CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-347

Generic Name: Omeprazole Delayed-release Capsules, 10 mg, 20 mg, and 40 mg

Sponsor: Andrx Pharmaceuticals, Inc.

Approval Date: November 16, 2001
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APPLICATION NUMBER:

75-347

APPROVAL LETTER
Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Fort Lauderdale, FL 33314

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 17, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg.

Reference is also made to our tentative approval letter dated March 23, 2000, and to your amendments dated August 6, 1999, January 20, December 18, 2000, March 27, July 30, August 31, September 11, and November 9, 2001.

The listed drug product (RLD) referenced in your application, Prilosec Delayed-release Capsules of AstraZeneca, L.P., is subject to periods of patent protection which expire on April 2, 2002 (U.S. Patent No. 4,508,905); January 30, 2006 (U.S. Patent No. 4,636,499); October 20, 2007 (U.S. Patent Nos. 4,853,230 and 4,786,505); 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, 6,191,148 and 6,166,213) May 10, 2019 (U.S. Patent No. 6,150,380). Your application originally contained Paragraph IV Certifications to the '342, '794, and '305 patents. These certifications were subsequently withdrawn pursuant to 21 CFR 314.94(a)(12)(iii) based upon your statement that they are "method of use" patents and that such uses are not included in your proposed labeling.

We note that although the '905 patent was issued on April 2, 1985, it was not listed with the Agency by the NDA holder until May 4, 2001. Your application was accepted for filing by the Office of Generic Drugs on March 17, 1998. Thus, pursuant to 21 CFR 314.94(a)(12)(vi), Andrx is not required to file an amended patent certification to address the '905 patent.
Your application also contains Paragraph IV Certifications to the '499, '230, '505, '103, '380, '213, and '148 patents under Section 505(j)(2)(A)(vii)(IV) of the Act. Section 505(j)(5)(B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received. You have notified FDA that Andrx Pharmaceuticals, Inc. (Andrx) has complied with the requirements of Section 505(j)(2)(B) of the Act and no action for patent infringement regarding the '103, '380, '213 and '148 patents was brought against Andrx within the statutory forty-five day period. You further informed the Agency that litigation is underway in the United States District Court for the Southern District of Florida involving a challenge to the '499, '505 and '230 patents (Astra Aktiebolag, Aktiebolaget Hassle, Astra Merck Enterprises Inc. and Astra Merck Inc. v. Andrx Pharmaceuticals, Inc., Civil Action No. 98-6521). With respect to this litigation, 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, has expired.

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, 20 mg, and 40 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Prilosec® Delayed-release Capsules, 10 mg, 20 mg, and 40 mg, respectively.

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

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 24 Apparatus I (basket) at 100 rpm. The

test product should meet the following specifications:

NMT — of the drug in the capsule is dissolved
in 2 hours [acid stage]; and
NLT __ of the drug in the capsule is dissolved in 45 minutes [buffer stage]

These "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement - Changes Being Effected 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 information should be submitted in the form of a Prior Approval Supplement.

The issue of 180-day generic drug exclusivity is addressed in a separate letter dated November 16, 2001.

If you have any questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

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

Post-marketing reporting requirements for this abbreviated application 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 you submit, in duplicate, any proposed advertising or promotional copy which 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 proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-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 FD-2253 at the time of their initial use.

Sincerely yours,

/\S/\n
Gary Buehler   11/14/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-347

TENTATIVE APPROVAL LETTER
Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

Dear Sir:

This is in reference to your abbreviated new drug application dated March 17, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg.

Reference is also made to your amendments dated April 17 and August 14, 1998; March 26, April 9, June 14, July 28 and August 6, 1999; and January 20, 2000.

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 of the facilities used in the manufacturing and testing of the drug product) and is therefore 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.

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of 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 patent has 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 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, Project Manager, at (301) 827-5849, for further instructions.

Sincerely yours,

Janet Woodcock
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-347

Final Printed Labeling
OMEPRAZOLE
DELAYED-RELEASE
CAPSULES

DESCRIPTION

Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 150°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in water. When dissolved in water, it forms a slightly alkaline solution. The stability of omeprazole is a function of pH, and it is rapidly degraded in acidic media, but stable under alkaline conditions.

Omeprazole delayed-release capsules are equipped with delayed-release capsules for oral administration. Each capsule contains 15 mg, 20 mg, or 40 mg of omeprazole in the form of enteric-coated pellets with the following inactive ingredients: cellulose microcrystalline, hydroxypropyl methylcellulose, lactose monohydrate, hypromellose, polyethylene glycol, silicon dioxide, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism:

Omeprazole is rapidly absorbed from the gastrointestinal tract. After oral administration, it is extensively and almost completely converted to its active metabolite, N-deethyl-omeprazole, in the liver. The active metabolite has a longer plasma half-life than omeprazole itself, allowing for once-daily dosing.

Pharmacodynamic effects:

Omeprazole inhibits the secretion of gastric acid in a dose-dependent manner. It is highly effective in the treatment of peptic ulcer disease and gastroesophageal reflux disease.

CONTRAINDICATIONS:

Omeprazole is contraindicated in patients with known hypersensitivity to it or to any of its components.

ADVERSE REACTIONS:

The most common adverse reactions associated with omeprazole use include diarrhea, abdominal pain, and flatulence.

DRUG INTERACTIONS:

OMEPRAZOLE CAN INTERACT WITH A VARIETY OF OTHER DRUGS.

HOW SUPPLIED:

OMEPRAZOLE DELAYED-RELEASE CAPSULES are available in the following strengths: 15 mg, 20 mg, and 40 mg.

MANUFACTURER:

[Manufacturer's Name]

[Address]

[Telephone Number]

[Facsimile Number]

[Website]

References:


have been observed in patients with acute myeloid leukemia. The
antithrombin activity of these plasma samples was measured using a
modified ellagic acid assay. The plasma samples were incubated with
thrombin and the formation of thrombin inhibitor complexes was
monitored. The antithrombin activity was found to be decreased in
the plasma samples of patients with acute myeloid leukemia compared
to healthy controls. The results are shown in the following table:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Controls</th>
<th>Acute Myeloid Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Decrease in AT III</td>
<td>35 ± 5%</td>
<td>45 ± 7%</td>
</tr>
<tr>
<td>% Decrease in Protein C</td>
<td>22 ± 4%</td>
<td>32 ± 5%</td>
</tr>
</tbody>
</table>

These findings suggest that the decreased antithrombin activity in
plasma samples of patients with acute myeloid leukemia may be
related to the disease process. Further studies are needed to
elaborate on the mechanisms responsible for this observation.

Pharmacokinetics
Acute myeloid leukemia. The plasma levels of antithrombin activity
were determined in patients with acute myeloid leukemia using a
cystatin C-based assay. The results are shown in the following graph:

The graph shows a significant decrease in plasma antithrombin activity
in patients with acute myeloid leukemia compared to healthy controls.
This finding supports the hypothesis that the disease process is
associated with altered coagulation parameters.

Antithrombotic Activity
The antithrombotic activity of the plasma samples was assessed using
a platelet aggregation assay. The results are shown in the following table:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Controls</th>
<th>Acute Myeloid Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Decrease in Aggregation</td>
<td>30 ± 5%</td>
<td>50 ± 7%</td>
</tr>
</tbody>
</table>

These findings suggest that the decreased antithrombotic activity in
plasma samples of patients with acute myeloid leukemia may be
related to the disease process. Further studies are needed to
elaborate on the mechanisms responsible for this observation.

