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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-410

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-410

APPROVAL LETTER

ANDA 75-410 NOV 1 2002

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 [redacted] (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 [redacted] 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 11/1/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-410

TENTATIVE APPROVAL LETTER

ANDA 75-410

OCT 4 2002

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 statuatory 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,

/S/

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

10/4/02

ANDA 75-410

MAY 3 2001

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.

The listed drug product referenced in your application, Prilosec Delayed-release Capsules of AstraZeneca LP, is subject to periods of patent protection which expire on May 30, 2005, (U.S. Patent No. 4,636,499; April 20, 2007, (U.S. Patent Nos. 4,786,505 and 4,853,230); February 2, 2010, (U.S. Patent No. 5,093,342); February 4,2014, (U.S. Patent Nos. 5,599,794 and 5,629,305); October 9, 2018, (U.S. Patent Nos. 6,147,103, 6,166,213, and 6,191,148) and November 10, 2018, (U.S. Patent

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,

/S/

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:

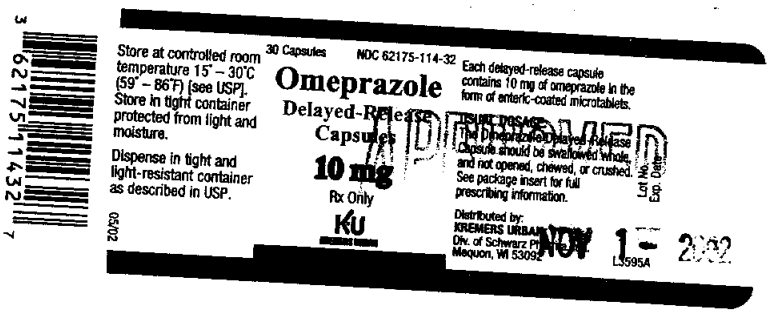
75-410

Final Printed Labeling

ANDA 75-410
KREMERS URBAN DEVELOPMENT COMPANY

Omeprazole Delayed-Release Capsules, 10 mg

Final Printed Labeling
Bottle Label - 30's

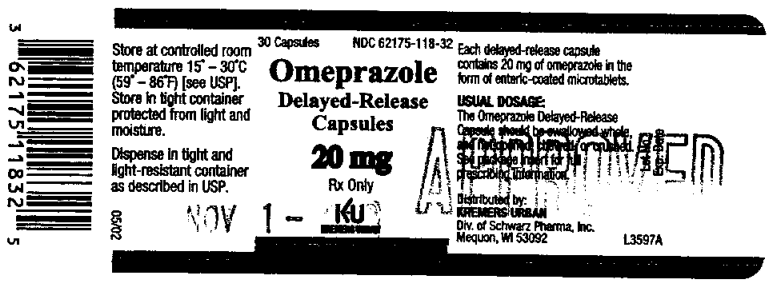


L3595A

ANDA 75-410
KREMERS URBAN DEVELOPMENT COMPANY

Omeprazole Delayed-Release Capsules, 20 mg

Final Printed Labeling
Bottle Label - 30's



L3597A

Omeprazole

Delayed-Release Capsules

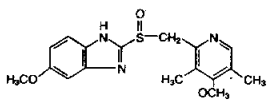
PC3599D

℞ Only

07/02

DESCRIPTION

The active ingredient in Omeprazole Delayed-Release Capsules is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42. The structural formula is:



Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155° C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and 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.

Each delayed-release capsule, for oral administration, contains either 10 mg or 20 mg of omeprazole in the form of enteric-coated microtablets. In addition, each capsule contains the following inactive ingredients: crospovidone, glyceryl behenate, hypromellose, lactose monohydrate, methacrylic acid copolymer dispersion, silicon dioxide, talc, titanium dioxide and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, titanium dioxide, sodium lauryl sulfate, synthetic black iron oxide, pharmaceutical glaze, and may contain ethylene glycol monoethyl ether, lecithin and simethicone; or propylene glycol, ammonium hydroxide and dimethylpolysiloxane. In addition, the 20 mg capsule shells also contain yellow iron oxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism Omeprazole Delayed-Release Capsules contain an enteric-coated microtablet formulation of omeprazole (because omeprazole is acid-labile), so that absorption of omeprazole begins only after the microtablets 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 of Omeprazole Delayed-Release Capsules.

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. Two were identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma — the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

In patients with chronic hepatic disease, the bioavailability increased to approximately 100% compared to an I.V. dose, reflecting decreased first-pass effect, and the plasma half-life of the drug increased to nearly 3 hours compared to the half-life in normals of 0.5-1 hour. Plasma clearance averaged 70 mL/min, compared to a value of 500-600 mL/min in normal subjects.

In patients with chronic renal impairment, whose creatinine clearance ranged between 10 and 62 mL/min/1.73 m2, the disposition of omeprazole was very similar to that in healthy volunteers, although there was a slight increase in bioavailability. Because urinary excretion is a primary route of excretion of omeprazole metabolites, their elimination slowed in proportion to the decreased creatinine clearance.

The elimination rate of omeprazole was somewhat decreased in the elderly, and bioavailability was increased. Omeprazole was 76% bioavailable when a single 40 mg oral dose of omeprazole (buffered solution) was administered to healthy elderly volunteers, versus 58% in young volunteers given the same dose. Nearly 70% of the dose was recovered in urine as metabolites of omeprazole and no unchanged drug was detected. 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.

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 should be considered.

Omeprazole Delayed-Release Capsule 40 mg was bioequivalent when administered with and without applesauce. However, Omeprazole Delayed-Release Capsule 20 mg was not bioequivalent when administered with and without applesauce. When administered with applesauce, a mean 25% reduction in C_{max} was observed without a significant change in AUC for Omeprazole Delayed-Release Capsule 20 mg. The clinical relevance of this finding is unknown.

Pharmacokinetic data from studies of pediatric patients are available for AstraZeneca's omeprazole. However, due to AstraZeneca's marketing exclusivity rights, this generic drug product is not labeled for pediatric use.

Pharmacodynamics

Mechanism of Action Omeprazole belongs to a new class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H_2 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. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Antisecretory Activity After oral administration, the onset of the antisecretory effect of omeprazole occurs within one hour, with the maximum effect occurring within two hours. Inhibition of secretion is about 50% of maximum at 24 hours and the duration of inhibition lasts up to 72 hours. The antisecretory effect thus lasts far longer than would be expected from the very short (less than one hour) plasma half-life, apparently due to prolonged binding to the parietal H^+/K^+ ATPase enzyme. When the drug is discontinued, secretory activity returns gradually, over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days.

Results from numerous studies of the antisecretory effect of multiple doses of 20 mg and 40 mg of omeprazole in normal volunteers and patients are shown below. The "max" value represents determinations at a time of maximum effect (2-6 hours after dosing), while "min" values are those 24 hours after the last dose of omeprazole.

Range of Mean Values from Multiple Studies of the Mean Antisecretory Effects of Omeprazole After Multiple Daily Dosing

Parameter	Omeprazole 20 mg		Omeprazole 40 mg	
	Max	Min	Max	Min
% Decrease in Basal Acid Output	78*	58-80	94*	80-93
% Decrease in Peak Acid Output	79*	50-59	88*	62-68
% Decrease in 24-hr. Intragastric Acidity		80-97		92-94

* Single Studies

Single daily oral doses of omeprazole ranging from a dose of 10 mg to 40 mg have produced 100% inhibition of 24-hour intragastric acidity in some patients.

Enterochromaffin-like (ECL) Cell Effects In 24-month carcinogenicity studies in rats, a dose-related significant increase in gastric carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see **PRECAUTIONS,** *Carcinogenesis, Mutagenesis, Impairment of Fertility*). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H_2-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients. (See also **CLINICAL PHARMACOLOGY,** *Pathological Hypersecretory Conditions.*) However, these studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant conditions.

Serum Gastrin Effects In studies involving more than 200 patients, serum gastrin levels increased during the first 1 to 2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued treatment. In comparison with histamine H_2-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3 to 3.6 fold vs. 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Other Effects Systemic effects of omeprazole in the CNS, cardiovascular and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2 to 4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single I.V. dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans.

However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within three days of stopping treatment.

The course of Barrett's esophagus in 106 patients was evaluated in a U.S. double-blind controlled study of omeprazole 40 mg b.i.d. for 12 months followed by 20 mg b.i.d. for 12 months or ranitidine 300 mg b.i.d. for 24 months. No clinically significant impact on Barrett's mucosa by antisecretory therapy was observed. Although neosquamous epithelium developed during antisecretory therapy, complete elimination of Barrett's mucosa was not achieved. No significant difference was observed between treatment groups in development of dysplasia in Barrett's mucosa and no patient developed esophageal carcinoma during treatment. No significant differences between treatment groups were observed in development of ECL cell hyperplasia, corpus atrophic gastritis, corpus intestinal metaplasia, or colon polyps exceeding 3 mm in diameter (see also **CLINICAL PHARMACOLOGY,** *Enterochromaffin-like (ECL) Cell Effects*).

Clinical Studies

Duodenal Ulcer Disease

Active Duodenal Ulcer: In a multicenter, double-blind, placebo-controlled study of 147 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 2 and 4 weeks was significantly higher with omeprazole 20 mg once a day than with placebo ($p \leq 0.01$).

Treatment of Active Duodenal Ulcer
% of Patients Healed

	Omeprazole 20 mg a.m. (n=99)	Placebo a.m. (n=48)
Week 2	*41	13
Week 4	*75	27

* ($p \leq 0.01$)

Complete daytime and nighttime pain relief occurred significantly faster ($p \leq 0.01$) in patients treated with omeprazole 20 mg than in patients treated with placebo. At the end of the study, significantly more patients who had received omeprazole had complete relief of daytime pain ($p \leq 0.05$) and nighttime pain ($p \leq 0.01$).

In a multicenter, double-blind study of 293 patients with endoscopically documented duodenal ulcer, the percentage of patients healed (per protocol) at 4 weeks was significantly higher with omeprazole 20 mg once a day than with ranitidine 150 mg b.i.d. ($p<0.01$).

Treatment of Active Duodenal Ulcer
% of Patients Healed

	Omeprazole 20 mg a.m. (n=145)	Ranitidine 150 mg b.i.d. (n=148)
Week 2	42	34
Week 4	*82	63

* ($p<0.01$)

Healing occurred significantly faster in patients treated with omeprazole than in those treated with ranitidine 150 mg b.i.d. ($p<0.01$).

