td>115.4(77)</td>
<td>129.3(79)</td>
</tr>
<tr>
<td>3.00</td>
<td>90.07(91)</td>
<td>122.1(84)</td>
<td>88.85(69)</td>
<td>110.0(86)</td>
</tr>
<tr>
<td>3.50</td>
<td>83.35(89)</td>
<td>92.75(81)</td>
<td>70.13(69)</td>
<td>75.41(88)</td>
</tr>
<tr>
<td>4.00</td>
<td>62.91(91)</td>
<td>58.30(90)</td>
<td>51.78(89)</td>
<td>50.13(90)</td>
</tr>
<tr>
<td>4.50</td>
<td>73.18(165)</td>
<td>41.35(85)</td>
<td>33.03(92)</td>
<td>36.25(90)</td>
</tr>
<tr>
<td>5.00</td>
<td>49.22(147)</td>
<td>46.11(159)</td>
<td>51.50(194)</td>
<td>48.69(191)</td>
</tr>
<tr>
<td>6.00</td>
<td>23.63(148)</td>
<td>23.32(165)</td>
<td>29.90(186)</td>
<td>23.00(198)</td>
</tr>
<tr>
<td>7.00</td>
<td>9.76(186)</td>
<td>9.94(158)</td>
<td>10.59(195)</td>
<td>11.72(231)</td>
</tr>
<tr>
<td>8.00</td>
<td>4.05(214)</td>
<td>3.57(196)</td>
<td>5.67(232)</td>
<td>4.71(271)</td>
</tr>
<tr>
<td>10.00</td>
<td>0.97(310.1)</td>
<td>0.60(323)</td>
<td>1.12(330)</td>
<td>0.37(458)</td>
</tr>
<tr>
<td>12.00</td>
<td>0.80(458)</td>
<td>0</td>
<td>1.32(458)</td>
<td>0.44(458)</td>
</tr>
<tr>
<td>AUCT</td>
<td>470.0(66)</td>
<td>464.2(69)</td>
<td>487.9(65)</td>
<td>514.6(66)</td>
</tr>
<tr>
<td>AUCI</td>
<td>494.6(67)</td>
<td>489.8(66)</td>
<td>504.5(65)</td>
<td>585.3(60)</td>
</tr>
<tr>
<td>CMAX</td>
<td>275.6(67)</td>
<td>264.9(63)</td>
<td>245.4(69)</td>
<td>248.6(62)</td>
</tr>
<tr>
<td>TMAX</td>
<td>2.55(52)</td>
<td>2.50(50)</td>
<td>2.53(61)</td>
<td>2.26(56)</td>
</tr>
<tr>
<td>T½h</td>
<td>0.855(44)</td>
<td>0.885(44)</td>
<td>0.803(32)</td>
<td>0.778(22)</td>
</tr>
<tr>
<td>KEL</td>
<td>0.926(35)</td>
<td>0.902(34)</td>
<td>0.957(34)</td>
<td>0.932(21)</td>
</tr>
</tbody>
</table>
5) Statistical Analysis: The statistical analysis used the approach of average bioequivalence in the replicate design study. A mixed linear model (ANOVA) was applied to the log-transformed AUC(0-T), AUC(0-Infinity) and CMAX, using SAS Proc Mixed. Twenty-one of 24 enrolled subjects completed the study. Subjects #16 and 23 completed one period of the study. Subject #18 completed 3 periods of the study. The firm used a total of 21 data sets of data in the statistical analysis for this study (excluding Subjects 16, 18 and 23). Dr. Rabi Patnaik reanalyzed the data with original assay values and the data with repeat assay values (see Repeat Samples under Analytical Methodology), using all subjects including Subjects #16, 18 and 23.

Conclusion: Both firm's analysis and Dr. Patnaik's reanalysis showed that the 90% C.I.'s for lnAUC(0-T), lnAUC(0-Infinity) and lnCMAX were within the acceptable limit of [0.80; 1.25]. The study is acceptable.

V. Waiver of In Vivo Sprinkle Bioequivalence Study for the 10 mg Strength: Since it has been shown previously (in the ANDA submission dated May 2, 2000) that the 10 mg strength of
the test product is compositionally proportional to the 20 mg strength of the test product, and the
dissolution data for both strengths are comparable, the in vivo sprinkle bioequivalence study is
waived for the 10 mg strength.

VI. Recommendations:

1. The single-dose, fasting sprinkle bioequivalence study conducted by Kremers Urban on the
test product, Omeprazole DR Capsules, 20 mg, Lot # 2159302, comparing it with the reference
product, Astra Zeneca’s Prisolec DR Capsules, 20 mg, Lot # L2537, has been found acceptable
by the Division of Bioequivalence. The study demonstrates that the test product, Kremers
Urban’s Omeprazole DR Capsules, 20 mg, is bioequivalent to the reference product, Astra
Zeneca’s Prilosec DR Capsules, 20 mg, when sprinkled in applesauce under fasting conditions.

2. The waiver of in vivo sprinkle bioequivalence study requirements for the 10 mg capsules is
granted. The firm’s Omeprazole DR Capsule, 10 mg, is deemed bioequivalent to AstraMerck’s
Prilosec 10 mg DR capsule, when sprinkled in applesauce under fasting conditions.

Hoamn Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG FT INITIALED YHUANG__ 1

Concur:

Dale P. Conner, Pharm
Director, Division of Bioequivalence

cc: ANDA # 75-410 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNgyuen/04-12-02/W #75410n0302.doc
Also as V:\frmsam\kremers-ul\下半年\rev\75410n0302.doc
Attachment: None
BIOEQUIVALENCY COMMENTS

ANDA: 75-410        APPLICANT: Kremers Urban Development Company

DRUG PRODUCT: Omeprazole DR Capsules, 10 mg & 20 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

In future applications, please include the address of the laboratories conducting the dissolution testing in the bioequivalence section of the ANDA.

The Division of Bioequivalence acknowledges that the following, FDA-recommended dissolution and acid-resistance testing are being incorporated into your stability and quality control programs:

(i) The dissolution testing should be conducted in _____ of 0.1N HCl for 2 hours [Acid stage]; followed by _____ of 0.05M phosphate buffer, pH 6.8 [Buffer stage], at 37°C using USP apparatus I (basket) at 100 rpm. The test product should meet the following specification:

NLT _____ (Q) of the drug in the capsule is dissolved in 45 minutes [at the end of the Buffer stage].

(ii) The separate acid resistance testing should be conducted in _____ of 0.1N HCl for 2 hours [Acid stage], and the omeprazole content of the granules should also be analyzed at the end of the Acid stage. The test product should meet the following specification:

NMT _____ of the drug in the capsule is dissolved in 120 minutes, as determined by the difference between the average potency assay (without acid exposure) and the potency assay of the remaining granules at the end of the Acid stage.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may
result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

\[\text{\[\text{Signature}\]}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
BIOEQUIVALENCY - ACCEPTABLE

1. FASTING STUDY (STF) (Sprinkle Study)  
   Clinical:  
   Analytical:  

2. STUDY AMENDMENT (SPA) (New Data diskette/Batch size)  
   NC

OUTCOME DECISIONS:  IC - Incomplete  
AC - Acceptable  
UN - Unacceptable (fatal flaw)

WINBIO COMMENTS:

Submission date: 03-29-02  
04-12-02

Strength: 20 MG  
Outcome: AC  

Strength: 20 MG  
Outcome: AC  

V:\FIRMSAM\kremers-ultrs&rev\75410n0302.doc  
Printed in final on / /
OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-410
SPONSOR: Kremers Urban
DRUG AND DOSAGE FORM: Omeprazole DR Capsules
STRENGTH(S): 20 mg & 10 mg
TYPES OF STUDIES: Sprinkle Study
CLINICAL STUDY SITE(S): ______________________________________
ANALYTICAL SITE(S): ______________________________________

STUDY SUMMARY: Acceptable
DISSOLUTION: Acceptable

<table>
<thead>
<tr>
<th>DSI INSPECTION STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspection needed: NO</td>
</tr>
<tr>
<td>First Generic _____</td>
</tr>
<tr>
<td>New facility _____</td>
</tr>
<tr>
<td>For cause _____</td>
</tr>
<tr>
<td>Other _____</td>
</tr>
</tbody>
</table>

PRIMARY REVIEWER: Hoainhon Nguyen
INITIAL: ___________ DATE: 5/16/02

TEAM LEADER: Yih-Chain Huang
INITIAL: ___________ DATE: 5/20/02

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.
INITIAL: ___________ DATE: 6/3/02
DIVISION APROVAL SUMMARY

ANDA: 75-410  
**DRUG PRODUCT:** Omeprazole Delayed-release Capsules, 10 mg and 20 mg

**FIRM:** Kremers Urban Development Company

**DOSAGE:** Capsules

**STRENGTH:** 10 mg, and 20 mg

**CGMP STATEMENT/EIR UPDATE STATUS:**
CGMP: Certification provided on page  
EIR: Satisfactory EER is pending. Alert is observed.

**BIO STUDIES/BIOEQUIVALENCE STATUS:**
Bio decision is granted on 7/14/00, for the 20 mg, the study was acceptable. Waiver granted for 10 mg.

**METHODS VALIDATION:**
Results are pending from Atlanta labs.

**STABILITY (conditions, containers and methods):**
Bio batch was setup on stability in the proposed container/closure systems and data reported. The following are the firm's stability tests and specifications.

<table>
<thead>
<tr>
<th>Test</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay (LC-label claim)</td>
<td>of label claim</td>
</tr>
<tr>
<td>Dissolution</td>
<td>0.1 N HCl :NMT — dissolved in 2 hours (acid stage)</td>
</tr>
<tr>
<td></td>
<td>0.05 M phosphate buffer: NLT — dissolved in 45 minutes (buffer stage)</td>
</tr>
<tr>
<td>Total Impurities</td>
<td>Individual known impurity: NMT —; Other unknown peaks: NMT —</td>
</tr>
<tr>
<td></td>
<td>Total: NMT — (including</td>
</tr>
<tr>
<td>Physical appearance</td>
<td>20 mg: No 1 Opaque capsules with — and gold body imprinted with 'KU 118' in black and filled with microtablets</td>
</tr>
<tr>
<td></td>
<td>10 mg: No 1 Opaque capsules with —</td>
</tr>
</tbody>
</table>
**Stability Specs**

| imprinted with 'KU 114' in black and filled with microtablets |

**LABELING REVIEW STATUS:**
Acceptable. See review dated 11/30/00.

**STERILIZATION VALIDATION (If Applicable):**
NA.

**BATCH SIZES:**
Bio batch (identity #, drug substance source):
UQUIFA, Micronized lot 909/97/1121 and unmicronized lot 910/97/1120.
Batch size: ______ capsules for 10 and 20 mg each

**STABILITY BATCH (different from bio batch, manu. Site, process):**
Stability batch is the same as bio batch.

**PROPOSED PRODUCTION BATCH:**
________ Capsules of 20 mg and ________ capsules of 10 mg are proposed.

**COMMENTS:**
Approval recommended pending satisfactory EES.

**CHEMISTRY REVIEWER:** Radhika Rajagopalan, Ph.D.
**DATE:** 2/6/01

F/T by pah/3/8/01
v:\firmsam\kramer-u\ltres\rev\75410r4f.doc
TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-410 Dates of Submission: November 30, 2000
Applicant's Name: Kremers Urban Development Company
Established Name: Omeprazole Delayed-release Capsules, 10 mg and 20 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? YES
- Container Labels: (30's & 100's) Satisfactory in FPL submitted on 11/30/00.
- Professional Package Insert Labeling: Satisfactory in FPL submitted on 11/30/00.
- Revisions needed post-approval: None

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Prilosec
- NDA Number: 19-810
- NDA Drug Name: Prilosec
- NDA Firm: AstraZeneca
- Date of Approval of NDA Insert and supplement #: February 23, 2000; S-062
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side by Side
- Basis of Approval for the Carton Labeling: Not Applicable

FOR THE RECORD:

1. Review based on the labeling of the listed drug ANDA 19-810/S-062 (Prilosec; Astra Merck; approved 2/23/00).
2. Patent/ Exclusivities:

PATENTS:
- 4255431 - Expires April 5, 2001, U-108 - Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic gerd, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis.
- 4636499 - Expires May 30, 2005
- 4786505 - Expires April 20, 2007, U-108 - Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic gerd, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis.
- 4853230 - Expires April 20, 2007, U-108 - Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic GERD, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis.

EXCLUSIVITIES:

The firm filed a paragraph IV certification against patent 4,853,230, 4,786,505, & 4,636,499 and a paragraph III against 4,255,431. The firm has not filed paragraph certification against # 5,093,342, 5,599,794, & 5,629,305 and made a statement that the indication covered by these
patents is not claimed in their application. Accordingly, the firm carved out information pertaining to this indication from the package insert labeling.

In the Firm's amendment dated June 3, 1999, they state in their Exclusivity Statement that their product will not infringe on the marketing exclusivity of I-229 since the use indication protected under I-229 is not claimed for their product.

4. Storage/Dispensing Conditions:
   - NDA: Store between 15°C and 30°C (59°F and 86°F). Protect from light and moisture.
   - AND: Store between 15°C and 30°C (59°F and 86°F). Protect from light and moisture.
   - USP: Not USP not NF.

5. Product Line: The innovator markets their product in three strengths (10 mg, 20 mg and 40 mg). They are supplied as follows:
   - 10 mg - unit of use bottles of 30, bottles of 100 and unit-dose 100s.
   - 20 mg - unit of use 30s, unit dose 100s and 1000s.
   - 40 mg - unit of use 30s, bottles of 100s, unit dose 100s and 1000s.

The applicant proposes to market their product (10 mg and 20 mg) in 30's & 100's bottle.

6. The capsules have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

7. Inactive Ingredients: The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition except for the

8. All manufacturing will be performed by Schwarz Pharma Manufacturing, Inc., Seymour, Indiana.

9. Container/Closure: Both strengths will be packaged in — bottles. The 30s will have CRC & the 100s will have Non-CRC.

10. Kremer's Omeprazole is formulated with enteric coated "microtablets" within a capsule. The RLD has enteric coated granules. Kremer submitted a Bioequivalence Study dated July 2, 1998, to support the labeled Tmax of 0.5 to 3.5 hours. The following was taken from the Bio Review of the 7/29/98 submission.

    The purpose of this study is to evaluate the bioequivalency of Kremer's Omeprazole DR Capsules, 20 mg, and Merck's Prilosec® 20 mg DR Capsules under fasting conditions.

| Table I |

<table>
<thead>
<tr>
<th>Omeprazole Comparative Pharmacokinetic Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Single-Dose Study: Dose = 20 mg; n = 46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Kremer's</th>
<th>Prilosec®</th>
<th>90% Ratio</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-T (ng/mL)</td>
<td>Mean (CV)</td>
<td>311.5*</td>
<td>335.3*</td>
<td>(0.88:0.98)</td>
</tr>
<tr>
<td>AUC0-inf (ng/mL)</td>
<td>Mean (CV)</td>
<td>332.2*</td>
<td>355.0*</td>
<td>(0.89:0.98)</td>
</tr>
<tr>
<td>CMAX (ng/mL)</td>
<td>Mean (CV)</td>
<td>200.0*</td>
<td>191.4*</td>
<td>(0.94:1.16)</td>
</tr>
<tr>
<td>Tmax (hrs)</td>
<td>Mean (CV)</td>
<td>2.196(52)</td>
<td>2.014(64)</td>
<td></td>
</tr>
</tbody>
</table>

The single-dose, fasting bioequivalence study conducted by Kremer on the test product, Omeprazole DR Capsules, 20 mg, lot # CJ-0591, comparing it with the reference product, Merck's Prilosec® DR Capsules, 20 mg, lot # E2621, has been found acceptable by the Division of Bioequivalence. The test product, Kremer's Omeprazole DR Capsules, 20 mg, is deemed bioequivalent to the reference listed drug product, Merck's Prilosec® DR Capsules, 20 mg.