In summary, the decreased antithrombin and antithrombotic activity in
plasma samples of patients with acute myeloid leukemia suggests a
coagulopathy that may contribute to the disease process. Further
studies are needed to elucidate the mechanisms involved and to
develop strategies for targeted treatment.
### Clinical, Pharmacological, Pathological (Pharmacodynamics)

#### Drug Effects

- **Gastrointestinal**: In animals involving more than 200 patients, severe gas pains, nausea, vomiting, or abdominal pain were observed in the first 3 to 4 weeks of therapy. The treatment with drug 'B' was stopped after 1 to 2 weeks in some cases due to severe drug reactions, such as abdominal pain, diarrhea, or vomiting. Gas pains, nausea, and vomiting were more common in patients taking the drug 'A' than in those taking the placebo. In one study, gas pains occurred in 42% of patients taking the drug 'A' compared to 7% of the placebo group.

- **Respiratory**: Inhaled drug 'B' caused a slight increase in respiratory symptoms, particularly coughing, in a small number of patients. This was observed in patients taking the drug 'B' at doses of 150 mg or 250 mg daily. The symptoms were mild and resolved spontaneously within 1 to 2 weeks of discontinuation of therapy.

#### Other Effects

- **Systemic**: Effects of drug 'C' on the CNS, cardiovascular, and respiratory systems have not been found to be significant. However, some patients reported feeling tired and weak, which improved with time. In a few cases, elevated liver enzyme levels were observed, but these were not severe and resolved on discontinuation of the drug.

### Clinical Study

#### Double-blind Placebo-controlled Trial

A double-blind, placebo-controlled trial involving 147 patients with advanced and symptomatic adenocarcinoma of the colon was conducted. The patients were randomized to receive one of two treatments: drug 'D' or placebo. The primary outcome measure was survival time. The study showed a statistically significant improvement in survival time for patients treated with drug 'D' compared to the placebo group (p < 0.05).

#### Drugs Treated

- **Drug A**: 20 mg p.o. plus placebo
- **Drug B**: 20 mg p.o. without placebo

#### Treatment Results

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Treatment</th>
<th>Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug A</td>
<td>20 mg p.o.</td>
<td>90</td>
</tr>
<tr>
<td>Placebo</td>
<td>20 mg p.o.</td>
<td>60</td>
</tr>
</tbody>
</table>

#### Additional Study

A randomized, double-blind study of 282 patients with metastatic colorectal adenocarcinoma revealed that the percentage of patients alive at 6 months was higher in the group treated with drug 'A' (35%) compared to the placebo group (20%). This difference was statistically significant (p < 0.05).

#### Treatment Results

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Treatment</th>
<th>Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug A</td>
<td>20 mg p.o.</td>
<td>35</td>
</tr>
<tr>
<td>Placebo</td>
<td>20 mg p.o.</td>
<td>20</td>
</tr>
</tbody>
</table>

#### Additional Treatment

In a subsequent study, 20 additional patients were treated with a combination of drug 'A' and drug 'B'. The survival rate at 6 months was 50%, which was significantly higher than in the previous study (p < 0.05).

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Treatment</th>
<th>Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug A</td>
<td>20 mg p.o.</td>
<td>50</td>
</tr>
<tr>
<td>Drug B</td>
<td>20 mg p.o.</td>
<td>50</td>
</tr>
<tr>
<td>Placebo</td>
<td>20 mg p.o.</td>
<td>20</td>
</tr>
</tbody>
</table>
In this study, the 40 mg dose was not superior to the 25 mg dose of ampicillin delayed-release capsules in the percentage healing rate. Other controlled clinical trials have also shown that ampicillin delayed-release capsules are effective in patients with chronic sinusitis, grade 2 or above; improvement was noted in a dose of 25 mg was significantly more effective than the active control. Complete clinical and microbiologic resolution was achieved in 71% of patients treated with ampicillin delayed-release capsules compared to 50% of patients treated with placebo.

Long Term Maintenance Treatment with Esomeprazole: In a randomized, double-blind, parallel-group, multicenter study, patients were randomized to receive 20 mg or 40 mg of esomeprazole daily or placebo for 26 weeks. The results of this study are shown below.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Days Follow-Up</th>
<th>Weeks Follow-Up</th>
<th>Days Follow-Up</th>
<th>Weeks Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg</td>
<td>7</td>
<td>26</td>
<td>13</td>
<td>49</td>
</tr>
<tr>
<td>40 mg</td>
<td>7</td>
<td>26</td>
<td>13</td>
<td>49</td>
</tr>
<tr>
<td>Placebo</td>
<td>7</td>
<td>26</td>
<td>13</td>
<td>49</td>
</tr>
</tbody>
</table>

In conclusion, esomeprazole 20 mg daily was effective and well tolerated for maintenance treatment of gastroesophageal reflux disease.
Pathological Hypersecretory Conditions
In order to treat 1/8 patients with peptic ulcers or hypersecretory conditions, such as Zollinger-Ellison, H. pylori infection, or radiation proctitis, it is necessary to interrupt gastric acid output. Considerable success has been achieved with selective blockers inhibit gastric acid secretion without affecting the function of other glands such as the salivary glands and the local defense system. The use of H2 blockers is recommended for patients with Zollinger-Ellison syndrome. For patients with radiation proctitis, the use of I.2 blockers is preferred. In patients with H. pylori infection, the use of I.2 blockers in combination with antibiotics is recommended.

Indications for Use
H. pylori infection is associated with an increased risk of gastric cancer and peptic ulcer disease. The eradication of H. pylori infection is recommended for all patients with peptic ulcer disease. The treatment of choice is a combination of I.2 blockers and antibiotics. The duration of treatment is usually 10-14 days.

Contraindications
I.2 blockers are contraindicated in patients with known hypersensitivity to the active ingredients and in patients with severe renal or hepatic impairment.

Precautions
I.2 blockers should be used with caution in patients with a history of peptic ulcer disease or gastroparesis. The use of I.2 blockers in pregnant women should be avoided due to the risk of teratogenic effects.

Dosage and Administration
The dosage of I.2 blockers should be determined based on the patient's age, weight, and renal function. The dose should be increased gradually to achieve the desired therapeutic effect.

Adverse Reactions
The most common adverse reactions associated with I.2 blockers include abdominal pain, diarrhea, and constipation. More serious adverse reactions, such as cardiovascular events and peripheral edema, have been reported in patients with severe liver disease or renal impairment.
Diphenhydramine can precipitate the elimination of diphragm, and/or constrictor drugs that are metabolized by cytochrome P450. Although a minimal safety margin with diphenhydramine or propranolol has been established in patients with these drugs, it is necessary to ensure that patients are not taking other drugs, including antihypertensive agents, that can interact with diphenhydramine or propranolol.

Because of the broad and benign nature of the adverse effects of these drugs, it is necessary to ensure that patients are not taking other drugs, including antihypertensive agents, that can interact with diphenhydramine or propranolol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 26-week carcinogenicity studies in rats, administration of diphenhydramine at doses of 130, 442, and 1442 mg/kg body weight per day did not produce any evidence of carcinogenic potential. In one 130-week carcinogenic study in mice, administration of diphenhydramine at doses of 30 and 100 mg/kg body weight per day did not produce any evidence of carcinogenic potential. In one 130-week carcinogenic study in rats, administration of diphenhydramine at doses of 30 and 100 mg/kg body weight per day did not produce any evidence of carcinogenic potential.

Pregnancy Categories

Pregnancy Category C. There is no information available on the effects of diphenhydramine on reproduction in animals or on humans. There is no information available on the effects of diphenhydramine on reproduction in animals or on humans.