In a foreign, multinational, randomized, double-blind study of 105 patients with endoscopically documented duodenal ulcer, 20 mg and 40 mg of omeprazole were compared to 150 mg b.i.d. of ranitidine at 2, 4 and 8 weeks. At 2 and 4 weeks both doses of omeprazole were statistically superior (per protocol) to ranitidine, but 40 mg was not superior to 20 mg of omeprazole, and at 8 weeks there was no significant difference between any of the active drugs.

Treatment of Active Duodenal Ulcer
% of Patients Healed

	Omeprazole 20 mg (n=34)	Omeprazole 40 mg (n=36)	Ranitidine 150 mg b.i.d. (n=35)
Week 2	83	*83	53
Week 4	97	*100	82
Week 8	100	100	94

* ($p \leq 0.01$)

Gastric Ulcer

In a U.S., multicenter, double-blind study of omeprazole 40 mg once a day, 20 mg once a day, and placebo in 520 patients with endoscopically diagnosed gastric ulcer, the following results were obtained.

Treatment of Gastric Ulcer
% of Patients Healed
(All Patients Treated)

	Omeprazole 20 mg q.d. (n=202)	Omeprazole 40 mg q.d. (n=214)	Placebo (n=104)
Week 4	47.5**	55.6**	30.8
Week 8	74.8**	82.7**,+	48.1

** ($p<0.01$) omeprazole 40 mg or 20 mg versus placebo
\+ ($p<0.05$) omeprazole 40 mg versus 20 mg

For the stratified groups of patients with ulcer size less than or equal to 1 cm, no difference in healing rates between 40 mg and 20 mg was detected at either 4 or 8 weeks. For patients with ulcer size greater than 1 cm, 40 mg was significantly more effective than 20 mg at 8 weeks.

In a foreign, multinational, double-blind study of 602 patients with endoscopically diagnosed gastric ulcer, omeprazole 40 mg once a day, 20 mg once a day, and ranitidine 150 mg twice a day were evaluated.

Treatment of Gastric Ulcer
% of Patients Healed
(All Patients Treated)

	Omeprazole 20 mg q.d. (n=200)	Omeprazole 40 mg q.d. (n=187)	Ranitidine 150 mg b.i.d. (n=199)
Week 4	63.5	78.1**,++	56.3
Week 8	81.5	91.4**,++	78.4

** ($p<0.01$) omeprazole 40 mg versus ranitidine
++ ($p<0.01$) omeprazole 40 mg versus 20 mg

Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD

A placebo-controlled study was conducted in Scandinavia to compare the efficacy of omeprazole 20 mg or 10 mg once daily for up to 4 weeks in the treatment of heartburn and other symptoms in GERD patients without erosive esophagitis. Results are shown below.

% Successful Symptomatic Outcome[a]

	Omeprazole 20 mg a.m.	Omeprazole 10 mg a.m.	Placebo a.m.
All patients	46*,+ (n=205)	31+ (n=199)	13 (n=105)
Patients with confirmed GERD	56*,+ (n=115)	36+ (n=109)	14 (n=59)

[a] Defined as complete resolution of heartburn
* ($p<0.005$) versus 10 mg
\+ ($p<0.005$) versus placebo

Erosive Esophagitis

In a U.S., multicenter, double-blind, placebo-controlled study of 20 mg or 40 mg of Omeprazole Delayed-Release Capsules in patients with symptoms of GERD and endoscopically diagnosed erosive esophagitis of grade 2 or above, the percentage healing rates (per protocol) were as follows:

Week	20 mg Omeprazole (n=83)	40 mg Omeprazole (n=87)	Placebo (n=43)
4	39**	45**	7
8	74**	75**	14

** ($p<0.01$) omeprazole versus placebo

In this study, the 40 mg dose was not superior to the 20 mg dose of omeprazole in the percentage healing rate. Other controlled clinical trials have also shown that omeprazole is effective in severe GERD. In comparisons with histamine H_2-receptor antagonists in patients with erosive esophagitis, grade 2 or above, omeprazole in a dose of 20 mg was significantly more effective than the active controls. Complete daytime and nighttime heartburn relief occurred significantly faster ($p<0.01$) in patients treated with omeprazole than in those taking placebo or histamine H_2-receptor antagonists.

In this and five other controlled GERD studies, significantly more patients taking 20 mg omeprazole (84%) reported complete relief of GERD symptoms than patients receiving placebo (12%).

Long Term Maintenance Treatment of Erosive Esophagitis

In a U.S., double-blind, randomized, multicenter, placebo-controlled study, two dose regimens of omeprazole were studied in

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patients with endoscopically confirmed healed esophagitis. Results to determine maintenance of healing of erosive esophagitis are shown below.

	Omeprazole 20 mg q.d. (n=138)	Life Table Analysis Omeprazole 20 mg 3 days per week (n=137)	Placebo (n=131)
Percent in endoscopic remission at 6 months	*70	34	11

*(p<0.01) omeprazole 20 mg q.d. versus omeprazole 20 mg 3 consecutive days per week or placebo.

In an international, multicenter, double-blind study, omeprazole 20 mg daily and 10 mg daily were compared to ranitidine 150 mg twice daily in patients with endoscopically confirmed healed esophagitis. The table below provides the results of this study for maintenance of healing of erosive esophagitis.

	Omeprazole 20 mg q.d. (n=131)	Life Table Analysis Omeprazole 10 mg q.d. (n=133)	Ranitidine 150 mg b.i.d. (n=128)
Percent in endoscopic remission at 12 months	*77	+58	46

* (p=0.01) omeprazole 20 mg q.d. versus omeprazole 10 mg q.d. or ranitidine.

+ (p=0.03) omeprazole 10 mg q.d. versus ranitidine.

In patients who initially had grades 3 or 4 erosive esophagitis, for maintenance after healing, 20 mg daily of omeprazole was effective, while 10 mg did not demonstrate effectiveness.

Pathological Hypersecretory Conditions In open studies of 136 patients with pathological hypersecretory conditions, such as Zollinger-Ellison (ZE) syndrome with or without multiple endocrine adenomas, Omeprazole Delayed-Release Capsules significantly inhibited gastric acid secretion and controlled associated symptoms of diarrhea, anorexia, and pain. Doses ranging from 20 mg every other day to 360 mg per day maintained basal acid secretion below 10 mEq/hr in patients without prior gastric surgery, and below 5 mEq/hr in patients with prior gastric surgery.

Initial doses were titrated to the individual patient need, and adjustments were necessary with time in some patients (see **DOSAGE AND ADMINISTRATION**). Omeprazole was well tolerated at these high dose levels for prolonged periods (>5 years in some patients). In most ZE patients, serum gastrin levels were not modified by omeprazole. However, in some patients, serum gastrin increased to levels greater than those present prior to initiation of omeprazole therapy. At least 11 patients with ZE syndrome on long-term treatment with omeprazole developed gastric carcinoids. These findings are believed to be a manifestation of the underlying condition, which is known to be associated with such tumors, rather than the result of the administration of omeprazole. (See **ADVERSE REACTIONS**.)

INDICATIONS AND USAGE

Duodenal Ulcer Omeprazole Delayed-Release Capsules are indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

Gastric Ulcer Omeprazole Delayed-Release Capsules are indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer. (See **CLINICAL PHARMACOLOGY**, *Clinical Studies, Gastric Ulcer*.)

Treatment of Gastroesophageal Reflux Disease (GERD)

Symptomatic GERD Omeprazole Delayed-Release Capsules are indicated for the treatment of heartburn and other symptoms associated with GERD.

Erosive Esophagitis Omeprazole Delayed-Release Capsules are indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy. (See **CLINICAL PHARMACOLOGY**, *Clinical Studies*.)

The efficacy of omeprazole used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (e.g., heartburn), additional 4-8 week courses of omeprazole may be considered.

Maintenance of Healing of Erosive Esophagitis Omeprazole Delayed-Release Capsules are indicated to maintain healing of erosive esophagitis. Controlled studies do not extend beyond 12 months.

Pathological Hypersecretory Conditions Omeprazole Delayed-Release Capsules are indicated for the long-term treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis).

CONTRAINDICATIONS

Omeprazole Delayed-Release Capsules are contraindicated in patients with known hypersensitivity to any component of the formulation.

PRECAUTIONS

General Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

Information for Patients Omeprazole Delayed-Release Capsules should be taken before eating. Patients should be cautioned that the Omeprazole Delayed-Release Capsule should not be opened, chewed or crushed, and should be swallowed whole.

For patients who have difficulty swallowing capsules, the contents of an Omeprazole Delayed-Release Capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the microtablets inside the capsule should be carefully emptied on the applesauce. The microtablets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the microtablets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The microtablets should not be chewed or crushed. The microtablets/applesauce mixture should not be stored for future use.

Drug Interactions

Other Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole.

Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts). In the clinical trials, antacids were used concomitantly with the administration of omeprazole.

Carcinogenesis, Mutagenesis, Impairment of Fertility In two 24-month carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 4 to 352 times the human dose, based on a patient weight of 50 kg and a human dose of 20 mg) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 35 times the human dose) for one year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. An unusual primary malignant tumor in the stomach was seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interprat. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive.

Omeprazole was not mutagenic in an *in vitro* Ames *Salmonella typhimurium* assay, an *in vitro* mouse lymphoma cell assay and an *in vivo* rat liver DNA damage assay. A mouse micronucleus test at 625 and 6250 times the human dose gave a borderline result, as did an *in vivo* bone marrow chromosome aberration test. A second mouse micronucleus study at 2000 times the human dose, but with different (suboptimal) sampling times, was negative.

In a rat fertility and general reproductive performance test, omeprazole in a dose range of 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose) was not toxic or deleterious to the reproductive performance of parental animals.

Pregnancy

Pregnancy Category C Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers It is not known whether omeprazole is excreted in human milk. In rats, omeprazole administration during late gestation and lactation at doses of 13.8 to 138 mg/kg/day (35 to 345 times the human dose) resulted in decreased weight gain in pups. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Pediatric usage and safety information is available for AstraZeneca's omeprazole. However, due to AstraZeneca's marketing exclusivity rights, this generic drug product is not labeled for pediatric use.

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 bioavailabilty 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**.)

ADVERSE REACTIONS

Omeprazole Delayed-Release Capsules were generally well tolerated during domestic and international clinical trials in 3096 patients.