Date of Review: January 30, 2001

Reviewer: Koung Lee

Team Leader: Charlie Hoppe

cc: ANDA 75-410
    DUP/DIVISION FILE
    HFD-613/KLee/CHoppe (to cc)
    V:FRMSAMKREMERULTRAS&REV75410TA:LABELING
    Review

Date of Submissions: November 30, 2000

Date: 11/07/01

Date: 2/7/01
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-410
Dates of Submission: June 3, 1999
July 1, 1999
July 21, 1999
Applicant's Name: Kremers Urban Development Company
Established Name: Omeprazole Delayed-release Capsules, 10 mg and 20 mg

Labeling Deficiencies:

1. GENERAL

   Add *(see USP)* after the storage temperature statement.

2. CONTAINER (30's and 100's)
   a. See GENERAL comment.
   b. We encourage you to differentiate the two different strengths from each other by using contrasting colors and/or boxing, or any other means.
   c. For the bottles of 100's for the 10 mg strength, revise the "USUAL DOSAGE" statement to read as "The Omeprazole Delayed-Release Capsule should be swallowed whole, and not opened..."

3. INSERT
   a. DESCRIPTION
      Include pharmaceutical glaze, ethylene glycol monoethyl ether, lecithin, and simethicone.
   b. ADVERSE REACTIONS
      i. Body As a Whole
         Revise to read "Allergic reactions, including, rarely, anaphylaxis (see also Skin below), fever, pain, fatigue, malaise, abdominal swelling."
      ii. Skin
         Add "purpura and/or petechiae (some with rechallenge);" between "multiforme (some severe);" and "skin inflammation".
   c. HOW SUPPLIED
      See GENERAL comment.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.
Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(5)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL
APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? Yes No
- Container Labels:
- Professional Package Insert Labeling:
- Revisions needed post-approval:

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form:
  - NDA Number:
  - NDA Drug Name:
  - NDA Firm:
  - Date of Approval of NDA insert and supplement #:
  - Has this been verified by the MIS system for the NDA? Yes No
  - Was this approval based upon an OGD labeling guidance?
  - Basis for Approval for the Container Labels: Container labels in file folder.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

<table>
<thead>
<tr>
<th>Element/Issue</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different name than on acceptance to file list?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Is the products USP than for an USP supplement in which verification was assured. USP 39</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Is this name different than that used in the College Brochure?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Yest USP, had the product name been proposed in the PFR?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Error Prevention Analysis</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Has the manufacturer's proprietary name? Yes, complete this subsection.</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Do you think the name appropriate? List reasons in PFR. For example, consider mon姓名s, sounds, or lacks the current name? USP name present? Prefix or suffix present?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Has the name been forward to the Licensing and Reimbursement Committee? Or, what were the recommendations? If the name was unacceptable, how were the objections handled?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Packaging</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in PFR.</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Is the package size intermediate with the recommended dosage? Yes, the Poison Prevention Act may require a CRC.</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Does the package proposed have any safety and/or regulatory concerns?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>If product packaged in vials, could there be adverse patient outcome if given by direct intravenous?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Certify whether or not ADVERSE REACTIONS and INDICATIONS sections and the packaging configuration?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Is the strength and/or concentration of the product unsuitable for the insert labeling?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Is the cost of the medicine (i.e., the order of the same generic component) or cap accessible?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Individual reference required? Issues for PFR. Innovator individually patented? Light sensitive product which might require cautioning? Must the package insert accompany the product?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Are there any other safety concerns?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Labeling</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>In the name of the drug use in print or taking in parenthesis? (Name should be the most prominent information on the label).</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Has package label to clearly differentiate multiple product strengths?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>In the corporate logo larger than 15 number label? (For examination, see MFH guidelines)</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Labeling (continued)</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Does the RLD have specific differentiation for the label? For example, Pediatric strength vs Adult. Oral solution vs Capsule. Warning statements that might be inappropriate for the NDA</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>In the Manufacturer or Distributor statement incorrect or fairly inconsistent between label and labeling? Is it clearly understandable?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Failure to describe side and drug from non-prescribing warnings in the HOW SUPPLIED?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Has this label sufficiently support a compatibility or stability claim which appear in the insert labeling? Note: Graph should confirm the data has been adequately supported.</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Scanning. Describe scanning configuration of RLD and application in PFR.</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Is the scanning configuration different than the RLD?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Has the label for the scanning in the how supplied section?</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Inactive ingredients? (PFR, list page on application when inactive are listed)</td>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>
QUESTION FOR THE CHEMIST

Please confirm that “silicon spray” is used as a lubricant and therefore should not be included in the inactive ingredient section.

FOR THE RECORD:


2. Patent/ Exclusivities:

PATENTS:

- 4255431 - Expires April 5, 2001, U-108 - Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic GERD, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis.

- 4636499 - Expires May 30, 2005

- 4786505 - Expires April 20, 2007, U-108 - Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic GERD, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis.

- 4853230 - Expires April 20, 2007, U-108 - Short-term treatment of active duodenal ulcer, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive symptomatic GERD, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis.


EXCLUSIVITIES:


The firm has filed a paragraph IV certification against patent numbers 4,853,230, 4,786,505, & 4,636,499 and a paragraph III against 4,255,431. The firm has not filed paragraph certification against # 5,093,342, 5,599,794, & 5,629,305 and made a statement that the indication covered by these patents is not claimed in their application. Accordingly, the firm carved out information pertaining to this indication from the package insert labeling. According to Peter Rickman, previously the Team Leader of the Regulatory Branch, this statement is sufficient for not requiring the filing of a paragraph certification.

In the Firm’s amendment dated June 3, 1999, they state in their Exclusivity Statement that their product will not infringe on the marketing exclusivity of I-229 since the use indication protected under I-229 is not claimed for their product.

4. Storage/Dispensing Conditions:
   - NDA: Store between 15°C and 30°C (59°F and 86°F). Protect from light and moisture.
   - AND: Store between 15°C and 30°C (59°F and 86°F). Protect from light and moisture.
   - USP: Not USP not NF.

5. Product Line:

The innovator markets their product in three strengths (10 mg, 20 mg and 40 mg). They are supplied as follows:

- 10 mg - unit of use bottles of 30, bottles of 100 and unit-dose 100s.
- 20 mg - unit of use 30s, unit dose 100s and 1000s.
- 40 mg - unit of use 30s, bottles of 100s, unit dose 100s and 1000s.

The applicant proposes to market their product (10 mg and 20 mg) in 30’s & 100’s bottle.

6. The capsules have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206 et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

7. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition except for the

8. All manufacturing will be performed by Schwarz Pharma Manufacturing, Inc., Seymour, Indiana.

9. Container/Closure:

Both strengths will be packaged in: bottles. The 30s will have CRC & the 100s will have Non-CRC.

<table>
<thead>
<tr>
<th>Date of Review:</th>
<th>November 18, 1998</th>
<th>Date of Submissions:</th>
<th>June 3, 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>July 1, 1999</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>July 21, 1999</td>
<td></td>
</tr>
</tbody>
</table>

Reviewer: Koung Lee

Team Leader: Charlie Hopper

cc: ANDA 75-410
DUP/DIVISION FILE
HFD-613/KLee/Choppes (no cc)
V:\FIRMSAM\KREMERULTR&S\REV75410NA2\LABELING

Review
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-410
Applicant's Name: Kremers Urban Development Company
Established Name: Omeprazole Delayed-release Capsules, 10 mg and 20 mg

Dates of Submission: February 8, 2000

Labeling Deficiencies:

INSERT

a. **PRECAUTIONS**

Add the following as the last subsection.

*Geriatric Use*

Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the US and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers. However, no dosage adjustment is necessary in the elderly. (See CLINICAL PHARMACOLOGY.)

b. **ADVERSE REACTIONS**

*Skin*

Revise to read as, "Rash and, rarely, cases of..."

c. **DOSAGE AND ADMINISTRATION**

*Pathological Hypersecretory Conditions*

Revise the second paragraph to read as, "...

Please revise your insert labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies of container labels and insert labeling for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rlid/labeling_review_branch.html
To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL
FOR THE RECORD:

1. Review based on the labeling of the listed drug ANDA 19-810/S-062 (Prilosec; Astra Merck; approved 2/23/00).

2. Patent/ Exclusivities:

PATENTS:

- 4255431 - Expires April 5, 2001, U-108 - Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic gerd, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis.
- 4636499 - Expires May 30, 2005
- 4786505 - Expires April 20, 2007, U-108 - Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic gerd, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis.
- 4853320 - Expires April 20, 2007, U-108 - Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic GERD, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis.

EXCLUSIVITIES:


The firm filed a paragraph IV certification against patent 4,853,230, 4,786,505, & 4,636,499 and a paragraph III against 4,255,431. The firm has not filed paragraph certification against # 5,093,342, 5,599,794, & 5,629,305 and made a statement that the indication covered by these patents is not claimed in their application. Accordingly, the firm carved out information pertaining to this indication from the package insert labeling.

In the Firm’s amendment dated June 3, 1999, they state in their Exclusivity Statement that their product will not infringe on the marketing exclusivity of I-229 since the use indication protected under I-229 is not claimed for their product.

4. Storage/Dispensing Conditions:

- NDA: Store between 15°C and 30°C (59°F and 86°F). Protect from light and moisture.
- AND: Store between 15°C and 30°C (59°F and 86°F). Protect from light and moisture.
- USP: Not USP not NF.

5. Product Line:

The innovator markets their product in three strengths (10 mg, 20 mg and 40 mg). They are supplied as follows:

- 10 mg - unit of use bottles of 30, bottles of 100 and unit-dose 100s.
- 20 mg - unit of use 30s, unit dose 100s and 1000s.
- 40 mg - unit of use 30s, bottles of 100s, unit dose 100s and 1000s.

The applicant proposes to market their product (10 mg and 20 mg) in 30’s & 100’s bottle.

6. The capsules have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).
7. Inactive Ingredients: The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition except for [---]

8. All manufacturing will be performed by Schwarz Pharma Manufacturing, Inc., Seymour, Indiana.

9. Container/Closure: Both strengths will be packaged in [---] bottles. The 30s will have CRC & the 100s will have Non-CRC.

10. Kremer's Omeprazole is formulated with enteric coated "microtablets" within a capsule. The RLD has enteric coated granules. Kremer submitted a Bioequivalence Study dated July 2, 1998, to support the labeled Tmax of 0.5 to 3.5 hours. The following was taken from the Bio Review of the 7/2/98 submission.

The purpose of this study is to evaluate the bioequivalency of Kremer's Omeprazole DR Capsules, 20 mg, and Merck's Priosec® 20 mg DR Capsules under fasting conditions.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Kremer*</th>
<th>Priosec®</th>
<th>90%</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀→T (n=46)</td>
<td>311.5*</td>
<td>335.3*</td>
<td>[0.88;0.98]</td>
<td>0.93</td>
</tr>
<tr>
<td>ng.hr/ml</td>
<td></td>
<td></td>
<td>[0.86;0.96]**</td>
<td></td>
</tr>
<tr>
<td>AUC₀→inf (n=44)</td>
<td>332.2*</td>
<td>355.0*</td>
<td>[0.89;0.98]</td>
<td>0.94</td>
</tr>
<tr>
<td>ng.hr/ml</td>
<td></td>
<td></td>
<td>[0.87;0.96]**</td>
<td></td>
</tr>
<tr>
<td>CMAX (ng/mL) (n=46)</td>
<td>200.0*</td>
<td>191.4*</td>
<td>[0.94;1.16]</td>
<td>1.04</td>
</tr>
<tr>
<td>TMAX (hrs)</td>
<td>2.196(52)</td>
<td>2.014(64)</td>
<td>[0.91;1.11]**</td>
<td></td>
</tr>
</tbody>
</table>

The single-dose, fasting bioequivalence study conducted by Kremer on the test product, Omeprazole DR Capsules, 20 mg, lot # CJ-0591, comparing it with the reference product, Merck's Priosec® DR Capsules, 20 mg, lot # E2621, has been found acceptable by the Division of Bioequivalence. The test product, Kremer's Omeprazole DR Capsules, 20 mg, is deemed bioequivalent to the reference listed drug product, Merck's Priosec® DR Capsules, 20 mg.

Date of Review: July 24, 2000
Date of Submissions: February 8, 2000

Reviewer: Kyoung Lee  Date: 3/100
Team Leader: Charlie Hoppes

cc: ANDA 75-410
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
V: FIRMASAM\KREMER\ULTRSR\REV\75410NA3.LABELING

Review
**APPROVAL SUMMARY**
**REVIEW OF PROFESSIONAL LABELING**
**DIVISION OF LABELING AND PROGRAM SUPPORT**
**LABELING REVIEW BRANCH**

ANDA Number: 75-410

Applicant's Name: Kremers Urban Development Company

Established Name: Omeprazole Delayed-release Capsules, 10 mg and 20 mg

Date of Submission: March 29, 2002

---

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? YES
- Container Labels (Bottles of 100, 10 mg and 20 mg revised 09/01): FPL submitted on October 18, 2001 are acceptable for approval.
- Professional Package Insert Labeling (PC3599B, revised 11/01): FPL submitted on March 29, 2002 is acceptable for approval.
- Revisions needed post-approval: None

**BASIS OF APPROVAL:**

- Was this approval based upon a petition? None
- What is the RLD on the 356(h) form: Prilosec
- NDA Number: 19-810
- NDA Drug Name: Prilosec (omeprazole) Delayed-release Capsules
- NDA Firm: AstraZeneca LP
- Date of Approval of NDA Insert and supplement #: October 30, 2001; S-073
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side By Side
- Basis of Approval for the Carton Labeling: NA

---

**REVIEW OF PROFESSIONAL LABELING CHECK LIST**

<table>
<thead>
<tr>
<th>Established Name</th>
<th>Yes</th>
<th>No</th>
<th>N.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different name than on acceptance to file letter?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this product a USP item? If so, USP supplement in which verification was assured. USP 23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this name different than that used in the Orange Book?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If not USP, has the product name been proposed in the PF?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Error Prevention Analysis**

Has the firm proposed a proprietary name? If yes, complete this subsection. | X |

Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present? | X |

Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? | X |

**Packaging**

Is this a new packaging configuration, never been approved by an AND or NDA? If yes, describe in FTR. | X |

Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. | X |

Does the package proposed have any safety and/or regulatory concerns? | X |
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>XA</th>
</tr>
</thead>
<tbody>
<tr>
<td>If IV product packaged in syringe, could there be adverse patient outcome if given direct IV injection?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Is the strength and/or concentration of the product unsupported by the insert labeling?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Is the color of the container (i.e., the color of the cap of a mydriatic ophthalmic) or cap incorrect?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Are there any other safety concerns?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Labeling</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Has applicant failed to clearly differentiate multiple product strengths?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Is the corporate logo larger than 1/3 container label? (No regulation - see ABHP guidelines)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Labeling (continued)</strong></td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is &quot;Jointly Manufactured by...&quot; statement needed?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Failure to describe solid oral dosage form identifying markings in NOW SUPPLIED?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Scoring:</strong> Describe scoring configuration of RLD and applicant (page #) in the PTR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the scoring configuration different than the RLD?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Has the firm failed to describe the scoring in the NOW SUPPLIED section?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Inactive Ingredients:</strong> (PFR: List page # in application where inactives are listed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Do any of the inactives differ in concentration for this route of administration?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Is there a discrepancy in inactives between DESCRIPTION and the composition statement?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Has the term &quot;other ingredients&quot; been used to protect a trade secret? If so, is claim supported?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Failure to list the coloring agents if the composition statement lists e.g., Opaque, OpaSpray?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>USP ISSUES:</strong> (PFR: List USP/NDA/AND dispensing/storage recommendations)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Does USP have labeling recommendations? If any, does AND meet them?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Is the product light sensitive? If so, is NDA and/or AND in a light resistant container?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Chax. Tmax, T 1/2 and date study acceptable)

Insert labeling references a food effect or a no-effect? If so, was a food study done?

Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.

Patent/Exclusivity Issues?: PRI: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.

FOR THE RECORD:

1. Review based on the labeling of the listed drug ANDA 19-810/S-073 (Prilosec; Astra Merck; approved 10/30/01).

2. Patent/ Exclusivities:

   PATENTS:

<table>
<thead>
<tr>
<th>No</th>
<th>Expiration</th>
<th>Use Code</th>
<th>Use Description</th>
<th>File</th>
</tr>
</thead>
<tbody>
<tr>
<td>4255431</td>
<td>October 5, 2001</td>
<td>U-108</td>
<td>Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic gerd, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis</td>
<td>P III</td>
</tr>
<tr>
<td>4636499</td>
<td>January 30, 2006</td>
<td></td>
<td></td>
<td>P IV</td>
</tr>
<tr>
<td>4786505</td>
<td>October 20, 2007</td>
<td>U-108</td>
<td>Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic GERD, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis.</td>
<td>P IV</td>
</tr>
<tr>
<td>4853230</td>
<td>October 20, 2007</td>
<td>U-108</td>
<td>Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic GERD, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis.</td>
<td>P IV</td>
</tr>
<tr>
<td>5093342</td>
<td>August 2, 2010</td>
<td>U-166</td>
<td>Treatment of H. Pylori associated duodenal ulcer.</td>
<td>MOU</td>
</tr>
<tr>
<td>5599794</td>
<td>August 4, 2014</td>
<td>U-166</td>
<td>Treatment of H. Pylori associated duodenal ulcer.</td>
<td>MOU</td>
</tr>
<tr>
<td>5629305</td>
<td>August 4, 2014</td>
<td>U-188</td>
<td>Treatment of H. Pylori associated duodenal ulcer.</td>
<td>MOU</td>
</tr>
<tr>
<td>6147103</td>
<td>April 9, 2019</td>
<td></td>
<td>The present invention describes an improved process for the preparation, isolation, and purification of the anti-ulcer agent esomeprazole whereby the sulfide precursor pyrimidazole is treated substantially with exactly one molar equivalent of methylaminopyrimidinyl acid in methylene chloride or tetrahydrofuran, residual organic solvents are removed from the aqueous layer by vacuum distillation, crude product is obtained by recrystallization with an ethyl formate and seeding, and pure product is isolated by recrystallization in methylated water containing aqueous NaOH by subsequent addition of aqueous acetic acid to pH 9.0, seeding, filtration, washing, and drying. Compounds containing n-chromatographically detectable levels of residual non-alkaloidal organic reaction solvent are also described.</td>
<td>P IV</td>
</tr>
<tr>
<td>6150380</td>
<td>May 10, 2019</td>
<td></td>
<td>The present invention relates to a novel crystalline form of 5-(2-methyl-3,5-dimethyl-2-pyridyl)methylpyridine-1H-benzimidazole, known under the generic name esomeprazole. Further, the present invention also relates to the use of the novel crystalline form of 5-(2-methyl-3,5-dimethyl-2-pyridyl)methylpyridine-1H-benzimidazole for the treatment of gastrointestinal disorders, pharmaceutical compositions containing it as well as processes for the preparation of the novel crystalline form of 5-(2-methyl-3,5-dimethyl-2-pyridyl)methylpyridine-1H-benzimidazole.</td>
<td>P IV</td>
</tr>
<tr>
<td>6166213</td>
<td>April 9, 2018</td>
<td></td>
<td>The present invention describes an improved process for the preparation, isolation, and purification of the anti-ulcer agent esomeprazole whereby the sulfide precursor pyrimidazole is treated substantially with exactly one molar equivalent of methylaminopyrimidinyl acid in methylene chloride or tetrahydrofuran, residual organic solvents are removed from the aqueous layer by vacuum distillation, crude product is obtained by recrystallization with an ethyl formate and seeding, and pure product is isolated by recrystallization in methylated water containing aqueous NaOH by subsequent addition of aqueous acetic acid to pH 9.0, seeding, filtration, washing, and drying. Compounds containing n-chromatographically detectable levels of residual non-alkaloidal organic reaction solvent are also described.</td>
<td>P IV</td>
</tr>
</tbody>
</table>
The present invention describes an improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole whereby the sulfide precursor pentyamine is reacted with an aldehyde to form the corresponding aldehyde, which is then treated with ammonia to form the primary amine. This amine is then treated with a chloroform solution of methoxybenzene to form an active intermediate which is then treated with water to form the desired omeprazole. The resulting compound is then isolated with its solvents and purified by recrystallization or through thin-layer chromatography, or other similar processes, to yield a stable, crystalline omeprazole product.

4. Storage/Dispensing Conditions:
   - NDA: Store between 15°C and 30°C (59°F and 86°F). Protect from light and moisture.
   - AND: Store between 15°C and 30°C (59°F and 86°F) (See USP). Protect from light and moisture.
   - USP: Not USP not NF.

5. Product Line:
The innovator markets their product in three strengths (10 mg, 20 mg and 40 mg). They are supplied as follows:
   - 10 mg - unit of use bottles of 30, bottles of 100 and unit-dose 100s.
   - 20 mg - unit of use 30s, unit dose 100s and 1000s.
   - 40 mg - unit of use 30s, bottles of 100s, unit dose 100s and 1000s.

6. The capsules have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

7. Inactive Ingredients: The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section.

8. All manufacturing will be performed by Schwarz Pharma Manufacturing, Inc., Seymour, Indiana.

9. Container/Closure: Both strengths will be packaged in airtight bottles. The bottle will have Non-CRC.

10. Kremer's Omeprazole is formulated with enteric coated "microtablets" within a capsule. The RLD has enteric coated granules. Kremer submitted a Bioequivalence Study dated July 2, 1998, to support the labeled Tmax of 0.5 to 3.5 hours. The following was taken from the Bio Review of the 7/2/98 submission.

   The purpose of this study is to evaluate the bioequivalency of Kremer's Omeprazole DR Capsules, 20 mg, and Merck's Prilosec® 20 mg DR Capsules under fasting conditions.

---

**Table I**

Omeprazole Comparative Pharmacokinetic Parameters
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Kremers* Mean (CV)</th>
<th>Prilosec® Mean (CV)</th>
<th>90% C.I.</th>
<th>Ratio T/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀₋₅₇₀ (n=46) ng.hr/ml</td>
<td>311.5*</td>
<td>335.3*</td>
<td>[0.88;0.98]</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[0.86;0.96]**</td>
<td></td>
</tr>
<tr>
<td>AUC₀₋inf (n=44) ng.hr/ml</td>
<td>332.2*</td>
<td>355.0*</td>
<td>[0.89;0.98]</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[0.87;0.96]**</td>
<td></td>
</tr>
<tr>
<td>CMAX (ng/mL) (n=48)</td>
<td>200.0*</td>
<td>191.4*</td>
<td>[0.94;1.16]</td>
<td>1.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[0.91;1.11]**</td>
<td></td>
</tr>
<tr>
<td>TMAX (hrs)</td>
<td>2.196(52)</td>
<td>2.014(64)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The **single-dose, fasting** bioequivalence study conducted by Kremers on the test product, Omeprazole DR Capsules, 20 mg, lot # CJ-0591, comparing it with the reference product, Merck’s Prilosec® DR Capsules, 20 mg, lot # E2621, has been found **acceptable** by the Division of Bioequivalence. The test product, Kremers’ Omeprazole DR Capsules, 20 mg, is deemed bioequivalent to the reference listed drug product, Merck’s Prilosec® DR Capsules, 20 mg.
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

AND Number: 75-410  Date of Submission: July 2, 1998
Applicant's Name: Kremers Urban Development Company
Established Name: Omeprazole Delayed-release Capsules, 20 mg

Labeling Deficiencies:

1. GENERAL
   a. Please update your Patent and Exclusivity Statement with regard to exclusivity for I-229. We refer you to the Orange Book 18th edition, supplement #6.
   b. We note that you have proposed a Non-Child Resistant Closure for your proposed package size of 30's. The Poison Prevention Packaging Act states that special packaging (child-resistant closures) should be the responsibility of the manufacturers when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). We believe that your proposed package size of 30's must comply with the Act. Please comment.

2. CONTAINER  (30s and 100s)
   a. We encourage you the relocation of "Rx Only" to the principal display panel and assure that the statement appears prominently.
   b. Include the following immediately after the "USUAL DOSAGE" statement and/or comment:

   The Omeprazole Delayed-Release Capsule should be swallowed whole, and not opened, chewed, or crushed.
c. Revise the storage requirement to read as follows and/or comment:

... protected from light and moisture.

d. Revise the "Dispense in" statement to read as follows and/or comment:

... in tight and light-resistant container...

e. Your drug product appears to be manufactured in the USA. ___ Delete the statement and/or comment. We refer you to 21 CFR 201.1 for guidance.

2. INSERT

a. GENERAL

i. We acknowledge your comments that there appears to be an inconsistency in the insert labeling of the reference listed drug. We have forwarded your comments to the Division of Special Pathogens and Immunologic Drug Products for their review and comment. We will inform you of their comments when they are available.

ii. We acknowledge that you have removed all information pertaining to the from your package insert labeling since you are not claiming this indication in your application.

iii. Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.

b. DESCRIPTION

i. Revise "empirical formula" to read "

ii. Third paragraph - We encourage you to revise as follows:
Each delayed-release capsule, for oral administration, contains 20 mg of omeprazole in the form enteric-coated microtablets. In addition, each capsule contains the following inactive ingredients:...

iii. We ask that you include the inactive ingredients contained in the at the minimum and/or comment.

c. PRECAUTIONS (Information for Patients)

i. We acknowledge your comments regarding "microtablets" formulation of your drug product in terms of dissolution profile. However, your labeling must be the same as the reference listed drug in this regard unless you obtain a Citizen's Suitability Petition for a different dosage form as stipulated in the 21 CFR 314.93. See 21 CFR 314.94 (a)(6)(i)(A) for guidance.

ii. Revise the second sentence to read:

...not be opened, chewed or crushed, and should be swallowed whole.

iii. Delete the penultimate and last sentences.

d. DOSAGE AND ADMINISTRATION

i. Delete this subsection heading and italicize the subsection heading "Short-Term... Ulcer".

ii. Last paragraph:

A) See comment (i) under PRECAUTIONS.

B) First sentence:

...not be opened, chewed or crushed, and should be swallowed whole.

C) Delete the penultimate and last sentences.
e. HOW SUPPLIED

i. First paragraph - Revise to read:

... 20 mg are opaque cap and opaque gold body capsules imprinted with "KU" and "118" in black ink. They...

ii. Storage

... protected from light and moisture.

iii. We encourage the inclusion of the "Dispense in" statement found on the container labels.

iv. Please include the revision date.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes  No

Container Labels:

Professional Package Insert Labeling:

Revisions needed post-approval:

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Prilosec®

NDA Number: 19-810

NDA Drug Name: Prilosec®

NDA Firm: Astra Merck

Date of Approval of NDA Insert and supplement #: Approved June 29, 1998/S-055

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Container labels in file folder.

**NOTE TO CHEMIST**

1. Please note that the sponsor has proposed their drug product in the microtablets formulation whereas the innovator has their drug formulation in the form of enteric-coated granules.

2. Please see the comment (b) under GENERAL COMMENT and follow-up on this issue, if deemed necessary. Thanks,

**REVIEW OF PROFESSIONAL LABELING CHECK LIST**

<table>
<thead>
<tr>
<th>Established Name</th>
<th>Yes</th>
<th>No</th>
<th>M.A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different name than on acceptance to file letter?</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Is this product a USP item? If so, USP supplement in which verification was assured. USP 23</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-----</td>
<td>----</td>
<td>-----</td>
</tr>
<tr>
<td>Is this name different than that used in the Orange Book?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If not USP, has the product name been proposed in the PFT?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Error Prevention Analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the firm proposed a proprietary name? If yes, complete this subsection.</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you find the name objectionable? List reasons in PFR. If so, Consider:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Packaging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this a new packaging configuration, never been approved by an AND or NDA? If yes, describe in PFR.</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the package proposed have any safety and/or regulatory concerns?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the strength and/or concentration of the product unsupported by the insert labeling?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are there any other safety concerns?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Labeling</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has applicant failed to clearly differentiate multiple product strengths?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Labeling (continued)</strong></td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Does ELD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the Manufacturer/distributor statement incorrect or falsely inconsistent between labels and labeling? 'Jointly Manufactured by...', statement needed?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the firm failed to adequately support quality or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Scoring:</strong> Describe scoring configuration of ELD and applicant (page #) in the PFR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the scoring configuration different than the ELD?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the firm failed to describe the scoring in the HOW SUPPLIED section?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Inactive Ingredients:

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?</td>
<td>X</td>
</tr>
<tr>
<td>Do any of the inactives differ in concentration for this route of administration?</td>
<td>X</td>
</tr>
<tr>
<td>Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?</td>
<td>X</td>
</tr>
<tr>
<td>Is there a discrepancy in inactives between DESCRIPTION and the composition statement?</td>
<td>X</td>
</tr>
<tr>
<td>Has the term &quot;other ingredients&quot; been used to protect a trade secret? If so, is claim supported?</td>
<td>X</td>
</tr>
<tr>
<td>Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?</td>
<td>X</td>
</tr>
<tr>
<td>Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?</td>
<td>X</td>
</tr>
<tr>
<td>Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)</td>
<td>X</td>
</tr>
</tbody>
</table>

### USP Issues:

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?</td>
<td>X</td>
</tr>
<tr>
<td>Does USP have labeling recommendations? If any, does AND meet them?</td>
<td>X</td>
</tr>
<tr>
<td>Is the product light sensitive? If so, is NDA and/or AND in a light resistant container?</td>
<td>X</td>
</tr>
<tr>
<td>Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.</td>
<td>X</td>
</tr>
</tbody>
</table>

### Bioequivalence Issues:

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insert labeling references a food effect or a no-effect? If so, was a food study done?</td>
<td>X</td>
</tr>
<tr>
<td>Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.</td>
<td>X</td>
</tr>
</tbody>
</table>

### Patent/Exclusivity Issues:

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATENTS:</td>
<td></td>
</tr>
<tr>
<td>4255431 - Expires April 5, 2001, U-108 - Short-term treatment of active duodenal ulcer, gastrosophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic gerd, pathological hypersecretory conditions and maintenance of healing of</td>
<td></td>
</tr>
</tbody>
</table>
erosive esophagitis.

4636499 - Expires May 30, 2005

4786505 - Expires April 20, 2007, U-108 - Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic gerd, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis.

4853230 - Expires April 20, 2007, U-108 - Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic gerd, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis.


EXCLUSIVITIES:


I-229 - Expires June 29, 2001 - Omeprazole, amoxicillin and clarithromycin for the eradication of H.Pylori in patients with duodenal ulcer disease.