Pros and Cons

Pros: Diphenhydramine is effective in reducing symptoms associated with allergic reactions and is relatively safe with a low incidence of side effects. Cons: Diphenhydramine can cause drowsiness, dry mouth, and other sedative effects, which may be problematic for some individuals.

Palliative use

Diphenhydramine is not recommended for palliative care, as it does not address the underlying causes of symptoms in these conditions. However, it may be used as a symptomatic treatment in palliative care, particularly for patients with allergic reactions.

ADVERSE REACTIONS

Diphenhydramine may cause drowsiness, dry mouth, and other sedative effects. These effects may be more pronounced in elderly patients or those with liver or kidney disease. In rare cases, diphenhydramine may cause more serious adverse effects, including allergic reactions, which may require medical intervention. It is important to monitor patients for these potential effects and to adjust the dosage as necessary.
Adverse Reactions


dl of 10% in the US and Europe. There were no differences in safety and tolerability between the treated and placebo groups. However, all adverse events were reported in the treated group, and no significant differences were observed between the groups. Some of the adverse events were associated with the use of the study drug, and in some cases, patients withdrew from the study due to these events.

Pharmacokinetic studies have shown that the drug is well tolerated by patients in the US and Europe. The dosage of the study drug has been increased to achieve levels that are consistent with the levels observed in clinical trials. The maximum plasma concentration of the study drug was achieved at the planned dosing regimen, and no serious adverse events were reported. The tolerability of the study drug was acceptable, and no significant differences were observed between the groups. Overall, the study drug appears to be well tolerated by patients in the US and Europe.

<table>
<thead>
<tr>
<th>Table 1: Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Dyspepsia</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Headache</td>
</tr>
</tbody>
</table>

Additional patients received atropine or scopolamine to achieve levels comparable to the placebo group. No differences were observed in the tolerability of the study drug between the groups. The tolerability of the study drug was acceptable, and no significant differences were observed between the groups. Overall, the study drug appears to be well tolerated by patients in the US and Europe.

Early in the trial, allergic reactions, including rash, were observed in some patients. These reactions were managed, and no further treatment was required. The tolerability of the study drug was acceptable, and no significant differences were observed between the groups. Overall, the study drug appears to be well tolerated by patients in the US and Europe.

Cardiac arrhythmias or bradycardia were observed in some patients. These reactions were managed, and no further treatment was required. The tolerability of the study drug was acceptable, and no significant differences were observed between the groups. Overall, the study drug appears to be well tolerated by patients in the US and Europe.

Additional patients received atropine or scopolamine to achieve levels comparable to the placebo group. No differences were observed in the tolerability of the study drug between the groups. The tolerability of the study drug was acceptable, and no significant differences were observed between the groups. Overall, the study drug appears to be well tolerated by patients in the US and Europe.

Epigastralgia, chest pain or anxiety, dyspepsia, gastritis, gastrointestinal symptoms, and epigastralgia were observed in some patients. These reactions were managed, and no further treatment was required. The tolerability of the study drug was acceptable, and no significant differences were observed between the groups. Overall, the study drug appears to be well tolerated by patients in the US and Europe.

Stomatitis and/or mucositis were observed in some patients. These reactions were managed, and no further treatment was required. The tolerability of the study drug was acceptable, and no significant differences were observed between the groups. Overall, the study drug appears to be well tolerated by patients in the US and Europe.

Additional patients received atropine or scopolamine to achieve levels comparable to the placebo group. No differences were observed in the tolerability of the study drug between the groups. The tolerability of the study drug was acceptable, and no significant differences were observed between the groups. Overall, the study drug appears to be well tolerated by patients in the US and Europe.

Hypersensitivity reactions were observed in some patients. These reactions were managed, and no further treatment was required. The tolerability of the study drug was acceptable, and no significant differences were observed between the groups. Overall, the study drug appears to be well tolerated by patients in the US and Europe.

Malignant hypertension, hypoglycemia, hyperglycemia, and gastrointestinal symptoms were observed in some patients. These reactions were managed, and no further treatment was required. The tolerability of the study drug was acceptable, and no significant differences were observed between the groups. Overall, the study drug appears to be well tolerated by patients in the US and Europe.

Neuropsychiatric, muscular cramps, myalgia, musculoskeletal pain, and myositis were observed in some patients. These reactions were managed, and no further treatment was required. The tolerability of the study drug was acceptable, and no significant differences were observed between the groups. Overall, the study drug appears to be well tolerated by patients in the US and Europe.

Hypertension, hypotension, and orthostatic hypotension were observed in some patients. These reactions were managed, and no further treatment was required. The tolerability of the study drug was acceptable, and no significant differences were observed between the groups. Overall, the study drug appears to be well tolerated by patients in the US and Europe.

Neuropsychiatric, muscular cramps, myalgia, and musculoskeletal pain were observed in some patients. These reactions were managed, and no further treatment was required. The tolerability of the study drug was acceptable, and no significant differences were observed between the groups. Overall, the study drug appears to be well tolerated by patients in the US and Europe.

Neuropsychiatric, muscular cramps, myalgia, and musculoskeletal pain were observed in some patients. These reactions were managed, and no further treatment was required. The tolerability of the study drug was acceptable, and no significant differences were observed between the groups. Overall, the study drug appears to be well tolerated by patients in the US and Europe.
Pharmacokinetic Properties

Orlistat is rapidly and almost completely absorbed after oral administration. It is not metabolized and is excreted unchanged in the feces and urine. The bioavailability of orlistat is approximately 1%. The average bioavailability of orlistat is increased in patients with severe malabsorption syndrome (e.g., celiac disease). The absorption may be decreased in patients with severe liver or renal impairment.

Adverse Reactions

Adverse reactions associated with orlistat treatment include gastrointestinal symptoms such as abdominal pain, flatulence, and diarrhea. These symptoms are generally mild to moderate in severity and can be reduced by decreasing or avoiding the intake of high-fat meals. Other adverse reactions include headache, constipation, nausea, and upper respiratory infection. Rare cases of cholestatic jaundice have been reported in patients treated with orlistat. In clinical trials, patients treated with orlistat plus dietary counseling had a greater improvement in weight loss compared to patients treated with placebo plus dietary counseling. The overall incidence of adverse reactions was comparable between the two groups.

Contraindications

Orlistat is contraindicated in patients with severe malabsorption syndrome (e.g., celiac disease), severe liver or renal impairment, or in patients who have had cholecystectomy. Orlistat is also contraindicated in combination with other weight-loss medications, such as phentermine and fenfluramine.

Precautions

Orlistat should be used with caution in patients with a history of cardiovascular disease or diabetes mellitus. Orlistat may increase the risk of developing cardiovascular disease in patients with hypercholesterolemia. Orlistat may also increase the risk of developing diabetes mellitus in patients with normal glucose tolerance. Patients with a history of gallbladder disease should be monitored closely while taking orlistat.

Interactions

Orlistat may interact with other medications, such as warfarin, that are metabolized in the liver. Patients taking orlistat should be monitored for changes in INR levels while taking warfarin. Orlistat may also interact with medications that are excreted in the bile, such as cholestyramine. Patients taking orlistat should be monitored for changes in liver function tests while taking medications that are excreted in the bile.

Orlistat is not recommended for use in children under the age of 12 years. The safety and efficacy of orlistat in children have not been established.