In the U.S. clinical trial population of 465 patients (including duodenal ulcer, Zollinger-Ellison syndrome and resistant ulcer patients), the following adverse experiences were reported to occur in 1% or more of patients on therapy with omeprazole. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug.

	Omeprazole (n=465)	Placebo (n=64)	Ranitidine (n=195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1 (1.6)	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0.0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

The following adverse reactions which occurred in 1% or more of omeprazole-treated patients have been reported in international double-blind, and open-label, clinical trials in which 2,631 patients and subjects received omeprazole.

Incidence of Adverse Experiences ≥ 1% Causal Relationship not Assessed	Omeprazole (n=2631)	Placebo (n=120)
Body as a Whole, site unspecified		
Abdominal Pain	5.2	3.3
Asthenia	1.3	0.8
Digestive System		
Constipation	1.5	0.8
Diarrhea	3.7	2.5
Flatulence	2.7	5.8
Nausea	4.0	6.7
Vomiting	3.2	10.0
Acid regurgitation	1.9	3.3
Nervous System/ Psychiatric		
Headache	2.9	2.5

Additional adverse experiences occurring in <1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to omeprazole was unclear.

Body As a Whole: Allergic reactions, including, rarely, anaphylaxis (see also *Skin* below), fever, pain, fatigue, malaise, abdominal swelling

Cardiovascular: Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, peripheral edema

Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued.

Gastro-duodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

Hepatic: Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.

Metabolic/Nutritional: Hyponatremia, hypoglycemia, weight gain

Musculoskeletal: Muscle cramps, myalgia, muscle weakness, joint pain, leg pain

Nervous System/Psychiatric: Psychic disturbances including depression, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; hemifacial dysesthesia

Respiratory: Epistaxis, pharyngeal pain

Skin: Rash and, rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, alopecia, dry skin, hyperhidrosis

Special Senses: Tinnitus, taste perversion

Urogenital: Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia

Hematologic: Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leucocytosis, and hemolytic anemia have been reported.

The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

OVERDOSAGE

Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. (See **ADVERSE REACTIONS**.) Symptoms were transient, and no serious clinical outcome has been reported when omeprazole was taken alone. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

DOSAGE AND ADMINISTRATION

Short-Term Treatment of Active Duodenal Ulcer The recommended adult oral dose of Omeprazole Delayed-Release Capsules is 20 mg once daily. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy. (See **INDICATIONS AND USAGE**.)

Gastric Ulcer The recommended adult oral dose is 40 mg once a day for 4-8 weeks. (See **CLINICAL PHARMACOLOGY**, *Clinical Studies, Gastric Ulcer*, and **INDICATIONS AND USAGE**, *Gastric Ulcer*.)

Gastroesophageal Reflux Disease (GERD) The recommended adult oral dose for the treatment of patients with symptomatic GERD and no esophageal lesions is 20 mg daily for up to 4 weeks. The recommended adult oral dose for the treatment of patients with erosive esophagitis and accompanying symptoms due to GERD is 20 mg daily for 4 to 8 weeks. (See **INDICATIONS AND USAGE**.)

Maintenance of Healing of Erosive Esophagitis The recommended adult oral dose is 20 mg daily. (See **CLINICAL PHARMACOLOGY**, *Clinical Studies*.)

Pathological Hypersecretory Conditions The dosage of omeprazole in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 120 mg t.i.d. have been administered. Daily dosages of greater than 80 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with omeprazole for more than 5 years.

Pediatric Patients Pediatric usage information is available for AstraZeneca's omeprazole. However, due to AstraZeneca's marketing exclusivity rights, this generic drug product is not labeled for pediatric use.

Alternative Administration Options

For patients who have difficulty swallowing capsules, the contents of an Omeprazole Delayed-Release Capsule can be added to applesauce. One tablespoon of applesauce should be added to an empty bowl and the capsule should be opened. All of the microtablets inside the capsule should be carefully emptied on the applesauce. The microtablets should be mixed with the applesauce and then swallowed immediately with a glass of cool water to ensure complete swallowing of the microtablets. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The microtablets should not be chewed or crushed. The microtablets/applesauce mixture should not be stored for future use.

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

Omeprazole Delayed-Release Capsules should be taken before eating. In the clinical trials, antacids were used concomitantly with omeprazole.

Patients should be cautioned that the Omeprazole Delayed-Release Capsule should not be opened, chewed or crushed, and should be swallowed whole.

HOW SUPPLIED

Omeprazole Delayed-Release Capsules 10 mg are opaque white cap and opaque white body capsules imprinted with "KU" and "114" in black ink. They are supplied as follows:

Bottles of 30 NDC 62175-114-32
Bottles of 100 NDC 62175-114-37

Omeprazole Delayed-Release Capsules 20 mg are opaque white cap and opaque gold body capsules imprinted with "KU" and "118" in black ink. They are supplied as follows:

Bottles of 30 NDC 62175-118-32
Bottles of 100 NDC 62175-118-37

Storage Store Omeprazole Delayed-Release Capsules in a tight container protected from light and moisture. Store at controlled room temperature 15°-30° C (59°-86° F) [see USP].

Dispense in a tight and light-resistant container as described in USP.

Distributed by:

KU
KREMERS URBAN

Div. of Schwarz Pharma, Inc.
Mequon, WI 53092, USA

PC3599O
Rev. 07/02

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

FDA
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

/S/

11/24/98

APPEARS THIS WAY
ON ORIGINAL

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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
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.

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 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

APPEARS THIS WAY
ON ORIGINAL

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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
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.

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

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

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

[redacted]

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

19. REVIEWER:
Radhika Rajagopalan, Ph.D.

DATE COMPLETED:
6/19/00; 6/29/00

/S/

7/13/00

APPEARS THIS WAY
ON ORIGINAL

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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
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

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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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

and 20 mg strengths.

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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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 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
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: DATE COMPLETED:
Radhika Rajagopalan, Ph.D. 5/9/02

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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
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
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
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
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

JUL 14 2000

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 Sabalka 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 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 completed. JAS

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MAJOR AMENDMENT

ANDA 75-410

FEB - 1 2002

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 Co. TEL: 262-238-5225

ATTN: ~~Steven R. Pollock~~ Elaine Cibulka 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, 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 (1 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:

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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 [redacted](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 [redacted] 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 [redacted] 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,

/S/

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
ANDA #75-410
Reviewer: Hoainhon Nguyen
W #75410a.500

Kremers Urban
Mequon, WI
Submission Date:
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."*

1. 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, teamleaders, 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 — 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: [redacted]
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:

Sampling Times (Min.)	Test Product Lot # CJ-0592 Strength (mg) 10		Reference Product Lot # H1616 Strength (mg) 10	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
15	91	[illegible]	102	[illegible]
30	94	[illegible]	103	[illegible]
45	95	[illegible]	102	[illegible]

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 HCl Volume [illegible] ml

Reference Drug: (Manuf.) Prisolec Capsules (Merck)

Assay Methodology: [illegible]

Specifications: Acid Stage: NMT [illegible]% dissolved in 2 hours*

*After 2 hours in the Acid Stage, the capsules were removed and assayed.

Results of Acid Resistance Testing:

Sampling Times (Min.)	Test Product Lot # CJ-0592 Strength (mg) 10		Reference Product Lot # H1616 Strength (mg) 10	
	Mean % Assayed(CV%)	Range	Mean % Assayed(CV%)	Range
Assay	96.6(1.9)	[illegible]	91.2(3.1)	[illegible]

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:

Sampling Times (Min.)	Test Product Lot # CJ-0591 Strength (mg) 20		Reference Product Lot # K3240 Strength (mg) 20	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
45	90.3(4.1)	_____	107.6(1.9)	_____

Sampling Times (Min.)	Test Product Lot # CJ-0592 Strength (mg) 10		Reference Product Lot # H1616 Strength (mg) 10	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
45	97.2(2.2)	_____	100.6(2.2)	_____

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: [redacted] ml
Reference Drug: (Manuf.) Prisolec Capsules (Merck)
Assay Methodology: [redacted]
Specifications: Acid Stage: NMT [redacted] dissolved in 2 hours*
*After 2 hours in the Acid Stage, the capsules were removed and assayed.

Results of Acid Resistance Testing:

Sampling Times (Min.)	Test Product Lot # CJ-0591 Strength (mg) 20		Reference Product Lot # K3240 Strength (mg) 20	
	Mean % Assayed(CV%)	Range	Mean % Assayed(CV%)	Range
Assay	90.6(3.1)	[redacted]	96.4(1.4)	[redacted]

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.

Sampling Times (Min.)	Test Product Lot # CJ-0592 Strength (mg) 10		Reference Product Lot # H1616 Strength (mg) 10	
	Mean % Assayed(CV%)	Range	Mean % Assayed(CV%)	Range
Assay	94.2(4.9)	[redacted]	91.1(3.6)	[redacted]

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.

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 [redacted] (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 [redacted] 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 [redacted] 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 ——— to 750 mL, and changing the Buffer Stage medium volume from ——— 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.

/S/

Hoaimon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

/S/ 7/20/2000

Concur: /S/ Date: 7/26/00

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

5.1

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* [redacted] *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 6.8 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 H HCl; Buffer Stage: 0.05 M Phosphate Buffer, pH 6.8
Volume: [redacted] ml (Both stages)
Reference Drug: (Manuf.) Prisolec Capsules (Merck)
Assay Methodology: [redacted]
Specifications: Acid Stage: NMT [redacted] dissolved in 2 hours
Buffer Stage: NLT [redacted] dissolved in 45 minutes

IB. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # CJ-0591 Strength (mg) 20		Reference Product Lot # H1852 Strength (mg) 20	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
Acid Stage				
120	0(249)	[redacted]	2(33)	[redacted]
Buffer Stage				
15	82(6.7)	[redacted]	98(2.3)	[redacted]
30	87(4.6)	[redacted]	97(2.0)	[redacted]
45	88(4.2)	[redacted]	97(2.1)	[redacted]

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 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: [redacted]
Specifications: Acid Stage: NMT [redacted] dissolved in 2 hours
Buffer Stage: NLT [redacted] dissolved in 45 minutes

ID. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # CJ-0591 Strength (mg) 20		Reference Product Lot # H1852 Strength (mg) 20	
	Mean % Dissolved(CV%)	Range	Mean % Dissolved(CV%)	Range
Acid Stage				
120	1(162)	[redacted]	2(42)	[redacted]
Buffer Stage				
15	83(6.3)	[redacted]	101(3.1)	[redacted]
30	88(4.9)	[redacted]	101(2.3)	[redacted]
45	90(4.3)	[redacted]	101(2.3)	[redacted]

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:

Sampling Times (Min.)	Test Product Lot # CJ-0591 Strength (mg) 20		Reference Product Lot # H1852 Strength (mg) 20	
	Mean % Dissolved(CV%) Or Assayed(CV%)	Range	Mean % Dissolved(CV%) Or Assayed(CV%)	Range
Acid Stage				
120 min	0.8(145)	_____	2.2(28)	_____
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:

Sampling Times (Min.)	Test Product Lot # CJ-0591 Strength (mg) 20		Reference Product Lot # H1852 Strength (mg) 20	
	Mean % Dissolved(CV%) Or Assayed(CV%)	Range	Mean % Dissolved(CV%) Or Assayed(CV%)	Range
Acid Stage				
120 min	0.1(244)	_____	2.7(38)	_____
Assay	90.0(3.7)	_____	90.4(3.4)	_____

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 [redacted] to 750 mL, and changing the Buffer Stage medium volume from [redacted] 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 [redacted] (with some individual capsules assayed for greater than [redacted] 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.