The firm has filed a paragraph IV certification against patent numbers 4,853,230, 4,786,505, & 4,636,499 and a paragraph III against 4,255,431. The firm has not filed paragraph certification against # 5,093,342, 5,599,794, & 5,629,305 and made a statement that the indication covered by these patents is not claimed in this application. Accordingly, the firm carved out information pertaining to this indication from the package insert labeling. According to Peter Rickman, Team Leader of the Regulatory Branch, this statement is sufficient not requiring filing of paragraph certification.
4. Storage/Dispensing Conditions:

NDA: Store between 15°C and 30°C (59°F and 86°F).
Protect from light and moisture.

AND: Store between 15°C and 30°C (59°F and 86°F).
Protect from moisture.

USP: Not USP not NF.

5. Product Line:

The innovator markets their product in three strengths
(10 mg, 20 mg and 40 mg). They are supplied as:
follows:

10 mg - unit of use bottles of 30, bottles of 100 and
unit-dose 100s.

20 mg - unit of use 30s, unit dose 100s and 1000s.

40 mg - unit of use 30s, bottles of 100s, unit dose
100s and 1000s.

The applicant proposes to market their product (20 mg)
in 30's & 100's bottle.

6. The capsule imprintings have been accurately described
in the HOW SUPPLIED section as required by 21 CFR
206, et al. (Imprinting of Solid Oral Dosage Form
Products for Human Use; Final Rule, effective 9/13/95).
See page P.003, vol.B.1.3. However, see the comment
(1) under H.S. section.

7. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION
section of the package insert appears to be consistent
with the listing of inactive ingredients found in the
statement of components and composition appearing on
page 002 & 51, Vol.B. 1.2. However, see the comment
(iii) under DESCRIPTION.

8. All manufacturing will be performed by Schwarz Pharma
Manufacturing, Inc., Seymour, Indiana.

9. Container/Closure:

This product will be packaged in bottles.
It appears that both 30s & 100s will be packaged with
Non-CRC closures (. See comment (b) under GENERAL COMMENT and P.289, vol.B.1.3.

10. The following is the e-mail sent to the P.M. for
Prilosec Capsules. We will inform the sponsor when
their response is available. (E-mail in the file
4. Storage/Dispensing Conditions:

NDA: Store between 15°C and 30°C (59°F and 86°F).
Protect from light and moisture.

AND: Store between 15°C and 30°C (59°F and 86°F).
Protect from moisture.

USP: Not USP not NF.

5. Product Line:

The innovator markets their product in three strengths
(10 mg, 20 mg and 40 mg). They are supplied as
follows:

10 mg - unit of use bottles of 30, bottles of 100 and
unit-dose 100s.

20 mg - unit of use 30s, unit dose 100s and 1000s.

40 mg - unit of use 30s, bottles of 100s, unit dose
100s and 1000s.

The applicant proposes to market their product (20 mg)
in 30's & 100's bottle.

6. The capsule imprintsings have been accurately described
in the HOW SUPPLIED section as required by 21 CFR
206, et al. (Imprinting of Solid Oral Dosage Form
Products for Human Use: Final Rule, effective 9/13/95).
See page P.003, vol.B.1.3. However, see the comment
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This product will be packaged in        bottles.
It appears that both 30s & 100s will be packaged with
Non-CRC closures . See
comment (b) under GENERAL COMMENT and P.289, vol.B.1.3.

10. The following is the e-mail sent to the P.M. for
Prilosec Capsules. We will inform the sponsor when
their response is available. (E-mail in the file
folder)

I am one of the labeling reviewers in Office of Generic Drugs. I would like to bring it to your attention that there appears to be an inconsistency in two statements in the package insert regarding dose adjustment, as pointed out by one of the generic firms. The exact statements I am referring to appear as follows:

CLINICAL PHARMACOLOGY (Pharmacokinetics and Metabolism)

Dose adjustment, particularly where maintenance of healing erosive esophagitis is indicated, for the hepatically impaired and Asian subjects should be considered.

DOSAGE AND ADMINISTRATION (pathological Hypersecretory conditions) - Second paragraph.

No dosage adjustment is necessary for patients with renal impairment, hepatic dysfunction or for the elderly.

I would appreciate it if you can bring this question to the medical officer and forward his/her response to me. Thank you for your help in this matter.

Chan

Date of Review: November 18, 1998
Date of Submission: July 2, 1998
Reviewer: [Signature] 11/30/98

Team Leader: [Signature] 11/1/98

CC:
ANDA 75-410
DUP/DIVISION FILE
HFD-613/CPark/Choppes (no CC)
X:\NEW\FIRMSAM\KREMER-U\LTRS&REV\75410NA1.L
Review
DIVISION APROVAL SUMMARY

ANDA: 75-410
DRUG PRODUCT: Omeprazole Delayed-release Capsules, 10 mg and 20 mg

FIRM: Kremers-Urban Development Company

DOSAGE: Capsules

STRENGTH: 10 mg, and 20 mg

CGMP STATEMENT/EIR UPDATE STATUS:
EIR: Satisfactory EIR is issued as of 2/9/01.

BIO STUDIES/BIOEQUIVALENCE STATUS:
Bio decision is granted on 7/14/00, for the 20 mg, the study was acceptable. Waiver granted for 10 mg. Sprinkle study was accepted on 6/13/02.

METHODS VALIDATION:
Results are pending from ____________

STABILITY (conditions, containers and methods):
Bio batch was set up on stability in the proposed container/closure systems and data reported. The following are the firm's stability tests and specifications.

<table>
<thead>
<tr>
<th>Stability Specs</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assay (LC-label claim)</td>
<td>of label claim</td>
</tr>
<tr>
<td>Dissolution</td>
<td>0.1 N HCl : NMT ≤ dissolved in 2 hours (acid stage)</td>
</tr>
<tr>
<td></td>
<td>0.05 M phosphate buffer: NLT ≤ dissolved in 45 minutes (buffer stage)</td>
</tr>
<tr>
<td>Total Impurities</td>
<td>Individual known impurity: NMT</td>
</tr>
<tr>
<td></td>
<td>Other unknown peaks: NMT</td>
</tr>
<tr>
<td></td>
<td>Total: NMT ≤ (including</td>
</tr>
<tr>
<td>Physical appearance</td>
<td>20 mg: No 1 Opaque capsules with</td>
</tr>
<tr>
<td></td>
<td>and gold body</td>
</tr>
<tr>
<td></td>
<td>imprinted with 'KU 118' in</td>
</tr>
<tr>
<td></td>
<td>black and filled with</td>
</tr>
</tbody>
</table>
### Stability Specs

<table>
<thead>
<tr>
<th>microtablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg: No 1 Opaque capsules with and gold body imprinted with 'KU 114' in black and filled with microtablets</td>
</tr>
</tbody>
</table>

**LABELING REVIEW STATUS:**
Acceptable. See review dated 9/20/02.

**STERILIZATION VALIDATION (If Applicable):**
NA.

**BATCH SIZES:**
Bio batch (identity #, drug substance source):
UQUIFA, Micronized lot 909/97/1121 and unmicronized lot 910/97/1120.
Batch size: ___ capsules for 10 and 20 mg each

**STABILITY BATCH (different from bio batch, manu. Site, process):**
Stability batch is the same as bio batch.

**PROPOSED PRODUCTION BATCH:**
Capsules of 20 mg and ___ capsules of 10 mg are proposed.

**COMMENTS:**
Approval recommended

**CHEMISTRY REVIEWER:** Radhika Rajagopalan, Ph.D.
**DATE:** 6/20/02
APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-410                        Date of Submission: June 25, 2002
Applicant's Name: Kremers Urban Development Company
Established Name: Omeprazole Delayed-release Capsules, 10 mg and 20 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? YES
- Container Labels: FPL for the bottles of 30's submitted on June 25, 2002, [Vol. 13.1]10 mg (L3595A) and 20 mg (L3597A) are satisfactory for approval. FPL for bottles of 100's submitted on October 18, 2001, [Vol. 11.1]10 mg (L3596A) and 20 mg (L3598A) are satisfactory for approval.
- Professional Package Insert Labeling: (Rev. 05/02, PC3599C) [Vol. 13.1] Satisfactory in FPL submitted on 8/25/02.
- Revisions needed post-approval: None

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Prilosec
- NDA Number: 19-810
- NDA Drug Name: Prilosec
- NDA Firm: AstraZeneca
- Date of Approval of NDA Insert and supplement #: October 30, 2001; S-073
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side by Side
- Basis of Approval for the Carton Labeling: Not Applicable

FOR THE RECORD:

1. Review based on the labeling of the listed drug ANDA 19-810/S-073 (Prilosec; Astra Merck; approved 10/30/01).
2. Patent/ Exclusivities:

<table>
<thead>
<tr>
<th>No</th>
<th>Expiration</th>
<th>Use Code</th>
<th>Use</th>
<th>File</th>
</tr>
</thead>
<tbody>
<tr>
<td>4636499</td>
<td>November 30, 2005</td>
<td>U-108</td>
<td>Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic gerd, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis</td>
<td>P IV</td>
</tr>
<tr>
<td>4786505</td>
<td>October 20, 2007</td>
<td>U-108</td>
<td>Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic GERD, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis</td>
<td>P IV</td>
</tr>
<tr>
<td>4853230</td>
<td>October 20, 2007</td>
<td>U-108</td>
<td>Short-term treatment of active duodenal ulcer, gastroesophageal reflex disease (GERD), severe erosive esophagitis, poorly responsive symptomatic GERD, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis</td>
<td>P IV</td>
</tr>
<tr>
<td>5093342</td>
<td>August 2, 2010</td>
<td>U-166</td>
<td>Treatment of H. Pylori associated duodenal ulcer.</td>
<td>MOU</td>
</tr>
<tr>
<td>5599794</td>
<td>August 4, 2014</td>
<td>U-166</td>
<td>Treatment of H. Pylori associated duodenal ulcer.</td>
<td>MOU</td>
</tr>
<tr>
<td>5629305</td>
<td>August 4, 2014</td>
<td>U-188</td>
<td>Treatment of H. Pylori associated duodenal ulcer.</td>
<td>MOU</td>
</tr>
</tbody>
</table>
4. Storage/Dispensing Conditions:
   - NDA: Store between 15°C and 30°C (59°F and 86°F). Protect from light and moisture.
   - ANDA: Store between 15°C and 30°C (59°F and 86°F) (See USP). Protect from light and moisture.
   - USP: Not USP not NF.

5. Product Line:
The innovator markets their product in three strengths (10 mg, 20 mg and 40 mg). They are supplied as follows:
   - 10 mg - unit of use bottles of 30, bottles of 100 and unit-dose 100s.
   - 20 mg - unit of use 30s, unit dose 100s and 1000s.
   - 40 mg - unit of use 30s, bottles of 100s, unit dose 100s and 1000s.

The applicant proposes to market its product (10 mg and 20 mg) in bottle of 30's and 100's.

The capsules have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). (Vol. 11.1 pages 164 and 178)

7. Inactive Ingredients: The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section. The inactive ingredients section was amended on December 7, 2001 [Vol. 11.1 page 007] to delete ingredients intended to affect the color of the capsule. This was reviewed in the chemist review # 5.

8. All manufacturing will be performed by Schwarz Pharma Manufacturing, Inc., Seymour, Indiana.

9. Container/Closure: Both strengths will be packaged in bottles. The bottle will have Non-CRC.

10. Kremer's Omeprazole is formulated with enteric coated "microtablets" within a capsule. The RLD has enteric coated granules. Kremer submitted a Bioequivalence Study dated July 2, 1998, to support the labeled Tmax of 0.5 to 3.5 hours. The following was taken from the Bio Review of the 7/2/98 submission.

   The purpose of this study is to evaluate the bioequivalency of Kremer's Omeprazole DR Capsules, 20 mg, and Merck's Prilosec® 20 mg DR Capsules under fasting conditions.

---

**Table 1**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Kremers*</th>
<th>Prilosec®</th>
<th>90% C.I.</th>
<th>Ratio T/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-T} (n=46)</td>
<td>311.5* (CV)</td>
<td>335.3* (CV)</td>
<td>[0.88;0.98]</td>
<td>0.93</td>
</tr>
<tr>
<td>ng.hr/ml</td>
<td></td>
<td></td>
<td>[0.86;0.96]**</td>
<td></td>
</tr>
<tr>
<td>AUC_{0-inf} (n=44)</td>
<td>332.2*</td>
<td>355.0*</td>
<td>[0.89;0.98]</td>
<td>0.94</td>
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<tr>
<td>ng.hr/ml</td>
<td></td>
<td></td>
<td>[0.87;0.96]**</td>
<td></td>
</tr>
<tr>
<td>CMAX (ng/mL) (n=46)</td>
<td>200.0*</td>
<td>191.4*</td>
<td>[0.94;1.16]</td>
<td>1.04</td>
</tr>
<tr>
<td>(hrs)</td>
<td></td>
<td></td>
<td>[0.91;1.11]**</td>
<td></td>
</tr>
<tr>
<td>TMAX (hrs)</td>
<td>2.196(52)</td>
<td>2.014(64)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The single-dose, fasting bioequivalence study conducted by Kremer on the test product, Omeprazole DR Capsules, 20 mg, lot # CJ-0591, comparing it with the reference product, Merck's Prilosec® DR Capsules, 20 mg, lot # E2821, has been found acceptable by the Division of Bioequivalence. The test product, Kremer's Omeprazole DR Capsules, 20 mg, is deemed
bioequivalent to the reference listed drug product, Merck’s Pritelis® DR Capsules, 20 mg.

Date of Review: July 15, 2002  Date of Submissions: June 25, 2002
Reviewer: Koung Lee  Date: 7/15/02
Team Leader: Lillie Golsor  Date: 7/15/02
cc: ANDA 75-410
    DUP/DIVISION FILE
    HFD-613/KLee/LGolsor (no cc)
    \:\FIRMSAM\KREMER\ULTRSR\REV\75410AP3\LABELING

Review
APPROVAL SUMMARY
(This supersedes the Approval Summary for the June 25, 2002 submission)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-410  Date of Submission: September 3, 2002
Applicant's Name: Kremers Urban Development Company
Established Name: Omeprazole Delayed-release Capsules, 10 mg and 20 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling?  YES
- Container Labels: FPL for the bottles of 30's submitted on June 25, 2002, [Vol. 13.1] 10 mg (L3595A) and 20 mg (L3597A) are satisfactory for approval. FPL for bottles of 100's submitted on October 18, 2001, [Vol. 11.1] 10 mg (L3596A) and 20 mg (L3598A) are satisfactory for approval.
- Professional Package Insert Labeling: (Rev. 07/02, PC3599D) [Vol. 13.1] Satisfactory in FPL submitted on 9/3/02.
- Revisions needed post-approval: Yes

INSERT
a. Replace "empirical" with "empirical" in the second sentence of the first paragraph.
b. PRECAUTIONS
   Revise the subsection heading to read "Pregnancy: 
   Pregnancy Category C."
c. Increase the prominence of the subsection headings to increase the readability.