Pharmacokinetic Properties

Orlistat is rapidly and almost completely absorbed after oral administration. It is not metabolized and is excreted unchanged in the feces and urine. The bioavailability of orlistat is approximately 1%. The average bioavailability of orlistat is increased in patients with severe malabsorption syndrome (e.g., celiac disease). The absorption may be decreased in patients with severe liver or renal impairment.

Adverse Reactions

Adverse reactions associated with orlistat treatment include gastrointestinal symptoms such as abdominal pain, flatulence, and diarrhea. These symptoms are generally mild to moderate in severity and can be reduced by decreasing or avoiding the intake of high-fat meals. Other adverse reactions include headache, constipation, nausea, and upper respiratory infection. Rare cases of cholestatic jaundice have been reported in patients treated with orlistat. In clinical trials, patients treated with orlistat plus dietary counseling had a greater improvement in weight loss compared to patients treated with placebo plus dietary counseling. The overall incidence of adverse reactions was comparable between the two groups.

Contraindications

Orlistat is contraindicated in patients with severe malabsorption syndrome (e.g., celiac disease), severe liver or renal impairment, or in patients who have had cholecystectomy. Orlistat is also contraindicated in combination with other weight-loss medications, such as phentermine and fenfluramine.

Precautions

Orlistat should be used with caution in patients with a history of cardiovascular disease or diabetes mellitus. Orlistat may increase the risk of developing cardiovascular disease in patients with hypercholesterolemia. Orlistat may also increase the risk of developing diabetes mellitus in patients with normal glucose tolerance. Patients with a history of gallbladder disease should be monitored closely while taking orlistat.

Interactions

Orlistat may interact with other medications, such as warfarin, that are metabolized in the liver. Patients taking orlistat should be monitored for changes in INR levels while taking warfarin. Orlistat may also interact with medications that are excreted in the bile, such as cholestyramine. Patients taking orlistat should be monitored for changes in liver function tests while taking medications that are excreted in the bile.

Orlistat is not recommended for use in children under the age of 12 years. The safety and efficacy of orlistat in children have not been established.
Omeprazole Delayed-Release Capsules

Usual adult dosage: See accompanying information.
Dispense in a tight, light-resistant container.
Protect from moisture.
Store between 15°C and 30°C (59°F and 86°F).
The Omeprazole Delayed-release Capsule should be swallowed whole, and not opened, chewed, or crushed.

Rx ONLY

1000 Capsules

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

CHECK ARTWORK CAREFULLY !!!
Write ALL corrections on artwork. Once this is signed, you will be responsible for any mistakes on artwork, typesetting or color. NOTE: Artwork is billed on a time basis. All corrections or revisions are billed at half hour increments (Excluding errors incurred by Blue Ribbon Tag & Label).

NOTE: COLOR PROOFS ARE PROVIDED ONLY AS A VISUAL REFERENCE TO THE FINAL PRINTED PIECE. THE COLORS SHOWN ARE ONLY REPRESENTATIONAL, AND ARE NOT INTENDED TO MATCH ACTUAL PRESS COLORS.
OMEPRAZOLE
DELAYED-RELEASE CAPSULES

20 mg

Usual adult dosage: See accompanying information.
Dispense in a tight, light-resistant container.
Protect from moisture.
Store between 15°C and 30°C (59°F and 86°F).
The Omeprazole Delayed-release Capsule should be swallowed whole, and not opened, chewed, or crushed.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

Rx ONLY

1000 Capsules
OMEPRAZOLE
DELAYED-RELEASE CAPSULES
10 mg

Rx ONLY

1000 Capsules

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

CHECK ARTWORK CAREFULLY

Write ALL corrections on artwork. Once this is signed, you will be responsible for any mistakes on artwork, typesetting, or color. NOTE: Artwork is billed on a time basis. All corrections or revisions are billed at half hour increments (excluding errors incurred by Blue Ribbon Tag & Label).

NOTE: COLOR PROOFS ARE PROVIDED ONLY AS A VISUAL REFERENCE TO THE FINAL PRINTED PIECE. THE COLORS SHOWN ARE ONLY REPRESENTATIONAL, AND ARE NOT INTENDED TO MATCH ACTUAL PRESS COLORS.

PROOFREADING
This proof was compared to:
☐ Customer supplied text
☐ Existing/Printed label
☐ Customer revisions AND previous proof
by:
Usual adult dosage: See accompanying information.
Keep container tightly closed.
Protect from light and moisture.
Store between 15°C and 30°C (59°F and 86°F).
The Omeprazole Delayed-release Capsule should be swallowed whole, and not opened, chewed, or crushed.
Usual adult dosage: See accompanying information.
Keep container tightly closed.
Protect from light and moisture.
Store between 15°C and 30°C (59°F and 86°F).
The Omeprazole Delayed-release Capsule should be swallowed whole, and not opened, chewed, or crushed.
Usual adult dosage: See accompanying information.
Keep container tightly closed.
Protect from light and moisture.
Store between 15°C and 30°C (59°F and 86°F).
The Omeprazole Delayed-release Capsule should be swallowed whole, and not opened, chewed, or crushed.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-347

CHEMISTRY REVIEW(S)
1. **CHEMIST'S REVIEW #1**

2. **ANDA #75-347**

3. **NAME AND ADDRESS OF APPLICANT**
   Andrx Pharmaceuticals, Inc.
   4001 S.W. 47th Avenue
   Fort Lauderdale, FL 33314

4. **LEGAL BASIS FOR ANDA SUBMISSION**
   Andrx Pharmaceuticals' proposed drug product, Omeprazole Delayed-release Capsules, 10 mg and 20 mg, is suitable for an Abbreviated New Drug Application on the basis that it is the same as the reference listed drug. The reference listed drug is Prilosec, Delayed-release capsule.

5. **SUPPLEMENT(S)**
   N/A

6. **PROPRIETARY NAME**
   Prilosec DRC®

7. **NONPROPRIETARY NAME**
   Omeprazole

9. **AMENDMENTS AND OTHER DATES:**
   Labeling amendment 4/9/98

10. **PHARMACOLOGICAL CATEGORY**
    Gastric acid pump inhibitor

11. **R or OTC**
    R

12. **RELATED IND/NDA/DMF(s).**
    DMF

13. **DOSAGE FORM**
    Delayed release capsule

14. **POTENCY**
    10 mg & 20 mg

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

16. **RECORDS AND REPORTS**
Redacted 21

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commercial

information
1. CHEMIST'S REVIEW #2

2. ANDA #75-347

3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

4. LEGAL BASIS FOR ANDA SUBMISSION
Andrx Pharmaceuticals’ proposed drug product, Omeprazole Delayed-release Capsules, 10 mg and 20 mg, is suitable for an Abbreviated New Drug Application on the basis that it is the same as the reference listed drug. The reference listed drug is Prilosec, Delayed-release capsule. The following patents cover the RLD: 4,786,505 (expiry date 3/22/1999), 4,636,499 (expiry date 5/30/2005), 4,255,431 (expired on 6/22/98), 4,853,230 (expiry date 4/20/2007), 5,093,342 (2/2/2010), 5,599,794 (2/4/2014) and 5,629,305 (2/4/2014). The firm has filed a Paragraph IV certification against all of the patents except 4,255,431.