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG /S/ 9/27/99
FT INITIALED YHUANG

Concur: /S/ Date: 11/16/99
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

SEP 3 1999

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 [redacted] 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,

1st

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

Omeprazole DR Capsules, 20 mg 10 mg
ANDA #75-410
Reviewer: Hoainhon Nguyen
W #75410w.799

Kremers Urban
Mequon, WI
Submission Date:
July 1, 1999

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 [redacted] 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.

/S/

Hoamhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG 7/30/99
FT INITIALED YHUANG /S/

Concur: /S/ Date: 9/1/99
for Dale P. Conner, 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\ltrs&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 [redacted] 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,

/S/

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

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[illegible]h Dates)
HFD-652/ HNguyer /S/
HFD-652/ YHuang /S/
HFD-617/ E. Hu
for HFD-650/ D. Conner /S/

V:\FIRMSAM\kremers\ltrs&rev\75410w.799
Printed in final on 9/1 /99

DISSOLUTION - DEFICIENT Submission date: 07-01-99

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

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

WINBIO COMMENTS:

BIOEQUIVALENCY AMENDMENT

AUG 16 1999

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 1 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.

SPECIAL INSTRUCTIONS:

X:\new\ogdadmin\glossary\biofax.frm

4.1

AUG 16 1999

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 [redacted] 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,

/S/

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 [redacted] 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,

/S/

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

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HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang /S/ 7/7/99
HFD-617/ E. H. /S/ 7/29/99
HFD-650/ D. Conner /S/ 7/12/99

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Printed in final on / /

DISSOLUTION - DEFICIENT Submission date: 06-04-99

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

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 [redacted] (with some individual capsules assayed for greater than [redacted] 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,

/S/

for 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 /S/
HFD-652/ YHuang /S/ 9/27/99
HFD-617/ E. Hu /S/ 11/16/99
HFD-650/ D. Conner /S/ 11/16/99

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Printed in final on / /

DISSOLUTION - DEFICIENT Submission date: 09-16-99

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

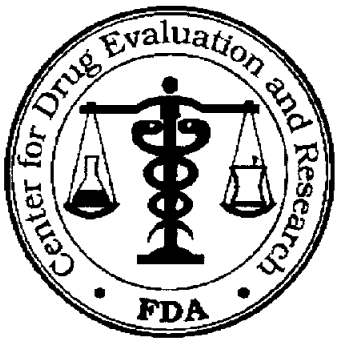
OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
AC - Acceptable

WINBIO COMMENTS:

BIOEQUIVALENCY AMENDMENT

ANDA 75-410

NOV 19 1999



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) 242-1641 ~~512-1108~~

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 1 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.

SPECIAL INSTRUCTIONS:

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/S/

11/18/99

NOV 19 1999

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,

/S/

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 [redacted] (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 [redacted] 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 [redacted] 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,

/S/

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: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 7/20/2000
HFD-617/ K. Scardina
HFD-650/ D. Conner 7/26/00

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Printed in final on / /

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

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

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

3. STUDY AMENDMENR (STA) Strength: 10 mg & 20 mg
ok **Outcome: AC**

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable
(fatal flaw)
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
CINICAL STUDY SITE(S) : [redacted]
ANALYTICAL SITE(S) : [redacted]

STUDY SUMMARY : Acceptable
DISSOLUTION : Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL /S/ _____ DATE : 7/20/00

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : /S/ _____ DATE : 7/20/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ _____ DATE : 7/26/00

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pages of trade secret and/or confidential commercial information

Omeprazole DR Capsules, 20 mg
ANDA #75-410
Reviewer: Hoainhon Nguyen
W #75410a.699

Kremers Urban
Mequon, WI
Submission Date:
June 4, 1999

Review of an Amendment: Dissolution Data

The firm has revised the dissolution testing method and submitted additional *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 [redacted] to 6.8.

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

iv. Due to the firm's *"use of the on-line [redacted] 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 6.8 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 ___ RPM 100 rpm Units Tested: [redacted]
Medium: Acid Stage: 0.1 H HCl; Buffer Stage: 0.05 M Phosphate Buffer, pH 6.8
Volume: [redacted] ml (Both stages)
Reference Drug: (Manuf.) Not used
Assay Methodology: [redacted]

Specifications: Acid Stage: NMT — dissolved in 2 hours
Buffer Stage: NLT — dissolved in 45 minutes

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # CJ-0591 Strength (mg) 20		Reference Product Lot # Strength (mg)	
	Mean % Dissolved	Range	Mean % Dissolved(CV%)	Range
Acid Stage				
120	0	0		
Buffer Stage				
15	86	—		
30	90	—		
45	91	—		

I. Conditions for Dissolution Testing: **Firm's proposed method**
USP XXIII 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.) 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:

Sampling Times (Min.)	Test Product Lot # CJ-0591 Strength (mg) 20		Reference Product Lot # Strength (mg)	
	Mean % Dissolved	Range	Mean % Dissolved(CV%)	Range
Acid Stage				
120	0	0-3		
Buffer Stage				
15	84	—		
30	87	—		
45	89	—		

Deficiencies:

1. The firm should use 12 units, instead of [redacted] 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 /S/ 7/7/99

Concur (S) Date: 7/12/99

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

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

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY AMENDMENT NOV 3

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 PHONE: 414-238-5715

ATTN: Jonathan A. Thiel FAX: 414-238-0957

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

Dear Sir:

This facsimile is in reference to the bioequivalency 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.

SPECIAL INSTRUCTIONS:

Pmrb 11/31/98

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NOV 3

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 [redacted] 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 [redacted]

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 [redacted] of 0.1N HCl for 2 hours [Acid stage]; followed by [redacted] 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 [redacted] of the drug in the capsule is dissolved in 2 hours [Acid stage] and NLT [redacted] (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,

/S/

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

Omeprazole DR Capsules, 20 mg
ANDA # 75-410
Reviewer: Hoainhon Nguyen
WP #75410sd.798

Kremers Urban
Mequon, WI
Submission Date:
July 2, 1998
October 6, 1998(Tel.Amend.)

Review of A Fasting Bioequivalence Study and Disolution Data

I. Background:

Omeprazole belongs to a new class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H_2 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 esphagitis 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. [redacted] 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 at [redacted] between April 18 and May 16, 1998. The principal investigator was [redacted] Plasma samples were assayed by [redacted], under the supervision of [redacted], 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 [redacted] 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.

[redacted]

Assay Methodology:

[redacted]

Redacted 1

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

Parameters	Kremers' Mean (CV)	Prilosec® Mean (CV)	90% C.I.	Ratio T/R
AUC_{0-T} (n=46) ng.hr/ml	311.5*	335.3*	[0.88;0.98] *[0.86;0.96]***	0.93
AUC_{0-Inf} (n=44) ng.hr/ml	332.2*	355.0*	[0.89;0.98] *[0.87;0.96]***	0.94
CMAX(ng/mL) (n=46)	200.0*	191.4*	[0.94;1.16] *[0.91;1.11]***	1.04
TMAX (hrs)	2.196(52)	2.014(64)		
KEL (hrs^{-1})	0.943(20)	0.873(24)		
T1/2(hrs)	0.782(36)	0.861(39)		
$AUC_{0-T,G1}$ (n=32)*** ng.hr/ml	305.1*	354.1*	[0.82;0.91]	0.86
$AUC_{0-Inf,G1}$ (n=30)*** ng.hr/ml	334.4*	382.8*	[0.83;0.92]	0.87
$CMAX_{G1}$(ng/mL)*** (n=32)	202.4*	218.2*	[0.82;1.04]	0.93
$AUC_{0-T,G2}$ (n=14)*** ng.hr/ml	331.6*	321.4*	[0.93;1.15]	1.03
$AUC_{0-Inf,G2}$ (n=13)*** ng.hr/ml	343.2*	333.8*	[0.93;1.14]	1.03
$CMAX_{G2}$(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)

Hour	Test	Reference
0	0	0
0.75	32.009238)	49.50(142)
1.0	65.22(169)	121.7(110)
1.33	117.9(115)	161.5(107)
1.67	139.7(97)	175.8(119)
2.0	133.2(93)	153.5(124)
2.33	121.7(112)	127.2(130)
2.67	112.2(141)	109.6(150)
3.0	91.99(149)	90.92(162)
3.5	81.33(158)	72.84(170)
4.0	61.67(190)	58.64(188)
5.0	36.18(271)	30.63(310)
6.0	17.60(411)	17.32(402)
8.0	6.81(593)	7.98(500)
10	3.53(678)	3.43(629)
12	1.91(678)	2.20(618)
$AUC_{0\text{-}T(ng.hr/ml)}$	446.5(152)	496.3(161)
$AUC_{0\text{-}I(ng.hr/ml)}$	478.1(153)	530.4(163)
$CMAX_{ng/ml}$	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 ANDA # 75-410
Submission Date: July 2, 1998

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: [redacted]
Firm's Specification:

Time	Amount Dissolved (%)
120 min	NMT [redacted] (acid)
135 min	NLT [redacted]

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 [redacted] 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 [redacted]

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/

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG /S/ 10/20/98

Concur: /S/ Date: 10/27/98

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

WP#75410SD.798 Attachment

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 tol 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 [redacted] 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 [redacted].