BASIS OF APPROVAL:

- Was this approval based upon a petition?  No
- What is the RLD on the 356(h) form: Prilosec
- NDA Number: 19-810
- NDA Drug Name: Prilosec
- NDA Firm: AstraZeneca
- Date of Approval of NDA Insert and supplement #: July 12, 2002; S-074
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels:
  Basis of Approval for the Carton Labeling:

FOR THE RECORD:
1. Review based on the labeling of the listed drug ANDA 19-810/S-074 (Prilosec; Astra Merck; approved 7/12/02).
2. Patent/ Exclusivities:

PATENTS:

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<td>P IV</td>
</tr>
<tr>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td>peptic ulcer, pathological hypersecretory condition</td>
<td></td>
</tr>
<tr>
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<td>Use Code</td>
<td>Description</td>
<td>Labeling Impact</td>
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<tr>
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<td>October 20, 2007</td>
<td>U-108</td>
<td>Short-term treatment of active duodenal ulcer, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive symptomatic GERD, pathological hypersecretory conditions and maintenance of healing of erosive esophagitis</td>
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<tr>
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<td>August 4, 2014</td>
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<td>MOU</td>
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<td>August 4, 2014</td>
<td>U-188</td>
<td>Treatment of H. Pylori associated duodenal ulcer</td>
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<td>6191148</td>
<td>April 9, 2019</td>
<td>PIV</td>
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</table>

**Exclusivity Data**

<table>
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<tr>
<th>Code/sup</th>
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<th>Use Code</th>
<th>Description</th>
<th>Labeling Impact</th>
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</thead>
<tbody>
<tr>
<td>M-19</td>
<td>Jan. 12, 2006</td>
<td>Use of Omeprazole in Pediatric Patients</td>
<td>Carved out Pediatric text</td>
<td></td>
</tr>
</tbody>
</table>

4. **Storage/Dispensing Conditions:**
   - NDA: Store between 15°C and 30°C (59°F and 86°F). Protect from light and moisture.
   - ANDA: Store between 15°C and 30°C (59°F and 86°F) (See USP). Protect from light and moisture.
   - USP: Not USP not NF.

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- 10 mg - unit of use bottles of 30, bottles of 100 and unit-dose 100s.
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The applicant proposes to market its product (10 mg and 20 mg) in bottle of 30's and 100's.

6. **The capsules have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).** (Vol. 11.1 pages 164 and 178)

7. **Inactive Ingredients:** The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section. The inactive ingredients section was amended on December 7, 2001 (Vol. 11.1 page 007) to delete ingredients intended to affect the color of the capsule. This was reviewed in the chemist review # 5.

8. **All manufacturing will be performed by Schwarz Pharma Manufacturing, Inc., Seymour, Indiana.**

9. **Container/Closure:** Both strengths will be packaged in bottles. The bottle will have Non-CRC.

10. **Kremer's Omeprazole is formulated with enteric coated ''microtablets'' within a capsule. The RLD has enteric coated granules.** Kremer submitted a Bioequivalence Study dated July 2, 1998, to support the labeled Tmax of 0.5 to 3.5 hours. The following was taken from the Bio Review of the 7/2/98 submission.

   **The purpose of this study is to evaluate the bioequivalency of Kremer's Omeprazole DR Capsules, 20 mg, and Merck's Priosec® 20 mg DR Capsules under fasting conditions.**

   **Table I**

   **Omeprazole Comparative Pharmacokinetic Parameters**

   **Fasting Single-Dose Study, Dose = 20 mg; n = 46**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Kremer's*</th>
<th>Priosec®</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{2-7} (n=46)</td>
<td>311.5*</td>
<td>335.3*</td>
</tr>
<tr>
<td>ng.hr/ml</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

   **90% CI: [0.88;0.98]**

   **Ratio**

   **[0.86;0.96]**

<table>
<thead>
<tr>
<th>Ratio</th>
<th>T/R</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.93</td>
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<td>Parameter</td>
<td>Value</td>
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<td>AUC_{0inf} (ng/hr/ml, n=44)</td>
<td>332.2*</td>
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<td>200.0*</td>
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<td></td>
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<td>TMAX (hrs)</td>
<td>2.196(52)</td>
</tr>
</tbody>
</table>

The single-dose, fasting bioequivalence study conducted by Kremers on the test product, Omeprazole DR Capsules, 20 mg, lot # CJ-0591, comparing it with the reference product, Merck's Prilosec® DR Capsules, 20 mg, lot # E2621, has been found acceptable by the Division of Bioequivalence. The test product, Kremers' Omeprazole DR Capsules, 20 mg, is deemed bioequivalent to the reference listed drug product, Merck's Prilosec® DR Capsules, 20 mg.

Date of Review: September 19, 2002
Date of Submissions: September 3, 2002
Reviewer: Koungh Lee
Team Leader: Lillie Golson
cc: ANDA 75-410
DUP/DIVISION FILE
HFD-613/KLee/L.Golson (no cc)
V:\FIRMSAM\KREMERULTRAS&REV\75410AP5.LABELING

Review

APPEARS THIS WAY ON ORIGINAL
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-410

CORRESPONDENCE
October 31, 2002

Food and Drug Administration
CDER, Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

Minor Amendment 030 – Final Approval Requested

Dear Sir/Madam:

Reference is made to above-listed ANDA 75-410. This application was tentatively approved on October 4, 2002. A copy of the Tentative Approval letter is included in this submission.

Per the instructions in the Tentative Approval letter, the sponsor herein submits a Minor Amendment – Final Approval Requested with information required by the Agency before final approval can be granted. Specific items that need to be included are herein reprinted from the Tentative Approval letter, with the responses provided in bold.

This amendment provides:

1. the date that the 180-day marketing exclusivity period granted to the prior applicants will expire. Alternatively, a settlement agreement between the parties, or a licensing agreement between you and the patent holder, or any other relevant information...

Response: Both co-exclusivity holders relinquish their eligibility for 180-day marketing exclusivity.

2. a. updated information related to final-printed labeling, or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

b. a statement that no such changes have been made to the application since the date of tentative approval.

Response: The sponsor herein states that no such changes have been made to the application since the date of tentative approval.

RECEIVED
NOV 01 2002
OGD/CDER
It is the sponsor's understanding that all open issues that need to be addressed before final approval can be granted are satisfied with the submission of this amendment.

This submission is being sent by facsimile with a hard copy to follow. If there are any questions regarding this submission, please contact Elaine Cibulka, Regulatory Affairs Manager, Schwarz Pharma, Inc., at 262-238-5225 (phone) or 262-238-0957 (fax).

Sincerely,

Steven R. Pollock  
Vice President  
Medical, Regulatory and Quality Assurance  
SCHWARZ PHARMA, Inc., representing  
Kremers Urban Development Company

APPEARS THIS WAY ON ORIGINAL
September 25, 2002

Food and Drug Administration
CDER, Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

General Correspondence

Dear Sir/Madam:

Reference is made to above-listed ANDA 75-410 which was tentatively approved on May 3, 2001 and to the teleconferences held on September 23, 2002 and September 24, 2002 between the sponsor and Office of Generic Drugs (OGD). During the teleconferences, the sponsor was notified of two new references for pediatric exclusivity published in the Orange Book for the RLD and asked to formally acknowledge these exclusivities in the above-listed application. KUDCO herein acknowledges the PED and M-19 exclusivities awarded the RLD and states that KUDCO will carve out those sections of the labeling which are protected by exclusivity to their generic product sold under ANDA 75-410.

With the submission of this letter and the previously submitted Final Printed Labeling in Amendment 029, the sponsor believes all outstanding issues have been resolved. It is our understanding that we can expect a second Tentative Approval letter following the review of this letter.

This submission is being transmitted via facsimile with a hard copy to follow. If there are questions or comments regarding this submission, please contact Elaine Cibulka, Manager, Regulatory Affairs, Schwarz Pharma, Inc. at (262) 238-5225 or by fax at (262) 238-0957.

Sincerely,

Elaine Cibulka

Steven R. Pollock
Vice President
Medical, Regulatory and Quality Assurance
SCHWARZ PHARMA, Inc., representing
Kremers Urban Development Company

RECEIVED
SEP 26 2002
OGD / CDER
September 24, 2002

Food and Drug Administration  
CDER, Office of Generic Drugs (HFD-600)  
Metro Park North II  
Document Control Room 150  
7500 Standish Place  
Rockville, MD  20855-2773

RE:  ANDA 75-410  
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

General Correspondence

Dear Sir/Madam:

Reference is made to above-listed ANDA 75-410 which was tentatively approved on May 3, 2001 and to the teleconference held on September 23, 2002 between the sponsor and Office of Generic Drugs (OGD), during which the sponsor was notified of two new references for pediatric exclusivity published in the Orange Book for the RLD. KUDCO herein acknowledges the exclusivity awarded the RLD and states that KUDCO will carve out those sections of the labeling which are protected by exclusivity to their generic product sold under ANDA 75-410.

With the submission of this letter and the previously submitted Final Printed Labeling in Amendment 029, the sponsor believes all outstanding issues have been resolved. It is our understanding that we can expect a second Tentative Approval letter following the review of this letter.

This submission is being transmitted via facsimile with a hard copy to follow. If there are questions or comments regarding this submission, please contact Elaine Cibulka, Manager, Regulatory Affairs, Schwarz Pharma, Inc. at (262) 238-5225 or by fax at (262) 238-0957.

Sincerely,

Elaine Cibulka for

Steven R. Pollock  
Vice President  
Medical, Regulatory and Quality Assurance  
SCHWARZ PHARMA, Inc., representing  
Kremers Urban Development Company

 RECEIVED
SEP 2 5 2002
OGD / CDER
September 3, 2002

Food and Drug Administration  
CDER, Office of Generic Drugs (HFD-600)  
Metro Park North II  
Document Control Room 150  
7500 Standish Place  
Rockville, MD 20855-2773

RE:  
ANDA 75-410  
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

Minor Amendment 029 – Final Printed Labeling

Dear Sir/Madam:

Reference is made to above-listed ANDA 75-410. This application was tentatively approved on May 3, 2001. A copy of the tentative approval letter is included in this submission.

On August 22, 2002, Office of Generic Drugs (OGD) sent a copy of the latest approved labeling for the Reference Listed Drug (RLD) to the sponsor. A letter from OGD which accompanied the RLD labeling included instructions to revise and submit labeling for Omeprazole Delayed-Release Capsules to ANDA 75-410. In accordance with Agency instructions, the sponsor herein submits a MINOR AMENDMENT with revised labeling for Omeprazole Delayed Release Capsules. A comparison of the proposed labeling to the last submitted labeling is included, as well as hard copies of Final Printed Labeling (FPL). With the submission of this amendment, the sponsor believes all outstanding issues have been resolved. It is our understanding that we can expect a second Tentative Approval letter following the review of this labeling.

If there are any questions regarding this submission, please contact Elaine Cibulka, Regulatory Affairs Manager, Schwarz Pharma, Inc., at 262-238-5225 (phone) or 262-238-0957 (fax).

Sincerely,

[Signature]

Elaine Cibulka
Vice President
Medical, Regulatory and Quality Assurance
SCHWARZ PHARMA, Inc., representing Kremers Urban Development Company

RECEIVED
SEP 04 2002
OGD / CDER
June 25, 2002

Food and Drug Administration
CDER, Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE:  ANDA 75-410
    Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

Minor Amendment 027 – CMC – Addition of Bottles of 30
Labeling Amendment 028 – Final Printed Labeling for Bottles of 30

Dear Sir/Madam:

Reference is made to above-listed ANDA 75-410. This application was tentatively approved on
May 3, 2001. A copy of the tentative approval letter is included in this submission. The tentative
approval letter instructed the sponsor to submit any CMC changes to the application prior to full
approval. The sponsor herein submits a change to the application to add bottles of 30 capsules as a
packaging size for each strength.

The initial submission of ANDA 75-410 included information for bottles of 30 as a packaging size.
During the review process, submissions included container/closure information as well as stability
studies under both Accelerated and Controlled Room Temperature conditions for bottles of 30 for both
the 10 mg and 20 mg strength capsules. Subsequent marketing decisions led the sponsor to determine
that bottles of 30 would not be needed as a launch size; therefore, final printed labeling (FPL) for the
bottles of 30 was not submitted in the last labeling submission which included bottle labels. However,
stability studies were continued through conclusion of the protocols and submitted to the application to
support an expiration date of 24 months for bottles of 30. These results have already been reviewed by
the Agency, as Accelerated stability studies through the conclusion of the protocol were reported in
Amendment 012, dated February 8, 2000, and Controlled Room Temperature in Amendment 023,

In addition, the sponsor retained bottles of 30 as an acceptable container/closure configuration in the
finished product specifications. The latest versions of these specifications were submitted in

To support the addition of bottles of 30 as a marketed product size, this amendment includes the most
recent versions of the packaging specifications (bottle, child-resistant cap, and cotton). Also included
are the results of container/closure testing on a lot of PM-0135, the bottles which are used to package
30 capsules. Letters of authorization to access the appropriate DMFs for the bottle, cap and cotton
were submitted to the application in Amendment 009 dated July 1, 1999.
Twelve copies of FPL are included for the 30-count bottles of both the 10 mg and 20 mg strength capsules, as well as the package insert, which has been updated to include bottles of 30 in the How Supplied section. An annotated copy of the revised portions of the insert compared to the last submitted insert is also included.

This statement verifies that a full and complete copy of Minor CMC Amendment 027 has been sent to the Detroit District Office of the FDA. If there are any questions regarding this submission, please contact Elaine Cibulka, Regulatory Affairs Manager, Schwarz Pharma, Inc., at 262-238-5225 (phone) or 262-238-0957 (fax).

Sincerely,

Elaine Cibulka

Steven R. Pollock
Vice President
Medical and Regulatory Affairs
SCHWARZ PHARMA, Inc., representing
Kremers Urban Development Company

APPEARS THIS WAY ON ORIGINAL
April 12, 2002

Food and Drug Administration
CDER, Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE:  ANDA 75-410
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

BE Telephone Amendment 001 to A-024
Bioequivalence Sprinkle Study

Dear Sir/Madam:

Reference is made to the above-listed ANDA 75-410 and to Amendment 024, the Bioequivalence Sprinkle Study, which was submitted on March 29, 2002. Reference is also made to a telephone conference between the sponsor and Division of Bioequivalence on April 11, 2002, in which the sponsor was asked to submit a diskette in ASCII plain text files in a format specified by the reviewer. The sponsor herein submits a diskette in the format specified by the reviewer as a Bioequivalence Telephone Amendment.

Additionally, the reviewer asked the sponsor to specify the batch size of the lot used in the Bioequivalence study, lot 2159302. This lot was a full-scale commercial-size lot with a batch size of

If there are any questions regarding this submission, please contact Elaine Cibulka, Regulatory Affairs Manager, Schwarz Pharma, Inc., at 262-238-5225 (phone) or 262-238-0957 (fax).

Sincerely,

Elaine Cibulka

Steven R. Pollock
Vice President
Medical and Regulatory Affairs
SCHWARZ PHARMA, Inc., representing
Kremers Urban Development Company

RECEIVED
APR 15 2002
OGD / CDER
March 29, 2002

Food and Drug Administration
CDER, Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

Major Amendment 024 – Bioequivalence Sprinkle Study
Labeling Amendment 025 – Labeling Changes
Minor Amendment 026 – CMC Changes

Dear Sir/Madam:

Reference is made to above-listed ANDA 75-410. This application was tentatively approved on May 3, 2001. A copy of the tentative approval letter is included in this submission. Following tentative approval, the sponsor received letters from Office of Generic Drugs (OGD) dated November 8 and December 22, 2001, copies of which are also included in this submission. The letters advised the sponsor that an additional bioequivalence study would be required prior to approval and corresponding labeling changes would need to be made.

The sponsor herein submits results of an additional study demonstrating bioequivalence of the product to the reference listed drug (RLD) when sprinkled on applesauce. The study conducted was a four-period, two-treatment replicate design study as recommended in the January 2001 guidance “Statistical Approaches to Establishing Bioequivalence”. It may be noted that this study design differs from that recommended in the November 8, 2001 OGD letter. However, during a teleconference between the sponsor and OGD Division of Bioequivalence (BE) on November 14, 2001, a replicate design study was deemed acceptable by the BE Division.