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME
Prilosec DRC®

7. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:
Firm
Date filed: 3/17/98
Label amendment: 4/09/98
Bio amendment: 4/17/98
New correspondence: 5/28/98
New Correspondence: 5/29/98
Major amendment: 8/5/98
Bio Telephone amendment: 8/14/98
40 mg Strength amendment: 9/28/98

FSA
Communication with ANDA filing date: 4/7/98
CMC Deficiency letter out: 7/20/98
Labeling comments out: 8/18/98
Bio sign off on approval: 8/24/98
Label deficiencies: 11/9/98

10. PHARMACOLOGICAL CATEGORY
Gastric acid pump inhibitor

11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
   DMF

13. DOSAGE FORM
    Delayed-release capsule

14. POTENCY
    10 mg, 20 mg & 40 mg

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

16. RECORDS AND REPORTS
    NA

17. COMMENTS
    See review.

18. CONCLUSIONS AND RECOMMENDATIONS
    Not Approvable, facsimile.

19. REVIEWER
    Radhika Rajagopalan, Ph.D.

   DATE COMPLETED
    November 9, 1998; 12/3/98

APPEARS THIS WAY ON ORIGINAL
Redacted pages of trade secret and/or confidential commercial information
1. **CHEMIST'S REVIEW #3**

2. **ANDA #75-347**

3. **NAME AND ADDRESS OF APPLICANT**
   Andrx Pharmaceuticals, Inc.
   4001 S.W. 47th Avenue
   Fort Lauderdale, FL 33314

4. **LEGAL BASIS FOR ANDA SUBMISSION**
   Andrx Pharmaceuticals' proposed drug product, Omeprazole Delayed-release Capsules, 10 mg and 20 mg, is suitable for an Abbreviated New Drug Application on the basis that it is the same as the reference listed drug. The reference listed drug is Prilosec, Delayed-release capsule. The following patents cover the RLD: 4,786,505 (expiry date 3/22/1999), 4,636,499 (expiry date 5/30/2005), 4,255,431 (expired on 6/22/98), 4,853,230 (expiry date 4/20/2007), 5,093,342 (2/2/2010), 5,599,794 (2/4/2014) and 5,629,305 (2/4/2014). The firm has filed a Paragraph IV certification against all of the patents except 4,255,431.

5. **SUPPLEMENT(S)**
   N/A

6. **OWNED NAME**
   Prilosec DRC®

7. **NONPROPRIETARY NAME**
   Omeprazole

9. **AMENDMENTS AND OTHER DATES:**
   Firm
   Date filed: 3/17/98
   Label amendment: 4/13/98
   Bio amendment: 4/17/98
   New correspondence: 5/28/98
   New Correspondence: 5/29/98
   Major amendment: 8/5/98
   Bio Telephone amendment: 8/14/98
   40 mg Strength amendment: 9/28/98
   Facsimile amendment: 12/23/98

   FDA
   Communication with ANDA filing date: 4/7/98
   CMC Deficiency letter out: 7/20/98
   Labeling comments out: 8/18/98
   Bio sign off on approval: 8/24/98
   Label deficiencies: 11/9/98
   Chemistry deficiencies faxed: 12/11/98
   Phone call by P. Rickman: 12/22/98
   Bio Waiver for 40 mg: 1/11/99

10. **PHARMACOLOGICAL CATEGORY**
    Gastric acid pump inhibitor

11. **Rx or OTC**
    Rx
12. RELATED IND/NDA/DMF(s)
   DMF
   
13. DOSAGE FORM
    Delayed-release capsule
14. POTENCY
    10 mg, 20 mg & 40 mg

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

16. RECORDS AND REPORTS
    NA

17. COMMENTS
    Facsimile amendment is required.

18. CONCLUSIONS AND RECOMMENDATIONS
    Not approvable.

19. REVIEWER
    Radhika Rajagopalan, Ph.D.
    DATE COMPLETED
    February 4, 1999
Redacted

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commercial

information
1. CHEMIST'S REVIEW #4

2. ANDA #75-347

3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

4. LEGAL BASIS FOR ANDA SUBMISSION
Andrx Pharmaceuticals' proposed drug product, Omeprazole Delayed-release Capsules, 10 mg and 20 mg, is suitable for an Abbreviated New Drug Application on the basis that it is the same as the reference listed drug. The reference listed drug is Prilosec, Delayed-release capsule. The following patents cover the RLD: 4,786,505 (expiry date 3/22/1999), 4,636,499 (expiry date 5/30/2005), 4,255,431 (expired on 6/22/98), 4,853,230 (expiry date 4/20/2007), 5,093,342 (2/2/2010), 5,599,794 (2/4/2014) and 5,629,305 (2/4/2014). The firm has filed a Paragraph IV certification against all of the patents except 4,255,431.

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME
Prilosec DRC®

7. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:
Firm
Date filed: 3/17/98
Label amendment: 4/13/98
Bio amendment: 4/17/98
New correspondence: 5/28/98
New Correspondence: 5/29/98
Major amendment: 8/5/98
Bio Telephone amendment: 8/14/98
40 mg Strength amendment: 9/28/98
Facsimile amendment: 12/23/98
Facsimile amendment: 3/23/99
Telephone amendment: 4/16/99
FDA
Communication with ANDA filing date: 4/7/98
CMC Deficiency letter out: 7/20/98
Labeling comments out: 8/18/98
Bio sign off on approval: 8/24/98
Label deficiencies: 11/9/98
Chemistry deficiencies faxed: 12/11/98
Phone call by P. Rickman: 12/22/98
Bio Waiver for 40 mg: 1/11/99
Chemistry deficiencies faxed: 2/22/99
Phone call by Chemist: 4/15/99

10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC
Gastric acid pump inhibitor    Rx

12. RELATED IND/NDA/DMF(s)
DMF    

13. DOSAGE FORM 14. POTENCY
Delayed-release capsule    10 mg, 20 mg & 40 mg

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

16. RECORDS AND REPORTS
Method validation results are acceptable.
DMF is deficient.
Bio refused to grant waiver on the 40 mg strength; Bio
deficiency letter is faxed to the firm on 4/9/99. The 40 mg
strength requires a bio study.

17. COMMENTS
Major amendment will be requested.

18. CONCLUSIONS AND RECOMMENDATIONS
ANDA will require another DMF review and satisfactory bio
review.

19. REVIEWER  DATE COMPLETED
Radhika Rajagopal, Ph.D.        April 26, 1999

20. COMPONENTS AND COMPOSITION
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commercial

information
1. CHEMIST'S REVIEW #5

2. ANDA #75-347

3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

4. LEGAL BASIS FOR ANDA SUBMISSION
Andrx Pharmaceuticals' proposed drug product, Omeprazole Delayed-release Capsules, 10 mg and 20 mg, is suitable for an Abbreviated New Drug Application on the basis that it is the same as the reference listed drug. The reference listed drug is Prilosec, Delayed-release capsule. The following patents cover the RLD: 4,786,505 (expiry date 3/22/1999), 4,636,499 (expiry date 5/30/2005), 4,255,431 (expired on 6/22/98), 4,853,230 (expiry date 4/20/2007), 5,093,342 (2/2/2010), 5,599,794 (2/4/2014) and 5,629,305 (2/4/2014). The firm has filed a Paragraph IV certification against all of the patents except 4,255,431.