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

NMT [redacted] of the drug in the capsule is dissolved in 2 hours [Acid stage] and NLT [redacted] (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,

/S/

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

BIOEQUIVALENCY - ACCEPTABLE
DISSOLUTION - DEFICIENT

Submission Date: July 2, 1998
October 6, 1998

1. **FASTING STUDY** (STF)
Clinical:
Analytical:

Strengths: 20 mg
Outcome: ~~AC~~ IC

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

WinBio Comments

Dissolution testing unacceptable.
Food study is needed

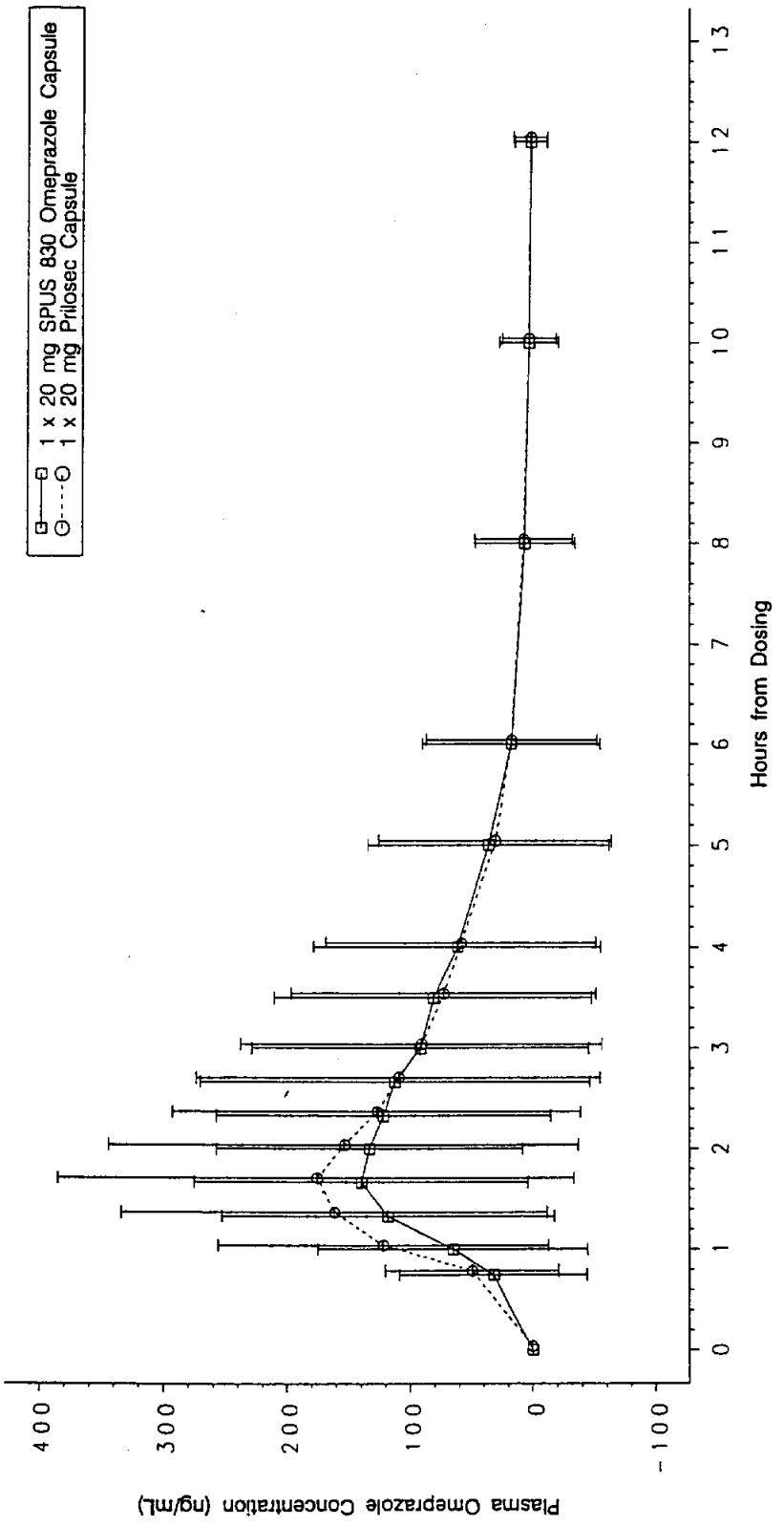
APPEARS THIS WAY
ON ORIGINAL

NP # 75410 sd. 798 Attachment 3 of 7

Figure 1

Mean (S.D.) Plasma Omeprazole Concentrations Versus Time

Linear Scale



Treatment B is shifted to the right for ease of reading

Kremers Urban Development Company (KUDCO)
Omeprazole Protocol #SPUS-830-004
MDS Harris Project 20330

WP # 75410 sd. 798 Attachment 4 of 7

QUANTITATIVE COMPOSITION

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

PRODUCTION OF MICROTABLETS

	PER MICROTABLET	PER CAPSULE
Lactose NF		
Crospovidone NF		
Omeprazole USP		
Hydroxypropyl Methylcellulose USP		
Omeprazole, Unmicronized USP		
Glyceryl Behenate NF		
TOTAL		

, FOR MICROTABLETS

	PER MICROTABLET	PER CAPSULE
Methacrylic Acid Copolymer Dispersion NF		
Talc USP		
Triethyl Citrate NF		
Titanium Dioxide USP		
Silicon Dioxide NF		
TOTAL		
TOTAL WEIGHT (AFTER APPLICATION OF BOTH		

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pages of trade secret and/or confidential 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
CINICAL STUDY SITE(S) : [redacted]
ANALYTICAL SITE(S) : [redacted]

STUDY SUMMARY : Acceptable
DISSOLUTION : Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic ____	Inspection requested: (date)	
New facility ____	Inspection completed: (date)	
For cause ____		
Other ____		

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : _____ DATE : 5/16/02

/S/

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : /S/ DATE : 5/20/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 6/13/02

A13.1

NKP

OMEPRAZOLE DR CAPSULES
10 mg & 20 mg
ANDA 75-410
Reviewer: Hoainhon Nguyen
75410N0302.doc

Kremers Urban Development Co.
Mequon, WI

Submission Date: 03/29/02
&04/12/02 (Telephone Amendment)

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 applessauce, 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 biolot of the test product, as requested.

Financial Disclosure: pp. 15-16, Vol. B12.1

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

TREATMENT INFORMATION

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

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2 (ABAB and BABA)	**Replicated Treatment Design:**	Y
No. of Periods:	4	**Balanced:**	N
No. of Treatments:	2	**Washout Period:**	7 days

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	24
Route of Administration:	Oral	**No. of Subjects Completing:**	21
		No. of Subjects Plasma Analyzed:	24(Only 21 were included in statistical analysis)
		No. of Dropouts:	3

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)

Exclusion/Inclusion Criteria: pp. 102-104, Vol. B12.1

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 Referenct 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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pages of trade secret and/or confidential commercial information

4) Pharmacokinetic Method:

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

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 greather 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

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

*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

TABLE II

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

TIME (HR)	TEST (First Replicate)	TEST(Second Replicate)	REFERENCE (First Replicate)	REFERENCE(Second Replicate)
Pre-dose	0	0	0	0
0.50	8.73(258)	1.67(368)	26.13(107)	42.71(147)
0.75	36.73(162)	24.20(224)	71.08(84)	74.04(126)
1.00	85.43(139)	57.93(175)	119.8(106)	118.2(119)
1.25	128.6(155)	86.61(160)	142.5(126)	149.7(106)
1.50	154.6(40)	118.6(143)	151.4(116)	163.0(92)
2.00	133.8(110)	148.1(115)	145.7(99)	155.0(85)
2.50	102.1(107)	151.4(87)	115.4(77)	129.3(79)
3.00	90.07(91)	122.1(84)	88.85(69)	110.0(86)
3.50	83.35(89)	92.75(81)	70.13(69)	75.41(88)
4.00	62.91(91)	58.30(90)	51.78(89)	50.13(90)
4.50	73.18(165)	41.35(85)	33.03(92)	36.25(90)
5.00	49.22(147)	46.11(159)	51.50(194)	48.69(191)
6.00	23.63(148)	23.32(165)	29.90(188)	23.00(198)
7.00	9.76(186)	9.94(158)	10.59(195)	11.72(231)
8.00	4.05(214)	3.57(196)	5.67(232)	4.71(271)
10.00	0.97(310.1)	0.60(323)	1.12(330)	0.37(458)
12.00	0.80(458)	0	1.32(458)	0.44(458)
AUCT Ng.hr/mL	470.0(66)	464.2(69)	487.9(65)	514.6(66)
AUCI Ng.hr/mL	494.6(67)	489.8(66)	504.5(65)	585.3(60)
CMAX Ng/mL	275.6(67)	264.9(63)	245.4(69)	248.6(62)
TMAX hr	2.55(52)	2.50(50)	2.53(61)	2.26(56)
T1/2 hr	0.855(44)	0.885(44)	0.803(32)	0.778(22)
KEL hr^{-1}	0.926(35)	0.902(34)	0.957(34)	0.932(21)