In addition to the BE study, this submission contains revised Final Printed Labeling with changes mandated due to the addition of the sprinkle study information. The added verbiage mirrors the RLD labeling. Since the sponsor is seeking approval of only 10 and 20 mg drug products, these changes were discussed with the OGD Division of Labeling and Program Support in a telephone conference on January 7, 2002. The sponsor was instructed to incorporate all changes as written in the RLD labeling, even though some of the additional verbiage refers to a 40 mg product.
Finally, the May 3, 2001 tentative approval letter advised the applicant to submit any CMC changes due to scale-up of the process in a minor amendment prior to full approval. An amendment was submitted on December 7, 2001, with changes due to the scale-up of the manufacturing process. A deficiency letter dated February 1, 2002 was sent in response to A-023 with the only deficiency noted to be the absence of the BE sprinkle study and corresponding labeling changes. A copy of the letter is included in this submission. Since the submission of A-023, process validation has been completed at the manufacturing site. During validation, it was determined that

is included in this submission.

Since this submission consists of three separate amendments, separate desk copies of each amendment have been provided for the appropriate reviewer. This statement verifies that a full and complete copy of the CMC amendment, Amendment 026, has been sent to the Detroit District Office of the FDA. If there are any questions regarding this submission, please contact Elaine Cibulka, Regulatory Affairs Manager, Schwarz Pharma, Inc., at 262-238-5225 (phone) or 262-238-0957 (fax).

Sincerely,

Elaine Cibulka for

Steven R. Pollock
Vice President
Medical and Regulatory Affairs
SCHWARZ PHARMA, Inc., representing
Kremers Urban Development Company

APPEARS THIS WAY ON ORIGINAL
February 8, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE:  ANDA 75-410
Omeprazole Delayed Release Capsules, 10 mg and 20 mg

FORM FDA 356h for INTENT TO AMEND

Dear Document Control Room:

Enclosed please find Form FDA 356h for ANDA 75-410, Omeprazole Delayed Release Capsules, 10 mg and 20 mg. Please attach this form to the Intent to Amend letter that was submitted to the Agency on February 4, 2002.

If there are any questions or comments regarding this correspondence, please contact Elaine Cibulka, Manager Regulatory Affairs, Schwarz Pharma, Inc, at 262-238-5225 or by fax at 262-238-0957.

Sincerely,

Cherie Godin
Regulatory Affairs Associate
SCHWARZ PHARMA, Inc., representing
Kremers Urban Development Company
February 4, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD  20855-2773

RE:  ANDA 75-410
Omeprazole Delayed Release Capsules, 10 mg and 20 mg

INTENT TO AMEND

Dear Sir/Madam:

Reference is made to the Agency major deficiency letter dated February 1, 2002 regarding the above-referenced ANDA. Pursuant to 21 CFR §314.120, Kremers Urban Development Company hereby notifies the Agency of its intent to amend the application by providing a full response to all deficiencies listed in the letter.

If there are any questions or comments regarding this correspondence, please contact Elaine Cibulka, Manager Regulatory Affairs, Schwarz Pharma, Inc, at 262-238-5225 or by fax at 262-238-0957.

Sincerely,

Elaine Cibulka for

Steven R. Pollock, R. Ph.
Vice President
Medical and Regulatory Affairs
SCHWARZ PHARMA, Inc., representing
Kremers Urban Development Company
December 27, 2001

Mr. Gary Buehler, Director
Office of Generic Drugs (HFD-600)
CDER, Food and Drug Administration
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

General Information

Dear Mr. Buehler:

Reference is made to the above-listed ANDA and to a November 8, 2001 letter from the Office of Generic Drugs (OGD). The referenced letter notified the sponsor, Kremers Urban Development Co. (KUDCo), that the FDA is requiring an additional bioequivalence (BE) study (applesauce sprinkle study) to be submitted to this tentatively approved application. Reference is also made to teleconferences between OGD and Schwarz Pharma, Inc., representing KUDCo on November 8, 13 and 20, 2001 in which the merits and the goals of a BE - sprinkle study were discussed.

KUDCo understands that the Agency is adamant in requiring an additional BE study and is therefore moving forward to conduct a sprinkle study in an expeditious fashion. Furthermore, KUDCo has full confidence in the performance of its formulation. It is this very formulation that has already been demonstrated to be bioequivalent to the Reference Listed Drug (RLD) in two biostudies, both of which have been reviewed by the Agency. The adequacy of these studies is underscored by the fact that this application has been granted tentative approval by OGD.

Nevertheless, KUDCo would like to register its concern regarding the rationale behind OGD's BE sprinkle study requirement that is mandated at this time. According to the innovator's recently approved labeling, the RLD has been found to be bioequivalent when administered with and without applesauce in the 40 mg dosage form. The 20 mg dosage form, however, was not found to be bioequivalent. Further, the labeling states that the clinical relevance of the in-equivalence at the 20 mg dose is unknown, but provides no further advice regarding sprinkle use of 20 mg capsules. As you know, the KUDCo application doesn't include a 40 mg dose, only 10 mg and 20 mg.
The draft Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling states that the effect of food on the absorption and BA of a drug product should be described in the CLINICAL PHARMACOLOGY section of the labeling. In addition, the DOSAGE AND ADMINISTRATION section of the labeling should provide instructions for drug administration in relation to food based on clinical relevance (i.e., when co-administration with food results in safety or efficacy concerns, or when drug substance causes GI irritation when taken without food). This leads to two related concerns on the part of KUDCo.

First, the requirement for a sprinkle study for Omeprazole Delayed Release capsules at the 20 mg dose sets a precedent that will assuredly provide innovator firms with yet another effective means of delaying the approval of generic drug products. It appears that innovator firms will now be able to conduct numerous bioavailability studies with various foods and introduce this information into the CLINICAL PHARMACOLOGY section of the labeling without being required to describe or establish relevance of these differences in the DOSAGE AND ADMINISTRATION section. It is apparent that the Agency believes that information related to food-effect requires specific information in the labeling based on the recently published draft guidance. In spite of its proposed requirements, the Agency is currently requiring ANDA applicants to perform studies for which the relevance has not even been established. This position provides a pathway for innovator firms to submit essentially any bioavailability information related to sprinkling of the product and be assured of delaying generic approvals even if the innovator has failed to establish any relevance to the results of the study. KUDCo remains concerned that study/labeling requirements are therefore being applied inconsistently to innovator and generic firms.

Secondly, in the case of Omeprazole Delayed Release Capsules, there are no recommendations in the RLD DOSAGE AND ADMINISTRATION section related to administration of the 20 mg omeprazole capsules with applesauce. Thus, one can only conclude that the bioavailability of the innovator’s 20 mg product in applesauce is irrelevant. It is therefore confusing to KUDCO, whose application (ANDA 75-410) seeks approval of only 10 mg and 20 mg dosage forms, as to why OGD is requiring a BE sprinkle study at the 20 mg dosage level for an irrelevant finding. If such a study is required, KUDCo would agree that the study should demonstrate bioavailability when taken with applesauce. However with no evidence of clinical relevance, the application of the tight pharmacokinetic parameters associated with fasting pharmacokinetic trials (i.e., 80 to 125% for PK parameter confidence intervals) seems to be overly restrictive. Perhaps as a reasonable alternative, when the labeling of the RLD does not establish relevance, KUDCo would suggest that the PK parameters should at best meet the point estimate ranges (i.e., no more than a 20% difference in means).

In summary, it is KUDCo’s position that an additional BE sprinkle study should not be required for applications where the highest strength is not 40 mg. As stated earlier, KUDCo is moving forward with a study and is confident in the performance of its highly stable formulation. However, we remain unclear about the objectives or relevance of this study. Even though KUDCo is proceeding with plans to conduct the study, we reserve the right to further discuss the appropriate parameters and apparent contradictions with the Agency at a future date.
December 27, 2001
ANDA 75-410
Omeprazole Delayed-Release Capsules
Page 3 of 3

If there are any questions regarding this communication, please contact Steven R. Pollock, Vice President Medical and Regulatory Affairs, Schwarz Pharma, Inc., at 262-238-5206.

Sincerely,

[Signature]

Steven R. Pollock
Vice President
Medical and Regulatory Affairs
SCHWARZ PHARMA Inc., representing
Kremers Urban Development Company

Desk Copy to: Jim Morrison, Ombudsman
Victor Raczkowski, M.D., Acting Director, Div. of Gastrointestinal & Coagulation Drug Products
Gary Buehler, Director, Office of Generic Drugs
December 7, 2001

Food and Drug Administration
CDER, Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

Minor Amendment 023 – CMC

Dear Sir/Madam:

Reference is made to above-listed ANDA 75-410 and the tentative approval letter dated May 3, 2001, a copy of which is included in this submission. Per the instructions in the tentative approval letter and following a teleconference with Office of Generic Drugs (OGD) on October 10, 2001, Kremers Urban Development Co. (KUDCo) herein submits Minor Amendment 023 with updated CMC information. The submission contains updates to Chemistry, Manufacturing and Controls data that have occurred due to scale-up of the process, and updated stability through the 36-month timepoint.

A separate amendment with Final Printed Labeling (FPL) was submitted as Amendment 022 on October 18, 2001 and is under review at the Agency. Since that time, KUDCo has received a letter from Office of Generic Drugs stating that an additional Bioequivalence “sprinkle” study will need to be submitted to the application before final approval is granted. It is anticipated that FPL may need to be re-submitted upon completion of the study. KUDCo herein commits to submit any additional changes to FPL that may be required.

This statement verifies that a full and complete copy of this submission has been sent to the Detroit District Office of the FDA. If there are any questions regarding this submission, please contact Elaine Cibulka, Regulatory Affairs Manager, Schwarz Pharma, Inc., at 262-238-5225 (phone) or 262-238-0957 (fax).

Sincerely,

Elaine Cibulka

Steven R. Pollock, R. Ph.
Vice President
Medical and Regulatory Affairs
SCHWARZ PHARMA, Inc., representing
Kremers Urban Development Company
Kremers Urban Development Company
Attention: Steven R. Pollock
Schwarz Pharma Inc.
6140 W. Executive Drive, Suite D
Mequon, WI 53092

Reference Number: ANDA# 75-410

Dear Mr. Pollock:

This letter is in reference to your tentatively approved abbreviated new drug application dated July 2, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Omeprazole Delayed-release Capsules, 20 mg and 10 mg.

1. The Agency has approved labeling that incorporates recommendations for administration of the product sprinkled in applesauce for Prilosec® Delayed-release Capsules.

2. A study to demonstrate bioequivalence of your product to the reference listed drug (RLD) when sprinkled on applesauce should be submitted to obtain approval for your product. The recommended design is a two-treatment, two-period, two-sequence, crossover comparing your product with the RLD sprinkled on a spoonful of applesauce under fasting conditions using the highest strength to be submitted for approval.

If you have any questions, please call Krista M. Scardina, Pharm.D., Project Manager, Division of Bioequivalence at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

[Signature]

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Kremers Urban Development Company
Attention: Elaine Cibulka
6100 Executive Drive, Suite D
Mequon, WI 53092

Dear Ms. Cibulka:

Please refer to your abbreviated new drug application (ANDA) dated July 2, 1998, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Omeprazole Delayed-Release Capsules, 10 mg and 20 mg.

This letter is to inform you that the Agency has received two submissions from Astra Zeneca LP which raise issues related to the bioequivalence and chemistry of omeprazole. The cover letters of both submissions dated July 5, 2001, are enclosed. The issues raised in these letters are currently under consideration by the Agency.

If you have any questions, please call Ms. Cecelia Parise, R.Ph., Special Assistant for Regulatory Policy, at (301) 827-5845. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosures: Letter dated July 5, 2001, addressed to Lilia Talarico
Letter dated July 5, 2001, addressed to Gary Buehler
Redacted 2

pages of trade

secret and /or

confidential

commercial

information
May 2, 2001

Food and Drug Administration
CDER, Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE:  ANDA 75-410
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

FAX Amendment 021 – Patent Certifications and Notifications

Dear Sir/Madam:

Reference is made to teleconferences held on March 15, 2001 and March 21, 2001 between the sponsor and Office of Generic Drugs (OGD), during which OGD notified the sponsor of four new patents for which OGD requires the sponsor to certify against in connection with the above-listed ANDA.

Accordingly, Kremers Urban Development Company (KUDCo) herein submits Amendment 021 to provide Paragraph IV patent certifications to the following patents: 6,150,380; 6,147,103; 6,166,213; and 6,191,148. In addition, this amendment certifies that the required Notice of Certification was provided to AstraZeneca, holder of the NDA for Prilosec®, and to Astra Aktiebolag and Merck & Co., Inc., owners of the above-mentioned patents.

Copies of the Notices of Certification are included in this submission. Statements of the legal and factual basis of KUDCo’s position, the contents of which meet the requirements set forth in 21 CFR §314.95(c), accompanied the notices. Also included in this submission are copies of FedEx receipts demonstrating that the NDA and patent holders received the Notices. In accordance with the March 30, 2001 telephone conversation between OGD and the sponsor, the use of FedEx courier service was acceptable to OGD to provide notifications to the NDA and patent holders.

This amendment is being transmitted as a FAX Amendment with a hard copy to follow. If there are questions or comments regarding this submission, please contact Elaine Cibulka, Manager, Regulatory Affairs, Schwarz Pharma, Inc. at (262) 238-5225 or by fax at (262) 238-0957.

Sincerely,

[Signature]

Elaine Cibulka
Manager, Regulatory Affairs
Schwarz Pharma, Inc.

John Vaughan
Vice President
Kremers Urban Development Company
March 5, 2001

Food and Drug Administration
CDER, Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

Amendment 020 – Telephone Amendment

Dear Sir/Madam:

Reference is made to the teleconference held on March 2, 2001 between the sponsor and Office of Generic Drugs, during which the Agency requested revisions to the expression of dissolution limits in the specifications submitted to this application. KUDCO herein submits Amendment 020 with revised specifications for the 10 mg, 20 mg and intermediate product (microtablets) to express the dissolution limit in the manner indicated in the teleconference. This expression is also stated in a fax to the sponsor from the Bioequivalence Division, which was received by the sponsor on March 2, 2001. A copy of the fax is also included with this response for ease of reference.

The specifications herein provided have revised the wording for the dissolution limit of “165 minutes NLT → (Q)” to “NLT → (Q) in 45 minutes (buffer)”. This change has been made to the Action Limits and Stability Protocol of the Intermediate Specifications and the Initial Release Limits and Stability Protocols for the 10 mg and 20 mg drug products.

As requested in the teleconference, this amendment is being faxed as a Telephone Amendment with a hard copy to follow. This statement verifies that a full and complete copy of this submission has been sent to the Detroit District Office of the FDA. If there are additional questions or comments regarding this submission, please contact Elaine Cibulka, Manager, Regulatory Affairs, Schwarz Pharma, Inc. at (262) 238-5225 or by fax at (262) 238-0957.

Sincerely,

Elaine Cibulka for

John Vaughan
Vice President
Kremers Urban Development Company
February 8, 2001

Food and Drug Administration
CDER, Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

Amendment 019 – Fax Amendment

Dear Sir/Madam:

Reference is made to the telephone conversation on February 8, 2001 wherein the Agency requested information regarding the lawsuits involving the above-referenced ANDA.

This amendment herein provides patent litigation information for both the 10 mg and 20 mg drug products. As instructed by the Agency, this amendment is being faxed with a hard copy to follow.

Attachment 1: Summons (Case Number 99-C-0131) dated February 11, 1999 received by KUDCO for the 20 mg product. The summons may also be referenced in Amendment 004 submitted on February 12, 1999.

Attachment 2: Summons (Case Number 99-C-0910) dated August 12, 1999 received by KUDCO for the 10 mg product.

Attachment 3: Consolidated Discovery: Multidistrict Litigation (Docket No. 1291).

If there are any questions or comments regarding this submission, please contact Elaine Cibulka, Manager, Regulatory Affairs, Schwarz Pharma, Inc. at 262-238-5225 or by fax at 262-238-0957.