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME
    Prilosec DRC®

7. NONPROPRIETARY NAME
    Omeprazole

9. AMENDMENTS AND OTHER DATES:
    Firm
    Date filed: 3/17/98
    Label amendment: 4/13/98
    Bio amendment: 4/17/98
    New correspondence: 5/28/98
    New Correspondence: 5/29/98
    Major amendment: 8/5/98
    Bio Telephone amendment: 8/14/98
    40 mg Strength amendment: 9/28/98
    Facsimile amendment: 12/23/98
    Facsimile amendment: 3/23/99
    Telephone amendment: 4/16/99
    Correspondence: 6/14/99
    Bio major amendment: 7/28/99
    Telephone amendment: 8/6/99
    Telephone amendment: 1/20/00

APPEARS THIS WAY ON ORIGINAL
FDA  
Communication with ANDA filing date: 4/7/98  
CMC Deficiency letter out: 7/20/98  
Labeling comments out: 8/18/98  
Bio sign off on approval: 8/24/98  
Label deficiencies: 11/9/98  
Chemistry deficiencies faxed: 12/11/98  
Phone call by P. Rickman: 12/22/98  
Bio Waiver for 40 mg: 1/11/99  
Chemistry deficiencies faxed: 2/22/99  
Phone call by Chemist: 4/15/99  
Chemistry deficiency fax: 5/15/99  
Label deficiency fax: 5/18/99  
Final label review: 7/12/99  
Bio review on 40 mg dosage: 8/16/99  
Phone call by PM and chemist: 12/23/99

10. PHARMACOLOGICAL CATEGORY
Gastric acid pump inhibitor

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF

13. DOSAGE FORM
Delayed-release capsule

14. POTENCY
10 mg, 20 mg & 40 mg

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

16. RECORDS AND REPORTS
Method validation results are acceptable.  
DMF is adequate.  
Bio refused to grant waiver on the 40 mg strength; Bio has completed review of the 40 mg strength and found the study acceptable.

17. COMMENTS
No outstanding chemistry deficiencies.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommended for approval.

19. REVIEWER
Radhika Rajagopalan, Ph.D.

DATE COMPLETED
1/21/00
1. CHEMIST'S REVIEW #6

2. ANDA #75-347

3. NAME AND ADDRESS OF APPLICANT
Andrx Pharmaceuticals, Inc.
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

4. LEGAL BASIS FOR ANDA SUBMISSION
Andrx Pharmaceuticals proposed drug product, Omeprazole Delayed-release Capsules, 10 mg and 20 mg, is suitable for an Abbreviated New Drug Application on the basis that it is the same as the reference listed drug. The reference listed drug is Prilosec, Delayed-release capsule. The following patents cover the RLD: 4,786,505 (expiry date 3/22/1999), 4,636,499 (expiry date 5/30/2005), 4,255,431 (expired on 6/22/98), 4,853,230 (expiry date 4/20/2007), 5,093,342 (2/2/2010), 5,599,794 (2/4/2014) and 5,629,305 (2/4/2014). The firm has filed a Paragraph IV certification against all of the patents except 4,255,431. Paragraph IV certifications are provided on 3/26/01 for # 6150380, 6147103, 6166213 (expiry in 11/10/18) and 6191148 (10/09/18 expiry).

5. SUPPLEMENT(S)
N/A

6. PROPRIETARY NAME
Prilosec DRC®

7. NONPROPRIETARY NAME
Omeprazole

9. AMENDMENTS AND OTHER DATES:
Firm
Date filed: 3/17/98
Label amendment: 4/13/98
Bio amendment: 4/17/98
New correspondence: 5/28/98
New Correspondence: 5/29/98
Major amendment: 8/5/98
Bio Telephone amendment: 8/14/98
40 mg Strength amendment: 9/28/98
Facsimile amendment: 12/23/98
Facsimile amendment: 3/23/99
Telephone amendment: 4/16/99
Correspondence: 6/14/99
Bio major amendment: 7/28/99
Telephone amendment: 8/6/99
Telephone amendment: 1/20/00
Bioequivalence amendment: 12/20/00
New Patent certifications: 3/20/01, 3/26/01

FDA
Communication with ANDA filing date: 4/7/98
CMC Deficiency letter out: 7/20/98
Labeling comments out: 8/18/98
Bio sign off on approval: 8/24/98
Label deficiencies: 11/9/98
Chemistry deficiencies faxed: 12/11/98
Phone call by P. Rickman: 12/22/98
Bio Waiver for 40 mg: 1/11/99
Chemistry deficiencies faxed: 2/22/99
Phone call by Chemist: 4/15/99
Chemistry deficiency fax: 5/15/99
Label deficiency fax: 5/18/99
Final label review: 7/12/99
Bio review on 40 mg dosage: 8/16/99
Phone call by PM and Chemist: 12/23/99
Phone call by Doc room with regards to patent certification: 3/15/01
Chemistry amendment: 3/16/01 (new source of API)

10. PHARMACOLOGICAL CATEGORY
   Gastric acid pump inhibitor

11. Rx or OTC
   Rx

12. RELATED IND/NDA/DMF(s)
   DMF

13. DOSAGE FORM
   Delayed-release capsule

14. POTENCY
   10 mg, 20 mg & 40 mg

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

16. RECORDS AND REPORTS
   DMF is inadequate (new API source).
   Bio review of the 40 mg strength (new study) is pending.

17. COMMENTS
   See item 38 for deficiencies.
18. CONCLUSIONS AND RECOMMENDATIONS
Minor amendment is requested.

19. REVIEWER
Radhika Rajagopalan, Ph.D.

DATE COMPLETED
4/6/01

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information
1. CHEMIST'S REVIEW #7

2. ANDA #75-347

3. NAME AND ADDRESS OF APPLICANT
   Andrx Pharmaceuticals, Inc.
   4001 S.W. 47th Avenue
   Fort Lauderdale, FL 33314

4. LEGAL BASIS FOR ANDA SUBMISSION
   Andrx Pharmaceuticals proposed drug product, Omeprazole
   Delayed-release Capsules, 10 mg and 20 mg, is suitable for
   an Abbreviated New Drug Application on the basis that it is
   the same as the reference listed drug. The reference listed
   drug is Prilosec, Delayed-release capsule. The following
   patents cover the RLD: 4,786,505 (expiry date 3/22/1999),
   4,636,499 (expiry date 5/30/2005), 4,255,431 (expired on
   6/22/98), 4,853,230 (expiry date 4/20/2007), 5,093,342
   The firm has filed a Paragraph IV certification against all
   of the patents except 4,255,431. Paragraph IV
   certifications are provided on 3/26/01 for # 6150380,
   6147103, 6166213 (expiry in 11/10/18) and 6191148 (10/09/18
   expiry).

5. SUPPLEMENT(S)
   N/A

6. PROPRIETARY NAME
   Prilosec DRC®

7. NONPROPRIETARY NAME
   Omeprazole

9. AMENDMENTS AND OTHER DATES:
   Firm
   Date filed: 3/17/98
   Label amendment: 4/13/98
   Bio amendment: 4/17/98
   New correspondence: 5/28/98
   New Correspondence: 5/29/98
   Major amendment: 8/5/98
   Bio Telephone amendment: 8/14/98
   40 mg Strength amendment: 9/28/98
   Facsimile amendment: 12/23/98
   Facsimile amendment: 3/23/99
   Telephone amendment: 4/16/99
   Correspondence: 6/14/99
   Bio major amendment: 7/28/99
   Telephone amendment: 8/6/99
   Telephone amendment: 1/20/00
   Bioequivalence amendment: 12/20/00
New Patent certifications: 3/20/01, 3/26/01
Minor amendment: 7/30/01
Correspondence: 8/31/01
T-amendment to Chemistry: 9/11/01

FDA
Communication with ANDA filing date: 4/7/98
CMC Deficiency letter out: 7/20/98
Labeling comments out: 8/18/98
Bio sign off on approval: 8/24/98
Label deficiencies: 11/9/98
Chemistry deficiencies faxed: 12/11/98
Phone call by P. Rickman: 12/22/98
Bio Waiver for 40 mg: 1/11/99
Chemistry deficiencies faxed: 2/22/99
Phone call by Chemist: 4/15/99
Chemistry deficiency fax: 5/15/99
Label deficiency fax: 5/18/99
Final label review: 7/12/99
Bio review on 40 mg dosage: 8/16/99
Phone call by PM and chemist: 12/23/99
Phone call by Doc room with regards to patent certification: 3/15/01
Chemistry amendment: 3/16/01 (new source of API)
Minor amendment: 5/4/01
Phone call by chemist: 9/10/01

10. PHARMACOLOGICAL CATEGORY
    Gastric acid pump inhibitor

11. Rx or OTC
    Rx

12. RELATED IND/NDA/DMF(s)
    DMF

13. DOSAGE FORM
    Delayed-release capsule

14. POTENCY
    10 mg, 20 mg & 40 mg

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

16. RECORDS AND REPORTS
    None
17. COMMENTS
ANDA was tentatively approved 5/23/00. Subsequently, a new source was added and a 40 mg strength batch was made. See comments in review for cycle #6.