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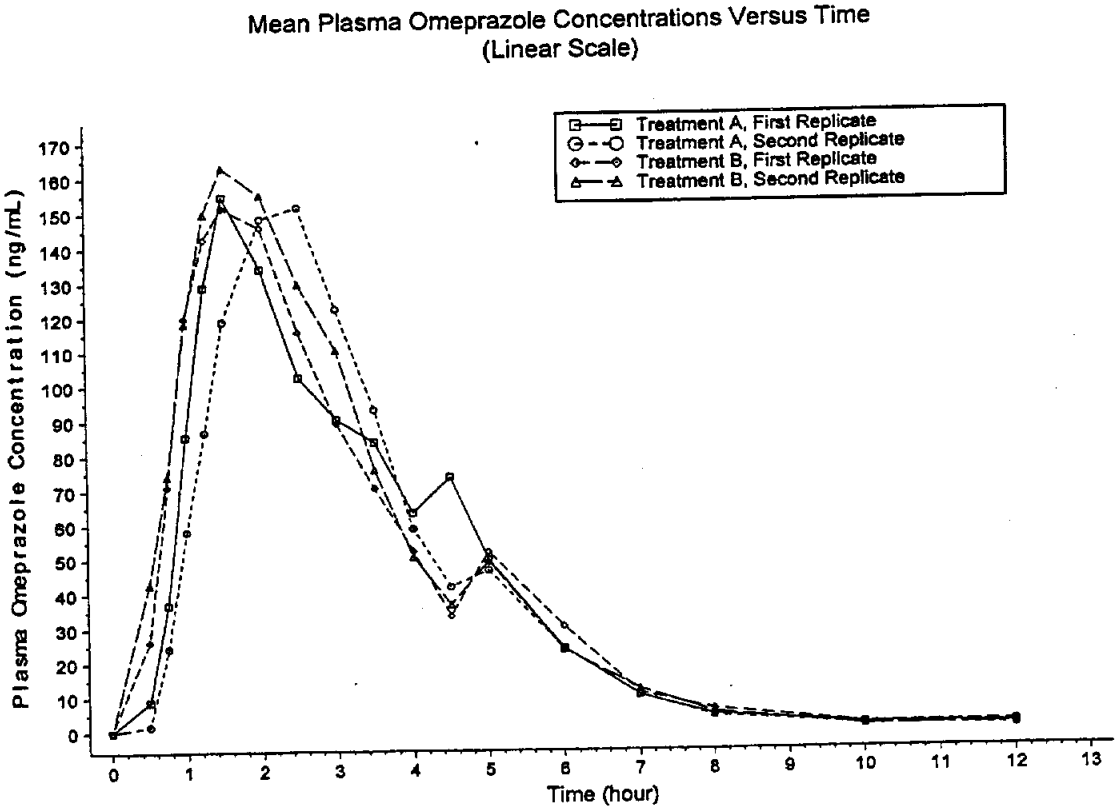
FIGURE 1

OMEPRAZOLE PLASMA CONCENTRATION (ng/mL) VERSUS TIME SINGLE-DOSE FASTING SPRINKLE STUDY #SP689



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.

/S/
Hoaminh Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG /S/ 5/20/2002

Concur: /S/ Date: 6/13/02
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
cc: ANDA # 75-410 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/04-12-02/W #75410n0302.doc
Also as V:\firmsam\kremers-u\ltrs&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 [redacted] of 0.1N HCl for 2 hours [Acid stage]; followed by [redacted] of 0.05M phosphate buffer, pH 6.8 [Buffer stage], at 37C using USP apparatus I(basket) at 100 rpm. The test product should meet the following specification:

> NLT [redacted] (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 [redacted] 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 [redacted] 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,

/s/

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: (Final with Dates)
HFD-652/ HNguyen /S/
HFD-652/ YHuang /S/ 6/20/2002
HFD-617/ K. Scardina
HFD-650/ D. Conner /S/ 6/13/02

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Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE

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

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

   Strength: 20 MG
   Outcome: AC

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

   Strength: 20 MG
   Outcome: ~~AC~~
   WC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
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) : 20 mg & 10 mg
TYPES OF STUDIES : Sprinkle Study
CINICAL STUDY SITE(S) : [redacted]
ANALYTICAL SITE(S) : [redacted]

STUDY SUMMARY : Acceptable
DISSOLUTION : Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : ____ /S/ _____ DATE : 5/16/02

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : ____ /S/ _____ DATE : 5/20/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : ___ /S/ _____ DATE : 6/13/02

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-410

ADMINISTRATIVE DOCUMENTS

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.

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

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.

/S/

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

3/8/01

/S/

3/12/01

F/T by pah/3/8/01
v:\firmsam\kramer-u\ltrs&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.
- **5093342** - Expires Feb 2, 2010, **U-166** - Treatment of H. Pylori associated duodenal ulcer.
- **5599794** - Expires Feb 4, 2014, **U-166** - Treatment of H. Pylori associated duodenal ulcer.
- **5629305** - Expires Feb 4, 2014, **U-188** - Treatment of H. Pylori associated duodenal ulcer.

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 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 7/2/98 submission.

    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.

Table I
Omeprazole Comparative Pharmacokinetic Parameters
Fasting Single-Dose Study; Dose = 20 mg; n = 46

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

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: January 30, 2001 **Date of Submissions: November 30, 2000**

Reviewer: Koung Lee /S/ **Date:** 02/07/01

Team Leader: Charlie Hoppes /S/ **Date:** 2/7/01

cc: ANDA 75-410
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
V:\FIRMSAM\KREMERU\LTRS&REV\75410TA.LABELING Review

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)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

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: Prilosec
- NDA Number: 19-810
- NDA Drug Name: Prilosec
- NDA Firm: Astra
- Date of Approval of NDA Insert and supplement #: Approved 12/10/98; S-053, S-055, S-057
- 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.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?		x	
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	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	**Yes**	**No**	**N.A.**
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)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
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.		x	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			x
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			

Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP issues: (FTR: List USP/NDA/AND dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does AND meet them?		x	
Is the product light sensitive? If so, is NDA and/or AND in a light resistant container?	x		
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.		x	
Bioequivalence issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T D and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity issues?: FTR: 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.			

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:

1. Review based on the labeling of the listed drug ANDA 19-810/S-057 (Prilosec; Astra Merck; Revised August 1998, approved 2/3/99).

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.
   - **5093342** - Expires February 2, 2010, **U-166** - Treatment of H. Pylori associated duodenal ulcer.
   - **5599794** - Expires February 4, 2014, **U-166** - Treatment of H. Pylori associated duodenal ulcer.
   - **5629305** - Expires on February 4, 2014, **U-188** - Treatment of H. Pylori associated duodenal ulcer.

   EXCLUSIVITIES:

   - **I-130** - Expired June 22, 1998 - Maintenance of healing of erosive esophagitis.
   - **I-23** - Expired March 22, 1999 - Short-term treatment of active benign gastric ulcer.
   - **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 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 [redacted].

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

9. Container/Closure:

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

Date of Review: **November 18, 1998** **Date of Submissions:** **June 3, 1999**
July 1, 1999
July 21, 1999

Reviewer: Koung Lee /S/ **Date:** 11/29/99

Team Leader: Charlie Hoppes /S/ **Date:** 11/30/99

cc: ANDA 75-410
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
V:\FIRMSAM\KREMERU\LTRS&REV\75410NA2.LABELING

Review

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

ANDA Number: **75-410** Dates of Submission: February 8, 2000

Applicant's Name: **Kremers Urban Development Company**

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

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/rld/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.

/S/

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).

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- **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.
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AUC_{0-T} (n=46) ng.hr/ml	311.5*	335.3*	[0.88;0.98] ***[0.86;0.96]****	0.93
AUC_{0-Inf} (n=44) ng.hr/ml	332.2*	355.0*	[0.89;0.98] ***[0.87;0.96]****	0.94
CMAX(ng/mL) (n=46)	200.0*	191.4*	[0.94;1.16] ***[0.91;1.11]****	1.04
TMAX (hrs)	2.196(52)	2.014(64)		

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

Reviewer: Koung Lee **Date:** 8/3/00

Team Leader: Charlie Hoppes **Date:**

cc: ANDA 75-410
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
V:\FIRMSAM\KREMERU\LTRS&REV\75410NA3.LABELING

Review

/S/

8/3/00

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

ANDA Number: **75-410** Date of Submission: March 29, 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(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

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

If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling (continued)	**Yes**	**No**	**N.A.**
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)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
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.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/AND dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does AND meet them?		X	
Is the product light sensitive? If so, is NDA and/or AND in a light resistant container?	X		
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.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: 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.		X	

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:

No	Expiration	Use Code	Use	File
4255431	October 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	**P III**
4636499	January 30, 3006			**P IV**
4786505	October 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.	**P IV**
4853230	October 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	**P IV**
5093342	August 2, 2010	U-166	Treatment of H. Pylori associated duodenal ulcer.	**MOU**
5599794	August 4, 2014	U-166	Treatment of H. Pylori associated duodenal ulcer	**MOU**
5629305	August 4, 2014	U-188	Treatment of H. Pylori associated duodenal ulcer.	**MOU**
6147103	April 9, 2019		The present invention describes an improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole whereby the sulfide precursor pyrmetazole is reacted subsurfacely with exactly one molar equivalent of meta-chloroperoxybenzoic acid in methylene chloride or toluene solution, residual organic solvent is removed from the aqueous layer by vacuum distillation, crude product is obtained by reactive crystallization with an alkyl formate and seeding; and pure product is isolated by recrystallization in methanol-water containing aqueous NaOH by subsurface addition of aqueous acetic acid to pH 9.0, seeding, filtration, washing, and drying. Compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent are also described.	**P IV**
6150380	May 10, 2019		The present invention relates to a novel crystalline form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benz imidazole, known under the generic name omeprazole. Further, the present invention also relates to the use of the novel crystalline form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benz imidazole for the treatment of gastrointestinal disorders, pharmaceutical compositions containing it as well as processes for the preparation of the novel crystalline form of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benz imidazole.	**P IV**
6166213	April 9, 2018		The present invention describes an improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole whereby the sulfide precursor pyrmetazole is	**P IV**

			reacted subsurfacely with exactly one molar equivalent of meta-chloroperoxybenzoic acid in methylene chloride or toluene solution, residual organic solvent is removed from the aqueous layer by vacuum distillation; crude product is obtained by reactive crystallization with an alkyl formate and seeding; and pure product is isolated by recrystallization in methanol-water containing aqueous NaOH by subsurface addition of aqueous acetic acid to pH 9.0, seeding, filtration, washing, and drying. Compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent are also described.	
6191148	April 9, 2019		The present invention describes an improved process for the preparation, isolation, and purification of the anti-ulcer agent omeprazole whereby the sulfide precursor pyrmetazole is reacted subsurfacely with exactly one molar equivalent of meta-chloroperoxybenzoic acid in a chlorinated aliphatic hydrocarbon or aromatic hydrocarbon solvent, such as methylene chloride or toluene; residual organic solvent is removed from the aqueous layer by vacuum distillation; crude product is obtained by reactive crystallization with an alkyl formate or formic acid solution and seeding; and pure product is isolated by recrystallization in methanol-water containing aqueous NaOH by subsurface addition of aqueous acetic acid to pH 9.0, seeding, filtration, washing, and drying. Omeprazole and compositions of omeprazole containing no chromatographically detectable levels of residual non-alcoholic organic reaction solvent and diminished levels of alcoholic solvent are also described.	**P IV**

The last four patent have no affect on the labeling however, the PM should inform the firm that they will need to certify each one before final approval.