Sincerely,

[Signature]

John Vaughan
Vice President
Kremers Urban Development Company
December 12, 2000

Food and Drug Administration
CDER, Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE:  ANDA 75-410
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

Amendment 018 – Major Amendment
CMC Response to Deficiency Letter

Dear Sir/Madam:

Reference is made to the Major Deficiency letter dated July 14, 2000 to the above-referenced ANDA. KUDCO herein submits Amendment 018 to provide a full and complete response to all CMC deficiencies in the 7/14/00 letter. For ease of review, a copy of the Agency letter is also included, with Agency questions printed in bold followed by KUDCO’s response.

Following receipt of this letter, teleconferences were held between the sponsor and the Agency on July 26, August 1, and August 28, 2000. As discussed during those teleconferences, the sponsor has revised the assay and impurities methodology for ANDA 75-410 to mirror the proposed method published in the Pharmacopeial Forum, Volume 25, No. 6. Therefore, this submission also contains a Method Validation package for the drug product assay and impurities/degradants analytical method. Two additional copies of the Methods Validation volume are provided with this submission.

The sponsor has taken all Agency comments contained in the letter and communicated in the teleconferences into consideration during development of the new methodology proposed in this submission. It is anticipated that this response and the proposed methodology meet with Agency approval and satisfactorily address all Agency concerns. If there are additional questions or comments regarding this submission, please contact Elaine Cibulka, Manager, Regulatory Affairs, Schwarz Pharma, Inc. at (262) 238-5225 or by fax at (262) 238-0957. Any Agency comments will receive immediate and full attention.

This statement will verify that a full and complete copy of this submission has been provided to the Detroit District Office of the FDA.

Sincerely,

Elaine Cibulka

John Vaughan
Vice President
Kremers Urban Development Company
November 30, 2000

Food and Drug Administration
CDER, Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

Amendment 017 – Final Printed Labeling

Dear Sir/Madam:

Reference is made to the labeling deficiency letter dated August 7, 2000 to the above-referenced ANDA. KUDCO herein submits Amendment 017 to provide revised labeling incorporating the changes requested in the 8/7/00 letter. For ease of review, a copy of the Agency letter is also included in this submission.

Enclosed herein are side-by-side comparisons of the labeling, as well as 12 copies of Final Printed Labeling. The labeling consists of container labels for bottles of 30 and bottles of 100 of both the 10 mg and 20 mg tablets, as well as a package insert. One copy of each is provided in the archival copy and 11 additional copies are provided in the review copy of this submission.

Also pending on this application is a Major Deficiency letter dated July 14, 2000 containing CMC deficiencies. A full and complete response to this letter will be provided to the Agency at a later date.

If there are any questions regarding this submission, please contact Elaine Cibulka, Manager, Regulatory Affairs, Schwarz Pharma, Inc. at (262) 238-5225 or by fax at (262) 238-0957.

Sincerely,

Elaine Cibulka

John Vaughan
Vice President
Kremers Urban Development Company
KREMER'S URBAN
DEVELOPMENT COMPANY

September 14, 2000

Food and Drug Administration
CDER, Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP

RE: ANDA 75-410 Omeprazole Delayed Release Capsules, 10 mg and 20 mg

GENERAL INFORMATION

Dear Sir/Madam:

The above-referenced ANDA was received by the Agency on July 6, 1998. ANDA 75-410 contains a Paragraph III certification for patent 4,255,431, which expires April 5, 2001, and Paragraph IV certifications for patents 4,636,499, expiring May 30, 2005, and 4,853,230 and 4,786,505, which both expire April 20, 2007. The remaining patents associated with the reference listed drug, Prilosec®, are for indications not being sought in ANDA 75-410 submitted by Kremers Urban Development Company (KUDCO).

Specifically, these patents are for the use of omeprazole as an antimicrobial agent (patent 5,093,342) and the use of omeprazole when combined with an acid degradable antibiotic (patents 5,599,794 and 5,629,305). Accordingly, it is KUDCO's request that upon approval of ANDA 75-410, this situation be noted in the "Orange Book" in the section entitled 1.8 Description of Special Situations in the Preface. KUDCO feels this notation would be justified, as it is stated on page xv of 20th Edition of the "Orange Book" that:

...in rare instances, there may be variations among therapeutically equivalent products in their use or in conditions of administration. Such differences may be due to patent or exclusivity rights associated with such use. When such variations may, in the Agency's opinion, affect prescribing or substitution decisions by health professionals, a note will be added to Section 1.8.

It is felt that the situation described above is a variation that would affect prescribing or substitution decisions by health care professionals due to possible infringement of patents 5,093,342, 5,599,794 and 5,629,305 and as such, warrants mention in Section 1.8.

If there are any questions regarding this correspondence, please contact Elaine Cibulka, Manager, Regulatory Affairs, Schwarz Pharma, Inc. at (262) 238-5225 or by fax at (262) 238-0957.

Sincerely,

Elaine Cibulka

John Vaughan
Vice President
Kremers Urban Development Company
September 14, 2000

Food and Drug Administration
CDER, Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed Release Capsules, 10 mg and 20 mg

Amendment 016 – CMC Information

Dear Sir/Madam:

KUDCO herein submits Amendment 016 to the above-referenced ANDA to provide additional information to the application regarding two inactive that are used in the formulation of the drug product. The documents included herein tighten the specifications for Hydroxypropyl Methylcellulose USP, to reflect and Crosovidone NF to reflect a

A major deficiency letter dated July 14, 2000 was received for this application. This amendment is not submitted as a response to the deficiency letter, but as a revision to existing information under 21 CFR § 314.96. A full and complete response to the deficiency letter will be submitted at a future date.

This statement will verify that a full and complete copy of this submission has been provided to the Detroit District Office of the FDA. If there are any questions regarding this submission, please contact Elaine Cibulka, Manager, Regulatory Affairs, Schwarz Pharma, Inc. at (262) 238-5225 or by fax at (262) 238-0957.

Sincerely,

Elaine Cibulka
Vice President
Kremers Urban Development Company
July 13, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD  20855-2773

RE:    ANDA 75-410
Omeprazole Delayed Release Capsules, 10 mg and 20 mg

BIOEQUIVALENCY TELEPHONE AMENDMENT 015

Dear Sir/Madam:

Reference is made to the teleconference on June 29, 2000 between Office of Generic Drugs Bioequivalency Division (BE) and Schwarz Pharma, Inc. representing the Kremers Urban Development Company (KUDCO). In that teleconference, the Agency requested KUDCO repeat acid resistance and dissolution testing for the 10 mg and 20 mg test and reference drug products and submit results to the Agency within ten working days. Reference is also made to the teleconference on June 30, 2000, in which it was explained that the sponsor did not have enough of the 20 mg reference drug product to perform repeat testing on the same lot that was tested previously. It was agreed that testing of a different lot of the 20 mg reference product would be acceptable.

This amendment herein provides the repeated acid resistance test results for both the 10 mg and 20 mg test and reference drug products. Results are supplied in tabular form with range, mean and %RSD noted. In addition, dissolution testing has been repeated and results are herein provided. Since the lot of the 20 mg reference drug product is not the same lot that was tested for previous submissions, the assay value of this new lot is also provided. As instructed by the Agency, this amendment is being faxed as a Telephone Amendment with a hard copy to follow.

This statement will verify that a full and complete copy of this submission has been provided to the Detroit District Office of the FDA. If there are any questions or comments regarding this submission, please contact Elaine Cibulka, Manager Regulatory Affairs, Schwarz Pharma, Inc, at 262-238-5225 or by fax at 262-238-0957.

Sincerely,

Elaine Cibulka for

John Vaughan
Vice President
Kremers Urban Development Company
June 23, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed Release Capsules, 10 mg and 20 mg

Amendment 001 to AMENDMENT 012 (dated February 8, 2000)

Dear Sir/Madam:

Reference is made to Amendment 012 to the above-mentioned ANDA, submitted February 8, 2000 in response to a Major Deficiency letter dated December 9, 1999. In A-012, Kremers Urban Development Company (KUDCO) provided revisions to assay methodology in response to a point in the deficiency letter, with a commitment to provide Methods Validation upon completion. It is assumed that, at this point in time, A-012 may have been assigned for review. To fulfill the commitment made in the February 8 submission and to provide for the most productive use of the Agency’s review time, KUDCO herein submits a Methods Validation package for the revised methodology for Omeprazole Delayed-Release Capsules, 10 and 20 mg.

During this methods validation process, it was found that a few minor changes were required to the methods submitted in A-012. For ease of review, provided in this submission is a summary of these changes and a table comparing the methods submitted in A-012 to the revised methods. A copy of the revised methodology is also provided in this submission. It is the opinion of KUDCO that the revised methodology provides increased assurance for the identity, strength, quality, purity and potency of the drug product.

Revisions to the methods necessitated updates to the product specifications to simply note the new version number of the methods. Therefore, included in this submission is a complete set of product specifications for the intermediate product (microtablets) as well as both strengths of the finished drug product. The documents submitted herein replace the specifications and methods submitted in A-012. As stated above, it is felt that this timely submission of these documents will coincide with the initiation of the Chemistry review of A-012, fulfilling our commitment to provide updated methods validation and at the same time provide the Chemistry review the final version of the CMC documents.
This statement will verify that a full and complete copy of this submission has been provided to the Detroit District Office of the FDA. If there are any questions or comments regarding this submission, please contact Elaine Cibulka, Manager Regulatory Affairs, Schwarz Pharma, Inc, at 262-238-5225 or by fax at 262-238-0957.

Sincerely,

Elaine Cibulka for

John Vaughan
Vice President
Kremers Urban Development Company
June 2, 2000

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Generic Drugs (HFD-600)  
Metro Park North II  
Document Control Room 150  
7500 Standish Place  
Rockville, MD 20855-2773

RE: ANDA 75-410  
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

BIOEQUIVALENCE TELEPHONE AMENDMENT

Dear Sir/Madam:

Reference is made to the teleconference on May 25, 2000 between Office of Generic Drugs  
Bioequivalence Division and Schwarz Pharma, Inc. representing the Kremers Urban Development Company (KUDCO). In that teleconference, the Agency requested KUDCO  
supply additional acid resistance and dissolution test results for the 10 mg test and reference drug products.

This amendment herein provides the dissolution profile that was submitted in Amendment 009 on  
July 1, 1999, for the 10 mg test and reference drug products. In addition, this amendment  
provides acid resistance test results for both the 10 mg test and reference drug products. The acid  
resistance test method was submitted in Amendment 013 on May 12, 2000. As instructed by the  
Agency, this amendment is being faxed as a Telephone Amendment with a hard copy to follow.

This statement will verify that a full and complete copy of this submission has been provided to  
the Detroit District Office of the FDA. If there are any questions or comments regarding this  
submission, please contact Elaine Cibulka, Manager Regulatory Affairs, Schwarz Pharma, Inc, at  
262-238-5225 or by fax at 262-238-0957.

Sincerely,

Elaine Cibulka for

John Vaughan  
Vice President  
Kremers Urban Development Company

RECD  
JUN 05 2000  
OGD
May 12, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD  20855-2773

RE:  ANDA 75-410
Omeprazole Delayed Release Capsules, 10 mg and 20 mg

Amendment 013: BIOEQUIVALENCY AMENDMENT
Response to Deficiency Letter

Dear Sir/Madam:

Reference is made to the Bioequivalency Deficiency Letter dated November 19, 1999 for the above-mentioned ANDA. Kremers Urban Development Company (KUDCO) herein provides a full and complete response to the referenced letter.

Reference is also made to the teleconference held between Office of Generic Drugs Bioequivalence Division and KUDCO representatives on April 18, 2000. In response to Agency comments during the teleconference, and in response to the above-mentioned letter, KUDCO herein provides additional information on acid resistance testing conducted at Schwarz Pharma Manufacturing, Inc, the proposed analytical testing laboratory for this product.

This statement will verify that a full and complete copy of this submission has been provided to the Detroit District Office of the FDA. If there are any questions or comments regarding this submission, please contact Elaine Cibulka, Manager Regulatory Affairs, Schwarz Pharma, Inc, at 262-238-5225 or by fax at 262-238-0957.

Sincerely,

Elaine Cibulka for

John Vaughan
Vice President
Kremers Urban Development Company
February 8, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed Release Capsules, 10 mg and 20 mg

Amendment 012: MAJOR AMENDMENT
CMC and Labeling Response to Not-Approvable Letter

Dear Sir/Madam:

Reference is made to a Major Deficiency letter dated December 9, 1999, in regard to Kremers Urban Development Company’s (KUDCO) Amendments 007 and 009, dated June 3 and July 1, 1999, respectively.

KUDCO herein submits a full and complete response to all items listed in the deficiency letter. To assist in the review of this submission, all Agency comments are reprinted in full and in bold type, with the sponsor’s point-by-point responses following. For additional reference, a copy of the Agency’s Major Deficiency letter, dated December 9, 1999, is included.

This statement will verify that a full and complete copy of this submission has been provided to the Detroit District Office of the FDA. If there are any questions regarding this submission, please contact Eric B. Foster, Manager, Regulatory Affairs, Schwarz Pharma, Inc. at (262) 238-5223 or by fax at (262) 238-0957.

Sincerely,

[Signature]
John Vaughan
Vice President
Kremers Urban Development Company
December 13, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 10 mg and 20 mg

General Correspondence

Dear Sir/Madam:

Reference is made to the Office of Generic Drugs (OGD) faxed deficiency letter dated December 9, 1999 and received by Kremers Urban Development Company (KUDCO) on that same day, regarding the above mentioned application. Pursuant to 21 CFR § 314.120, KUDCO notifies OGD of its intent to amend the application to address all the noted deficiencies.

If there are any questions regarding this correspondence, please contact Eric B. Foster, Manager, Regulatory Affairs, at (262) 238-5223.

Sincerely,

John Vaughan
Vice President
Kremers Urban Development Company
November 22, 1999

Food and Drug Administration
Office of Drug Evaluation and Research
Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 20 mg

General Correspondence

Dear Sir/Madam:

Reference is made to the Office of Generic Drugs (OGD) faxed deficiency letter dated November 19, 1999 and received by Kremers Urban Development Company (KUDCO) on that same day, regarding the above mentioned application. Pursuant to 21 CFR § 314.120, KUDCO notifies OGD of its intent to amend the application to address all the noted deficiencies.

If there are any questions regarding this correspondence, please contact Eric B. Foster, Manager, Regulatory Affairs, at (262) 238-5223.

Sincerely,

John Vaughan
Vice President
Kremers Urban Development Company
September 16, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs (HFD-600)
Metro Park North II
Document Control Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 20 mg

Amendment 011 -Bioequivalency Amendment

Dear Sir/Madam:

Reference is made to ANDA 75-410, submitted July 2, 1998, and to Bioequivalency Amendment 008 submitted on June 4, 1999. Further reference is made to the Agency’s faxed Bioequivalency Deficiency letter dated August 16, 1999. Pursuant to 21 CFR § 314.96, Kremers Urban Development Company (KUDCO) herein submits Amendment 011 to provide a full and complete response to all items in the August 16 Deficiency letter. This submission contains revised dissolution data in answer to the points raised by the Agency.

A copy of the Agency's August 16, 1999 letter is also provided in this submission.

If there are any questions or comments, please contact Eric B. Foster, at (414) 238-5223 (phone) or (414) 238-0957 (fax).