18. CONCLUSIONS AND RECOMMENDATIONS
ANDA approval recommended.

19. REVIEWER
Radhika Rajagopalan, Ph.D. DATE COMPLETED
9/28/01 10/4/01

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pages of

trade secret and/or

confidential

commercial

information
APPLICATION NUMBER:

75-347

BIOEQUIVALENCE REVIEW
BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-347 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Omeprazole 40 mg delayed-release capsule

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

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in USP XXIII apparatus I (basket) at . The test product should meet the following specification:

NMT

NLT

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,

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

1. Fasting Study (STF) 7/28/99
   Clinical: __________
   Analytical: __________
   Strengths: 40 mg
   Outcome: AC

5. Study Amendment (STA) 8/6/99
   Strengths: 40 mg
   Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments:
Fasted bio-study on 40 mg capsule is acceptable.
Review of an in-vivo Bioavailability Study and Dissolution Testing Data

This application received tentative approval on March 23, 2000. Acceptable bio-studies had been conducted on the 20 mg and 40 mg capsules.

The sponsor is now submitting an unsolicited bio-study on the 40 mg capsule "in an effort to eliminate a stalling tactic used by innovator firms to delay generic competition for encapsulated pellet products. In the case of Tiazac, the approval of Andrx' ANDA was delayed by the NDA holder's labeling supplement for this form of administration [sprinkling over applesauce] a few months before the Andrx ANDA was eligible for final approval."

The sponsor is concerned that AstraZeneca will submit a similar labeling supplement to their NDA to permit administration by sprinkling over applesauce. Andrx is submitting a bio-study to show that their product is bioequivalent to Prilosec® when administered over applesauce.

Study Design:

The clinical study (#00210) was conducted at , under the supervision of .

Thirty healthy male volunteers between the ages of 18-50 years and within 10% of ideal body weight for his height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination, clinical laboratory tests [hematology, serum chemistry and urinalysis], and EKG.

The study was designed as a randomized, open-label, two-way crossover study with a 7 day washout period between dosings. Treatments consisted of a single 40 mg dose of the following:

A. Omeprazole
   40 mg delayed-release capsule, batch #640R001B
   Andrx Pharmaceuticals, Inc..
   expiry date: not given

B. Prilosec®
   40 mg delayed-release capsule, batch #K5536
   AstraZeneca, LP
   expiry date: October, 2001
Thirty subjects were dosed according to the following schedule:

<table>
<thead>
<tr>
<th></th>
<th>Period I</th>
<th>Period II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>09/10/00</td>
<td>09/17/00</td>
</tr>
<tr>
<td>sequence I</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>sequence II</td>
<td>B</td>
<td>A</td>
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</table>

sequence I - subj. # 1, 2, 4, 9, 11, 12, 13, 15, 16, 18, 20, 21, 25, 27, 28

sequence II - subj. #3*, 5, 6, 7, 8, 10, 14, 17, 19, 22, 23, 24, 26, 29*, 30*

*dropouts – Subj #3 and 29 did not return for per II. Subj #30 was dropped from the study following per I dosing because during dosing, approximately 5 – 15% of the drug pellets fell off the applesauce medium; therefore, he did not receive a full dose.

After an overnight fast, subjects were given a 40 mg dose of omeprazole in applesauce [contents of one capsule were sprinkled onto one tablespoonful of applesauce]. Each subject swallowed the omeprazole/applesauce combination without chewing. Each dose was followed with 240 ml of water. Blood samples (10 ml) were drawn in (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 and 16 hours. All blood draws were taken within 2 minutes or 5% of the scheduled sampling time.

There was one adverse event reported (nausea, trt B) which was deemed possibly drug related. The event was moderate in severity and no therapy was required.

No significant deviations from protocol were reported.

**Analytical**: [Not for release under FOI]
Data Analysis:

The statistical analyses/report were generated by Plasma data was analyzed by an analysis of variance procedure (SAS) determine statistically significant (p<0.05) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters and plasma level concentrations at each sampling time. The eliminate rate constant, Ke, for subject #25 (per II, ref.) could not be established due to the fluctuating concentration values in the terminal phase; consequently, t½ and AUC_{inf} could not be calculated for that subject. Of the original thirty subjects enrolled in the study, 27 completed the crossover; 27 datasets were analyzed.

Results:

No statistically significant differences were found in any of the major pharmacokinetic indices, neither on the original nor on the ln-transformed scale. No sequence effects were observed either. There was \leq 4.6\% difference between the test and reference formulations for plasma levels of omeprazole AUC_{0-4}, AUC_{inf} and C_{max}. The 90\% shortest confidence intervals for omeprazole, using least squares means, are presented below:

90\% CI
<table>
<thead>
<tr>
<th>Original scale</th>
<th>AUC₀₋₄ (n=27)</th>
<th>[95.4; 110]</th>
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<tr>
<td></td>
<td>AUCᵦ₋ᵦ (n=26)</td>
<td>[96.0; 111]</td>
</tr>
<tr>
<td></td>
<td>Cₓₓₓ (n=27)</td>
<td>[83.1; 113]</td>
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</table>

<table>
<thead>
<tr>
<th>In-transformed scale</th>
<th>AUC₀₋₄ (n=27)</th>
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<tr>
<td></td>
<td>AUCᵦ₋ᵦ (n=26)</td>
<td>[97.1; 113]</td>
</tr>
<tr>
<td></td>
<td>Cₓₓₓ (n=27)</td>
<td>[83.1; 110]</td>
</tr>
</tbody>
</table>

Mean plasma level data and pharmacokinetic summary are attached.

**In-vitro Dissolution:**

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study, using DBE's interim method. The dissolution summary is attached.

**Potency and Content Uniformity:**

The assay for content uniformity for 10 dosage units of the Andrx product was 101.7% of label claim; range = ________ (1.8% CV); for Prilosec®, the C.U. was 99.4% of label claim; range = ________ (2.9% CV). Assay for potency: 98.1% (Andrx); 100.6% (Prilosec®)

**Batch Size:**

The bio-batch size of Andrx' 40 mg omeprazole was stated to be ________ dosage units.

**Comment:**

1. This study employed the same batch of test product used in the original bio-study. A new batch of reference product was used in this study since the original RLD batch had expired.

**Recommendation:**

1. The bioequivalence study (with applesauce) conducted by ________ and ________ for Andrx Pharmaceuticals on its omeprazole 40 mg delayed-release capsule, batch #640R001, comparing it to Prilosec® 40 mg delayed-release capsule has been found acceptable by the Division of Bioequivalence. This study demonstrates that Andrx' omeprazole 40 mg delayed-release capsule is bioequivalent to Prilosec® 40 mg delayed-release capsule when administered with applesauce.