Exclusivity Data -

Code/sup	Expiration	Use Code	Description		Labeling Impact
I-229	December 29, 2001		Omeprazole, amoxicillin and clarithromycin for the eradication of H.Pylori in patients with duodenal ulcer disease		No impact on labeling since treatment of H. Pylori is also protected under three patents.

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.
   The applicant proposes to market their product (10 mg and 20 mg) in bottles of 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).
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 [redacted] 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 Kremers' Omeprazole DR Capsules, 20 mg, and Merck's Prilosec® 20 mg DR Capsules under fasting conditions.

Table I
Omeprazole Comparative Pharmacokinetic Parameters

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

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

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: May 3, 2002 |S| **Date of Submissions: March 29, 2002**

Reviewer: Koung Lee **Date:** 5/8/02

Team Leader: Lillie Golson |S| **Date:** 5/8/02

cc: ANDA 75-410
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSAM\KREMERU\LTRS&REV\75410APF.LABELING

Review

APPEARS THIS WAY
ON ORIGINAL

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, [redacted] Delete the statement [redacted] 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 [redacted] 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 "[redacted]

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 [redacted] 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. [redacted]

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.

/S/

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

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	

Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
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	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling (continued)	**Yes**	**No**	**N.A.**
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)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
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.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X

Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/AND dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does AND meet them?		X	
Is the product light sensitive? If so, is NDA and/or AND in a light resistant container?	X		
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.		X	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: 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 (Prilosec®; Astra Merck; Approved June 29, 1998; Revised June 1998).

2. The firm has proposed 20 mg strength only.

3. 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.

5093342 - Expires February 2, 2010, **U-166** - Treatment of H. Pylori associated duodenal ulcer.

5599794 - Expires February 4, 2014, **U-166** - Treatment of H. Pylori associated duodenal ulcer.

5629305 - Expires on February 4, 2014, **U-188** - Treatment of H. Pylori associated duodenal ulcer.

EXCLUSIVITIES:

I-130 - Expired June 22, 1998 - Maintenance of healing of erosive esophagitis.

I-23 - Expires March 22, 1999 - Short-term treatment of active benign gastric ulcer.

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 (i) 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 [redacted] bottles. It appears that both 30s & 100s will be packaged with Non-CRC closures ([redacted]. 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 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 (i) 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 [redacted] bottles. It appears that both 30s & 100s will be packaged with Non-CRC closures [redacted]. 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: /S/ 11/30/98 **Date:**

Team Leader: /S/ 12/1/98 **Date:**

---

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 EER 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 [redacted]

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.

Stability Specs	
Test	Limits
Assay (LC-label claim)	[redacted] of label claim
Dissolution	0.1 N HCl :NMT [redacted]% dissolved in 2 hours (acid stage) 0.05 M phosphate buffer: NLT [redacted] dissolved in 45 minutes (buffer stage)
Total Impurities	Individual known impurity: NMT [redacted] Other unknown peaks: NMT [redacted] Total: NMT [redacted] (including
Physical appearance	20 mg: No 1 Opaque capsules with [redacted] and gold body imprinted with 'KU 118' in black and filled with

Stability Specs	
	microtablets 10 mg: No 1 Opaque capsules with [redacted] and gold body imprinted with 'KU 114' in black and filled with microtablets

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: [redacted] 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:
[redacted] Capsules of 20 mg and [redacted] capsules of 10 mg are proposed.

COMMENTS:
Approval recommended

CHEMISTRY REVIEWER: Radhika Rajagopalan, Ph.D.
DATE: 6/20/02

/S/
9/27/02
/S/ 10/2/02

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 6/25/02.
- 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:

PATENTS:

No	Expiration	Use Code	Use	File
4636499	November 30, 2005			**P IV**
4786505	October 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.	**P IV**
4853230	October 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	**P IV**
5093342	August 2, 2010	U-166	Treatment of H. Pylori associated duodenal ulcer.	**MOU**
5599794	August 4, 2014	U-166	Treatment of H. Pylori associated duodenal ulcer	**MOU**
5629305	August 4, 2014	U-188	Treatment of H. Pylori associated duodenal ulcer.	**MOU**

6147103	April 9, 2019			**PIV**
6150380	May 10, 2019			**PIV**
6166213	April 19, 2019			**PIV**
6191148	April 9, 2019			**PIV**

Exclusivity Data -

Code/sup	Expiration	Use Code	Description		Labeling Impact
			None		

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.

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 [redacted] 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 Kremers' Omeprazole DR Capsules, 20 mg, and Merck's Prilosec® 20 mg DR Capsules under fasting conditions.

Table I
Omeprazole Comparative Pharmacokinetic Parameters
Fasting Single-Dose Study; Dose = 20 mg; n = 46

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

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: July 15, 2002 **Date of Submissions:** June 25, 2002

Reviewer: Koung Lee /S/ **Date:** 7/15/02

Team Leader: Lillie Golson /S/ **Date:** 7/15/02

cc: ANDA 75-410
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSAM\KREMERU\LTRS&REV\75410AP3.LABELING

Review

APPEARS THIS WAY
ON ORIGINAL

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 " [redacted] " in the second sentence of the first paragraph.

b. PRECAUTIONS

Revise the subsection heading to read " Pregnancy: [redacted] 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:	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-074 (Prilosec; Astra Merck; approved 7/12/02).
2. Patent/ Exclusivities:

PATENTS:

No	Expiration	Use Code	Use	File
4636499	November 30, 2005			**P IV**
4786505	October 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	**P IV**

			maintenance of healing of erosive esophagitis.	
4853230	October 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	**P IV**
5093342	August 2, 2010	U-166	Treatment of H. Pylori associated duodenal ulcer.	**MOU**
5599794	August 4, 2014	U-166	Treatment of H. Pylori associated duodenal ulcer	**MOU**
5629305	August 4, 2014	U-188	Treatment of H. Pylori associated duodenal ulcer.	**MOU**
6147103	April 9, 2019			**PIV**
6150380	May 10, 2019			**PIV**
6166213	April 19, 2019			**PIV**
6191148	April 9, 2019			**PIV**

Exclusivity Data -

Code/sup	Expiration	Use Code	Description		Labeling Impact
	Jan. 12, 2006	M-19	Use of Omeprazole in Pediatric Patients		Carved out Pediatric text

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.
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 Kremers' Omeprazole DR Capsules, 20 mg, and Merck's Prilosec® 20 mg DR Capsules under fasting conditions.

Table I
Omeprazole Comparative Pharmacokinetic Parameters
Fasting Single-Dose Study; Dose = 20 mg; n = 46

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AUC_{0-Inf} (n=44) ng.hr/ml	332.2*	355.0*	[0.89;0.98] ***[0.87;0.96]****	0.94
CMAX(ng/mL) (n=46)	200.0*	191.4*	[0.94;1.16] ***[0.91;1.11]****	1.04
TMAX (hrs)	2.196(52)	2.014(64)		

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: Koung Lee /S/ **Date:** 9/20/02

Team Leader: Lillie Golson /S/ **Date:** 9/20/02

cc: ANDA 75-410
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSAM\KREMERU\LTRS&REV\75410AP5.LABELING

Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-410

CORRESPONDENCE

KREMERS URBAN
DEVELOPMENT COMPANY

October 31, 2002

NEW CORRESP
NC
Hard Copy to FAX

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.

MAILING ADDRESS: 6100 W. EXECUTIVE DRIVE, SUITE D, MEQUON, WI 53092 · SHIPPING ADDRESS: 6140 W. EXECUTIVE DRIVE, MEQUON, WI 53092
PHONE: 414.512.1107 · FAX: 414.512.1108

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,

Donna Multhauf
for

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

APPEARS THIS WAY
ON ORIGINAL

NEW Mpeak 10/31/02

KREMERS URBAN
DEVELOPMENT COMPANY

September 25, 2002

NEW CORRESP
NC

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 for

RECEIVED
SEP 26 2002
OGD / CDER

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

NEW 10/31/02

MAILING ADDRESS: 6100 W. EXECUTIVE DRIVE, SUITE D, MEQUON, WI 53092 · SHIPPING ADDRESS: 6140 W. EXECUTIVE DRIVE, MEQUON, WI 53092
PHONE: 414.512.1107 · FAX: 414.512.1108

KREMERS URBAN
DEVELOPMENT COMPANY

NEW CORRESP
NC

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 25 2002
OGD / CDER

/S/ 10/1/02

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PHONE: 414.512.1107 · FAX: 414.512.1108

KREMERS URBAN
DEVELOPMENT COMPANY

ORIG AMENDMENT
N/AF

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,

Elaine Cibulka for

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

RECEIVED
SEP 0 4 2002
OGD / CDER

MAILING ADDRESS: 6100 W. EXECUTIVE DRIVE, SUITE D, MEQUON, WI 53092 · SHIPPING ADDRESS: 6140 W. EXECUTIVE DRIVE, MEQUON, WI 53092
PHONE: 414.512.1107 · FAX: 414.512.1108

KREMERS URBAN
DEVELOPMENT COMPANY

June 25, 2002

NDA

ORIG AMENDMENT

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, dated December 7, 2001.

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 Amendment 023 dated December 7, 2001.

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.

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PHONE: 414.512.1107 · FAX: 414.512.1108

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 for

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

KREMERS URBAN
DEVELOPMENT COMPANY

April 12, 2002

NEW CORRESP
NC

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 [redacted].

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

RECEIVED
APR 15 2002
OGD / CDER

MAILING ADDRESS: 6100 W. EXECUTIVE DRIVE, SUITE D, MEQUON, WI 53092 · SHIPPING ADDRESS: 6140 W. EXECUTIVE DRIVE, MEQUON, WI 53092
PHONE: 414.512.1107 · FAX: 414.512.1108

SCHWARZ

ORIG AMENDMENT

N/Am

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.

RECEIVED
APR 01 2002
OGD / CDER

Mail P.O. Box 2038 • Milwaukee, WI 53201-2038 • 6140 West Executive Dr. • Mequon, WI 53092-4467
Telephone 262-238-9994 • Toll Free 800-558-5114 • Fax 262-238-0311
www.schwarzusa.com

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 [redacted] 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

KREMERS URBAN
DEVELOPMENT COMPANY

NEW CORRESP
NC + (2/4/02 sworn)

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

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 11 2002
OGD

Cherie Godin
Regulatory Affairs Associate
SCHWARZ PHARMA, Inc., representing
Kremers Urban Development Company

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PHONE: 414.512.1107 · FAX: 414.512.1108

KREMERS URBAN
DEVELOPMENT COMPANY

NAI
MMB 2-11-02

February 4, 2002

NEW CORRESP
NC

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

CENTER FOR DRUG EVALUATION AND RESEARCH
FEB 06 2002
DGD

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

KREMERS URBAN
DEVELOPMENT COMPANY

BIOAVAILABILITY

NEW CORRESP
NC

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.