Sincerely,

Eric B. Foster

John Vaughan
Vice President
Kremers Urban Development Company
July 21, 1999

Douglas Sporn, Director
Office of Generic Drugs
Document Control Room 150
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410 Omeprazole Delayed-Release Capsules, 20 and 10 mg
Amendment 010 - Patent Certification of 10 mg Strength Capsule

Dear Mr. Sporn:

Reference is made to the above-referenced ANDA submitted to the agency on July 2, 1998 and to Amendment 009 submitted on July 1, 1999 which amended the application to include a 10 mg capsule. In accordance with 21 CFR § 314.95 (b), Kremers Urban Development Company (KUDCO) is submitting this amendment to certify that the required notice of certification was provided to Astra Merck, Inc., the sponsor of NDA 19-810, for Prilosec®, the reference listed drug product and to Astra Hässle AB, the owner of U.S. patents No. 4,786,505, 4,853,230, and 4,636,499. Furthermore, the content of the notice met the requirements established in CFR § 314.95 (c). The certification letters were originally sent to Astra Merck, Inc. and Astra Hässle AB on July 1, 1999, the same day that KUDCO submitted Amendment 009 to this application adding the 10 mg omeprazole capsule to the application.

Enclosed are copies of the notice of certification without the attachment sent to Astra Merck, Inc. and Astra Hässle AB. The attachment consisted of the statement of the factual and legal basis of KUDCO's opinion. Along with the certification is a copy of the mailing label and return receipt verifying that delivery was received through the US Postal Service.

If there are any questions, please contact Eric B. Foster, Manager, Regulatory Affairs, at (414) 238-5223 (phone) or (414) 238-0957 (fax).

Sincerely,

John Vaughan
Vice President
Kremers Urban Development Company
July 1, 1999

Douglas Sporn, Director
Office of Generic Drugs
Document Control Room 150
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

ANDA 75-410 Omeprazole Delayed-Release Capsules, 20 mg
Amendment 009 - Addition of 10 mg Strength Capsule

Dear Mr. Sporn:

Reference is made to the above-referenced ANDA submitted to the agency on July 2, 1998 and currently under review at the Agency.

Additional reference is made to our June 3 and June 4, 1999 submissions, wherein Kremers Urban Development Company (KUDCO) submitted Amendments 007 and 008. Amendment 007 responded to chemistry, manufacturing, and control and labeling deficiencies noted in Agency correspondence dated December 11, 1999. Amendment 008 responded to bioequivalence deficiencies noted in Agency correspondence dated November 3, 1998.

KUDCO herein amends the above application to include 10 mg strength of the drug product in addition to the previously submitted 20 mg strength. The reference listed drug, Prilosec® Delayed-Release Capsules, Astra Merck, Inc., NDA 19-810 is available in 10 mg, 20 mg, and 40 mg strengths. The proposed expiration date will be 24 months.

This submission consists of two (2) volumes. A request for a waiver for conducting bioequivalence studies is made in Section VI of the application since the 10 mg strength is dose proportional to the 20 mg strength.

Please note the following corporate relationships. The applicant, Kremers Urban Development Company (KUDCO) of Mequon, Wisconsin, is a wholly-owned subsidiary of Schwarz Pharma, Inc. of Milwaukee, Wisconsin. The distributor of the product, Kremers Urban, is the generic sales and marketing division of Schwarz Pharma, Inc. Schwarz Pharma, Inc. and Schwarz Pharma Manufacturing Inc. of Seymour, Indiana are affiliated companies owned by a common parent company.
The applicant hereby certifies that a true and complete copy of the entire application has been sent to the Minneapolis District Office. If there are any questions, please contact Eric B. Foster, Manager, Regulatory Affairs, at (414) 238-5223 (phone) or (414) 238-0957 (fax).

Sincerely,

[Signature]

John Vaughn
Vice President
Kremers Urban Development Company
June 4, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 75-410
Omeprazole Delayed-Release Capsules, 20 mg

Bioequivalency Amendment 008 - Response to Deficiency Letter

Dear Mr. Sporn:

Reference is made to ANDA 75-410, submitted July 2, 1998, and to the Bioequivalency Deficiency letter dated November 3, 1998. Pursuant to 21 CFR § 314.96, Kremers Urban Development Company (KUDCO) hereby submits Amendment 008 to provide a full and complete point-by-point response to all items in the Deficiency letter. This submission contains revised dissolution methodology and a dissolution profile demonstrating the equivalency of the applicant's proposed method to the method recommended by the agency. The applicant also would like to acknowledge the Agency letter dated May 10, 1999 from the Division of Bioequivalence, which stated that there were no further questions from the Division at this time.

A Not Approvable letter dated December 11, 1998 containing CMC and Labeling deficiencies has been answered by the applicant in a separate submission, Amendment 007 dated June 3, 1999. If there are any questions or comments, please feel free to contact Eric Foster at 414-238-9994 (phone) or 414-238-0957 (fax).

Sincerely,

[Signature]

John Vaughan
Vice President
Kremers Urban Development Company
December 29, 1998

Kremers Urban Development Company

DOUGLAS SPORN, DIRECTOR
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 20 mg

Amendment 003: Clinical Trial Report of Single-Dose Fed Study

Dear Mr. Sporn:

Reference is made to our July 2, 1998, submission of an original Abbreviated New Drug Application (ANDA) for a 20 mg Omeprazole Delayed-Release capsule that is bioequivalent to Prilosec® Delayed-Release Capsules, NDA 19-810. Shortly before the ANDA was submitted, Kremers Urban Development Company (KUDCO) discovered that an additional fed bioequivalence study was required. Since the change in requirement was not published and KUDCO’s last contact with the agency was for only a fasted study, KUDCO appealed to the Agency to be allowed to submit the ANDA with the understanding that the fed study would be conducted as soon as possible and the results submitted as soon as they became available.

Additional reference is made to the teleconference between KUDCO and the Agency on June 24 and 25, 1998, as well as our letter to Gordon Johnson, Deputy Director of the Office of Generic Drugs, dated June 26, 1998, which documents this issue.

Submitted herewith is Amendment 003 to our pending ANDA 75-410 which contains the final Clinical Trial Report, entitled, “A Pharmacokinetic Study to Assess the Effects of Food on the Single Dose Bioavailability of a 20 mg Formulation of SPUS 830 and a Reference Product.”

KUDCO will also notify the application holder and listed patent holders, now that our application is complete.

If there are any questions with this submission, please contact Eric B. Foster, Regulatory Affairs Manager at (414) 238-5718 or via facsimile at (414) 238-0957.

Sincerely,

Donna Bischak
Vice President
Kremers Urban Development Company

RECEIVED
DEC 30 1998
December 15, 1998

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 20 mg

General Correspondence

Dear Mr. Sporn:

Reference is made to the Office of Generic Drugs (OGD) faxed letter, dated December 11, 1998, which lists chemistry, manufacturing, and controls and labeling deficiencies. Pursuant to 21 § 314.120 (a) (1), Kremers Urban Development Company hereby notifies OGD of its intent to amend the application to address all noted deficiencies.

If there are any questions regarding this correspondence, please contact Eric B. Foster, Manager of Regulatory Affairs, at (414) 238-5718 or via facsimile at (414) 238-0957.

Best regards,

Jonathan A. Thiel
Vice President
Kremers Urban Development Company
November 9, 1998

Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 20 mg

Bioequivalence Deficiency Letter

Dear Mr. Sporn:

Reference is made to the Office of Generic Drugs (OGD) faxed letter of bioequivalence deficiencies, dated November 3, 1998 and received by Kremers Urban Development Company (KUDCO) on the same day. Pursuant to 21 CFR § 314.120 (a)(1), KUDCO hereby notifies OGD of its intent to amend the application to address the noted deficiencies.

If there are any questions regarding this correspondence, please contact Eric B. Foster, Regulatory Affairs Manager, at (414) 238-5718.

Sincerely,

[Signature]

Jonathan A. Thiel
Vice President
Kremers Urban Development Company
October 6, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 20 mg
Fax Amendment 002 to Original Submission

Dear Mr. Sporn:

Reference is made to the above ANDA submitted July 2, 1998 and to a phone conversation on October 6, 1998, between Lizzie Sanchez, Regulatory Project Manager, OGD, and Donna Multhauf, Associate Director of Regulatory Affairs, Schwarz Pharma Inc. (SPInc). Ms. Sanchez called for potency data on the reference listed drug, Prilosec®.

Kremers Urban Development Company (KUDCO) amends the above application to include potency data for Prilosec® lot E2621, which is the lot used in the bioequivalence study. The results for the requested time points are given in Attachment 1.

This amendment is being sent as a fax amendment as agreed upon by Ms Sanchez and KUDCO. A hard copy will follow.

If there are any questions regarding this correspondence, please contact Donna Multhauf, Associate Director of Regulatory Affairs (SPInc) at (414) 238-5473.

Sincerely,

Jonathan A. Thiel
Vice President
Kremers Urban Development Company

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 20 mg
Fax Amendment 002 to Original Submission

Dear Mr. Sporn:

Reference is made to the above ANDA submitted July 2, 1998 and to a phone conversation on October 6, 1998, between Lizzie Sanchez, Regulatory Project Manager, OGD, and Donna Multhauf, Associate Director of Regulatory Affairs, Schwarz Pharma Inc. (SPInc). Ms. Sanchez called for potency data on the reference listed drug, Prilosec®.

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If there are any questions regarding this correspondence, please contact Donna Multhauf, Associate Director of Regulatory Affairs (SPInc) at (414) 238-5473.

Sincerely,

Jonathan A. Thiel
Vice President
Kremers Urban Development Company
Kremers Urban Development Company  
Attention: Johnathan A. Thiel  
6140 W. Executive Drive  
Mequon, WI 53092  

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated July 28, 1998 and your faxed correspondence dated August 4, 1998.

NAME OF DRUG: Omeprazole Delayed-release Capsules, 20 mg

DATE OF APPLICATION: July 2, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 6, 1998

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(I)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

**CONTENTS OF THE NOTICE**

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

**SENDING THE NOTICE**

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:
1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.
You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Peter Rickman, Chief, Regulatory Support Branch, at (301) 827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-410
DUP/Jacket
Field Copy
HFD-600/Reading File
HFD-610/J. Phillips
HFD-92
HFD-615/M. Bennett

Endorsement: HFD-615/PRickman, Chief date 8/7/58
HFD-615, NMahmud, CSO date 8/6/98
HFD-645, BArnwine, Súp. Chem. date
WP File x:\new\firms\sam\kremers\ltrs&rev\75410.ack
FT/mj1/8/6/98
ANDA Acknowledgment Letter!
August 4, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 75-410
Omeprazole Delayed-Release Capsules, 20 mg

Amendment 001 to Original Submission

Dear Mr. Sporn:

Reference is made to the above ANDA submitted July 2, 1998 and to a phone conversation on July 28, 1998 between Nasser Mahmud, Regulatory Project Manager, OGD, and Donna Multhauf, Associate Director of Regulatory Affairs, Schwarz Pharma, Inc. (SPInc).

The outcome of the telephone conversation was that Mr. Mahmud had two issues with the application. The issues were.

1. Patent 4,636,499 must have either a Paragraph III or Paragraph IV certification.

2. A side-by-side comparison of the container label from the reference drug with the proposed label for the applicant’s product.

Kremers Urban Development Company (KUDCO) amends the above application in response to the two issues. Included in this submission is a Paragraph IV certification for Patent 4,636,499 (see Attachment 1). Also included are side-by-side comparisons between a Prilosec® bottle label and the proposed labels for KUDCO's omeprazole product (see Attachment 2). Note that Prilosec® 20 mg capsules are not available in a 100 capsules bottle, therefore, the side-by-side comparison between KUDCO's proposed labels for both bottles of 100 and 30 capsules use the label from a Prilosec® bottle of 30 capsules for comparison.

If there are any questions regarding this correspondence, please contact Donna Multhauf, Associate Director of Regulatory Affairs (SPInc) at (414) 238-5473.

Sincerely,

[Signature]

Jonna A. Thiel
Vice President
Kremers Urban Development Company
July 2, 1998

Mr. Douglas Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD  20855

Re:  Abbreviated New Drug Application
Omeprazole Delayed-Release Capsules, 20 mg

Original Submission

Dear Mr. Sporn:

Pursuant to 21 CFR § 314.94 Kremers Urban Development Company (KUDCO) hereby submits an original Abbreviated New Drug Application (ANDA) for a 20 mg Omeprazole Delayed-Release capsule that is bioequivalent to the reference listed drug, Prilosec® Delayed-Release Capsules, Astra Merck, Inc., NDA 19-810.

This submission consists of six (6) volumes. Included in this submission is an archival copy (in blue folders) of the ANDA that contains all the required information and a technical review copy (in red folders) which contains all the information in the archival copy with the exception of the Bioequivalence section (VI). A separate copy of the Bioequivalence section is provided in an orange folder. Please note that Volume 2 contains two diskettes in ASCII format with pharmacokinetic data and model codes used in the statistical analysis of the bioequivalence study.

The bioequivalence study submitted in this application was conducted to evaluate Omeprazole Delayed-Release Capsules, 20 mg in comparison with the reference listed drug, Prilosec Delayed-Release Capsules, 20 mg in the fasted state. The applicant is aware that the current reference standard for omeprazole is the 40 mg capsule; however, at the time the biostudy was conducted, the 20 mg dosage form was the highest dosage available to industry. Prilosec 40 mg capsule was not approved until January 15, 1998. In a telephone conference with OGD Division of Bioequivalence on June 24, 1998, it was confirmed by the applicant that under these circumstances, use of the 20 mg capsule as the reference standard is acceptable.

It should be noted that this application was prepared after conferring with OGD Bioequivalence Division on August 18, 1996. In that telephone conference, it was communicated to the applicant that one single-dose fasting study was the only bioequivalency study required to submit a reviewable ANDA. Based on this information, the applicant proceeded to conduct one single-dose fasting study to demonstrate bioequivalency to the reference listed drug.

It has come to the attention of the applicant that bioequivalence requirements have since been revised to include a single-dose fed study. Reference is made to telephone conversations on June 24 and 25, 1998 among the applicant, outside regulatory consultant Mr. David Rosen, and OGD, wherein bioequivalence and filing requirements were discussed. Reference is also made to
Abbreviated New Drug Application
Omeprazole Delayed-Release Capsules, 20 mg
July 2, 1998

correspondence dated June 25, 1998, a copy of which follows this letter for ease of review. In
the above-mentioned correspondence, the applicant presented to OGD the chronology of events
in the development of this ANDA. Finally, reference is made to a telephone conference between
Mr. David Rosen (on behalf of the applicant) and Mr. Gordon Johnston, Deputy Director, OGD,
in which agreement was reached whereby this application would be acceptable with the
completed study as well as a commitment to conduct a single-dose fed study as soon as possible.
KUDCO hereby commits to conduct such a bio study and has made preliminary plans to begin
this study within the next 45 days. The application will be amended as soon as study results are
available. KUDCO appreciates this consideration from the agency.

During development of this ANDA, the applicant noted two statements in the current labeling of
the reference listed drug that appear to be inconsistent. These statements are presented in
Section V, Labeling, and the applicant seeks agency guidance to resolve the apparent
discrepancy.

Please note the following corporate relationships. The applicant, Kremers Urban Development
Company of Mequon, Wisconsin, is a wholly-owned subsidiary of Schwarz Pharma, Inc. of
Milwaukee, Wisconsin. The distributor of the product, Kremers Urban, is the generic sales and
marketing division of Schwarz Pharma, Inc. Schwarz Pharma, Inc. and Schwarz Pharma
Manufacturing, Inc. of Seymour, Indiana are affiliated companies owned by a common parent.

The applicant hereby certifies that a true and complete copy of the technical sections of this
application has been sent to the Minneapolis District Office. If there are any questions, please
feel free to contact Donna Multhauf at 414-238-5473 (phone) or 414-238-0957 (fax).

Sincerely,

[Signature]
Jonathan A. Thiel
Vice President
Kremers Urban Development Company