CENTER FOR DRUG
DEC 2 8 2001
OGD
EVALUATION AND RESEARCH

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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.

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,

Donna Multhauf
for

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

APPEARS THIS WAY
ON ORIGINAL

KREMERS URBAN
DEVELOPMENT COMPANY

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

ORIG AMENDMENT

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 for

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 10 2001

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

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PHONE: 414.512.1107 · FAX: 414.512.1108

Kremers Urban Development Company
Attention: Steven R. Pollock
Schwarz Pharma Inc.
6140 W. Executive Drive, Suite D
Mequon, WI 53092

NOV - 8 2001

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,

/S/ 11/7/01

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 75-410

OCT - 2 2001

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,

/S/

Gary Buehler 10/2/01
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

KREMERS URBAN
DEVELOPMENT COMPANY

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

NEW CORRESP
NC

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,

Elaine Cibulka for

John Vaughan
Vice President
Kremers Urban Development Company

MAILING ADDRESS: 6100 W. EXECUTIVE DRIVE, SUITE D, MEQUON, WI 53092 · SHIPPING ADDRESS: 6140 W. EXECUTIVE DRIVE, MEQUON, WI 53092
PHONE: 414.512.1107 · FAX: 414.512.1108

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

ORIG AMENDMENT
N/AC

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

MAILING ADDRESS: 6100 W. EXECUTIVE DRIVE, SUITE D, MEQUON, WI 53092 · SHIPPING ADDRESS: 6140 W. EXECUTIVE DRIVE, MEQUON, WI 53092
PHONE: 414.512.1107 · FAX: 414.512.1108

KREMERS URBAN
DEVELOPMENT COMPANY

Called Elaine Cibulka on 2/27/01 to request copy of civil action or verification of civil action litigation date and case number

NEW CORRESPT

2/27/2001

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,

Donna Mutchler
for

John Vaughan
Vice President
Kremers Urban Development Company

CENTER FOR DRUG
RECD
FEB - 9 2001
OGD
EVALUATION AND RESEARCH

MAILING ADDRESS: 6100 W. EXECUTIVE DRIVE, SUITE D, MEQUON, WI 53092 · SHIPPING ADDRESS: 6140 W. EXECUTIVE DRIVE, MEQUON, WI 53092
PHONE: 414.512.1107 · FAX: 414.512.1108

KREMERS URBAN
DEVELOPMENT COMPANY

ORIG AMENDMENT
ORIG AMENDMENT
N/AC

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 for

John Vaughan
Vice President
Kremers Urban Development Company

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
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OGD

G ADDRESS: 6100 W. EXECUTIVE DRIVE, SUITE D, MEQUON, WI 53092 · SHIPPING ADDRESS: 6140 W. EXECUTIVE DRIVE, MEQUON, WI 53092
PHONE: 414.512.1107 · FAX: 414.512.1108

KREMERS URBAN
DEVELOPMENT COMPANY

November 30, 2000

ORIG AMENDMENT
N/AF

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.

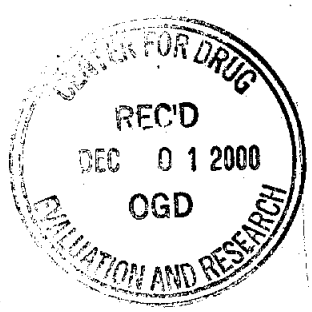
Also pending on this application is a Major Deficiency letter dated July 14, 2000 containing CMC deficiencies. A full and complete response to this letter will be provided to the Agency at a later date.

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 for

John Vaughan
Vice President
Kremers Urban Development Company



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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

NEW CORRESP
NC

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) 238-0951.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
SEP 15 2000
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Sincerely,

Elaine Cibulka for

John Vaughan
Vice President
Kremers Urban Development Company

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KREMERS URBAN
DEVELOPMENT COMPANY

September 14, 2000

NEW CORRESP

NC

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 a ———— and Crospovidone 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 for

John Vaughan
Vice President
Kremers Urban Development Company

CENTER FOR DRUG
RECD
SEP 15 2000
OGD
EVALUATION AND RESEARCH

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KREMERS URBAN
DEVELOPMENT COMPANY

July 13, 2000

NDA ORIG AMENDMENT
N/AB

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

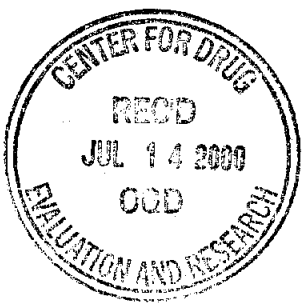
BIOEQUIVALENCY TELEPHONE AMENDMENT 015

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

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KREMERS URBAN
DEVELOPMENT COMPANY

June 23, 2000

ORIG AMENDMENT
N/A C.

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 reviewer the final version of the CMC documents.

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ANDA 75-410
Omeprazole Delayed Release Capsules, 10 mg and 20 mg
Amendment 001 to A-012

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

APPEARS THIS WAY
ON ORIGINAL

KREMERS URBAN
DEVELOPMENT COMPANY

June 2, 2000

ORIG AMENDMENT
N|AB

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

Dear Sir/Madam:

Reference is made to the teleconference on May 25, 2000 between Office of Generic Drugs Bioequivalency 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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 05 2000
OGD

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KREMERS URBAN
DEVELOPMENT COMPANY

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

NDA ORIG AMENDMENT
N/AB

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.

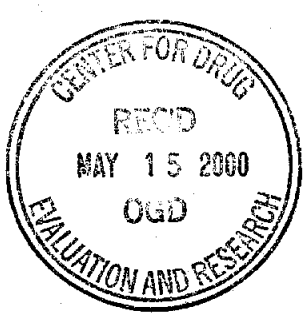
Reference is also made to the teleconference held between Office of Generic Drugs Bioequivalence Division and KUDCO representatives on April 18, 2000. In response to Agency comments during the teleconference, and in response to the above-mentioned letter, KUDCO herein provides additional information 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



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6.1

KREMERS URBAN
DEVELOPMENT COMPANY

February 8, 2000

ORIG AMENDMENT

NIAC

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,

Donna Mullhaupt
for

John Vaughan
Vice President
Kremers Urban Development Company

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KREMERS URBAN
DEVELOPMENT COMPANY

NEW CORRESP

NC

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,

Eric B. Foster for

John Vaughan
Vice President
Kremers Urban Development Company

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 14 1999
OGD

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KREMERS URBAN
DEVELOPMENT COMPANY

NEW CORRESP
NC

November 22, 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

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

NOV 23 1999

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KREMERS URBAN
DEVELOPMENT COMPANY

September 16, 1999

NDA ORIG AMENDMENT
N/A6

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 for

John Vaughan
Vice President
Kremers Urban Development Company

CENTER FOR DRUG EVALUATION AND RESEARCH
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SEP 17 1999
OGD

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PHONE: 414.512.1107 · FAX: 414.512.1108

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:

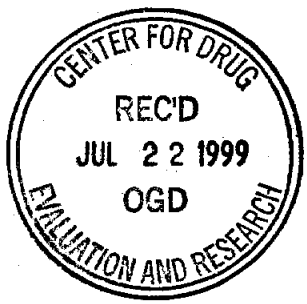
Reference is made to the above-referenced ANDA submitted to the agency on July 2, 1998 and to Amendment 009 submitted on July 1, 1999 which amended the application to include a 10 mg capsule. In accordance with 21 CFR § 314.95 (b), Kremers Urban Development Company (KUDCO) is submitting this amendment 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



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PHONE: 414.512.1107 · FAX: 414.512.1108

KREMERS URBAN
DEVELOPMENT COMPANY

July 1, 1999

NDA ORIG AMENDMENT
N/Ac

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:

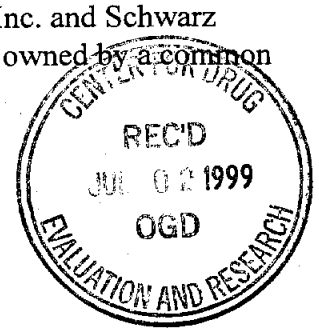
Reference is made to the above-referenced ANDA submitted to the agency on July 2, 1998 and currently under review at the Agency.

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 submissions 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.



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PHONE: 414.512.1107 · FAX: 414.512.1108

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,

John Vaughn
Vice President
Kremers Urban Development Company

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

KREMERS URBAN
DEVELOPMENT COMPANY

June 4, 1999

NDA ORIG AMENDMENT
N/AB

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,

Elaine Abutka for

John Vaughan
Vice President
Kremers Urban Development Company

CENTER FOR DRUG
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JUN 07 1999
OGD
EVALUATION AND RESEARCH

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KREMERS URBAN
DEVELOPMENT COMPANY

December 29, 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

NDA ORIG AMENDMENT

AB

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 Multhauf
for

Jonathan A. Thiel
Vice President
Kremers Urban Development Company

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KREMERS URBAN
DEVELOPMENT COMPANY

NEW CORRESP
NC

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

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KREMERS URBAN
DEVELOPMENT COMPANY

November 9, 1998

CORRESP
NC

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,

Jonathan A. Thiel
Vice President
Kremers Urban Development Company

Nadine 1-12-99

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BIOAVAILABILITY

1

KREMERS URBAN
DEVELOPMENT COMPANY

ORIG AMENDMENT
N/AB

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,

Donna Multhauf
for

Jonathan A. Thiel
Vice President
Kremers Urban Development Company

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ANDA 75-410

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,

/S/

Jerry Phillips 8/7/98
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, DSP /S/ date 8/7/98
HFD-615,NMahmud, CSO date 8/6/98
HFD-645,BArnwine, Sup. Chem. /S/ date
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ANDA Acknowledgment Letter!

KREMERS URBAN
DEVELOPMENT COMPANY

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

NEW CORRESP
NC

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,

Donna Multhauf
for
Jonathan A. Thiel
Vice President
Kremers Urban Development Company

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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 conferences 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

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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 biostudy 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,

Jonathan A. Thiel
Vice President
Kremers Urban Development Company