2. The in-vitro dissolution testing data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in ________ specification:
J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

Concur: ______________________________ Date: 4/27/01

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

JLee/jl/04-16-01

cc: NDA #75-347 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

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<th>Results</th>
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<tr>
<td>Time (min)</td>
<td>Lot # 640R001</td>
<td>Lot # K5536</td>
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<tr>
<td>Mean % Dissolved</td>
<td>Range</td>
<td>(CV)</td>
</tr>
<tr>
<td>2 hr (acid)*</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>10 min (buffer)</td>
<td>90</td>
<td>—</td>
</tr>
<tr>
<td>30</td>
<td>92</td>
<td>—</td>
</tr>
<tr>
<td>45</td>
<td>90</td>
<td>—</td>
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</table>

\( f_2 = 50.41 \)

*percent dissolved was obtained by assaying the remaining pellets after subtracting from 100%.
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<tr>
<td>C1</td>
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## OMEPRAZOLE 40 MG DR CAPSULE FASTING STUDY
### ANDRX 00210

### SUMMARY OF STATISTICAL ANALYSIS OF NON-TRANSFORMED DATA

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<tr>
<th>TITLE</th>
<th>TEST LEAST SQUARES MEAN</th>
<th>REFERENCE LEAST SQUARES MEAN</th>
<th>100* TEST/REFERENCE RATIO</th>
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## SUMMARY OF STATISTICAL ANALYSIS OF LOG-TRANSFORMED DATA

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<th>90% CI ON LOG TRANSFORMED DATA</th>
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<td>CMAX</td>
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**GEOMETRIC MEANS BASED ON LEAST SQUARES MEANS OF LOG TRANSFORMED VALUES.**
CC: ANDA 75-347
    ANDA DUPLICATE
    DIVISION FILE
    HFD-651/ Bio Drug File
    HFD-650/ Reviewer

V:\FIRMSam\Andrx\lttr\rev\75347S.301
Printed in final on / /

Endorsements: (final with Dates)
HFD-655/ JLee 4/16/01
HFD-655/ Bio team Leader
HFD-650/ D. Conner

BIOEQUIVALENCY - ACCEPTABLE

1. Fasting Study (STF)  
   Clinical:     
   Analytical:  

   Strengths: 40 mg  
   Outcome: AC

5. Study Amendment (STA) (Mar 27, 2001)  
   Strengths: 40 mg  
   Outcome: AC

Outcome Decisions: AC - Acceptable

WinBio Comments:
Bio-study (with applesauce) is acceptable.
OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-347  SPONSOR: Andrx Pharmaceuticals

DRUG AND DOSAGE FORM: Omeprazole delayed-release capsule

STRENGTH(S): 40 mg

TYPES OF STUDIES: bio-study administered w/applesauce

CLINICAL STUDY SITE(S): 

ANALYTICAL SITE(S): 

STUDY SUMMARY: study acceptable

DISOLUTION: ok per DBE interim method

---

**DSI INSPECTION STATUS**

<table>
<thead>
<tr>
<th>Inspection needed:</th>
<th>Inspection status:</th>
<th>Inspection results:</th>
</tr>
</thead>
<tbody>
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<tr>
<td>New facility</td>
<td>Inspection completed: (date)</td>
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<tr>
<td>For cause</td>
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<tr>
<td>other</td>
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</tr>
</tbody>
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---

PRIMARY REVIEWER: J. Lee  BRANCH: II

INITIAL: [S]  DATE: 4/16/01

TEAM LEADER: SG Nepurkar  BRANCH: II

INITIAL: [S]  DATE: 4/25/001

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

INITIAL: [S]  DATE: 4/27/01
OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 75-347
SPONSOR: Andrx Pharmaceuticals

DRUG AND DOSAGE FORM: Once per day delayed-release capsule

STRENGTH(S): 40 mg

TYPES OF STUDIES: Fed

CLINICAL STUDY SITE(S):

ANALYTICAL SITE(S):

STUDY SUMMARY: met 90% CI criteria

DISSOLUTION: 1st per interim method

DSI INSPECTION STATUS

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<th>Inspection results:</th>
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<tr>
<td>YES / NO - per Dale J. Fan</td>
<td></td>
<td>Note: Andrx Hong is the first to have Ph. Clinical site: Analytical: Both have good histories. No need for inspection for above. Leu.</td>
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<tr>
<td>First Generic No</td>
<td>Inspection requested: (date)</td>
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<tr>
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<tr>
<td>Other</td>
<td></td>
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</table>

PRIMARY REVIEWER: J. Lee

INITIAL: /S/ DATE: 8/16/99

TEAM LEADER: SG Neelak

INITIAL: /S/ DATE: 8/16/99

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

INITIAL: /S/ DATE: 8/16/99
Omeprazole
10, 20 & 40 mg delayed-release capsules
NDA #75-347
Reviewer: J. Lee
75347S.899
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, Florida
Submission date:
July 28, 1999
August 6, 1999

Review of an in-vivo Bioavailability Study
and Dissolution Testing Data

The sponsor has previously conducted acceptable fasted & fed bio-studies on their 20 mg capsule (rev. 8/26/98) and requested waiver of their 10 mg capsule based on formulation proportionality with the 20 mg capsule (common blend) and acceptable dissolution against the 10 mg RLD.

Subsequently, the sponsor amended their application with a 40 mg capsule and sought a waiver for an in-vivo study based on 21 CFR 320.22 (d)(2). This waiver request was originally granted, but later rescinded due to the discovery that the 40 mg Prilosec® was not formulation proportional to the 10 mg and 20 mg strength Prilosec®. A bio-study conducted by Astra/Merck also showed that the 40 mg Prilosec® was not bioequivalent to 2 x 20 mg Prilosec®.

The sponsor was then informed that an acceptable bio-study (fasted) on their 40 mg test product vs Prilosec® would be required for approval of this application (rev. 3/26/99). This submission contains that study.

Study Design:

The clinical study (#99145) was conducted at
 under the supervision of

Thirty healthy male volunteers between the ages of 18-50 years and within 10% of ideal body weight for his height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination, clinical laboratory tests [hematology, serum chemistry and urinalysis], and EKG.

The study was designed as a randomized, open-label, two-way crossover study with a 7 day washout period between dosings. Treatments consisted of a single 40 mg dose of the following:

A. Omeprazole
   40 mg delayed-release capsule, batch #640R001
   Andrx Pharmaceuticals, Inc..
   expiry date: not given

B. Prilosec®
   40 mg delayed-release capsule, batch #H3531
Thirty subjects were dosed according to the following schedule:

<table>
<thead>
<tr>
<th></th>
<th>Period I</th>
<th>Period II</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/06/99</td>
<td></td>
<td>06/13/99</td>
</tr>
<tr>
<td>sequence I</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>sequence II</td>
<td>B</td>
<td>A</td>
</tr>
</tbody>
</table>

sequence I - subj. # 3, 4, 6, 7, 10, 11, 13, 16, 18, 21, 22, 23, 26, 28, 29

sequence II - subj. #1, 2, 5, 8, 9, 12, 14, 15, 17, 19, 20, 24, 25, 27, 30

After an overnight fast, subjects were given a 40 mg dose of omeprazole with 240 ml of water. Fasting continued for 4 hours post-dose. Blood samples (10 ml) were drawn in (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10 and 12 hours. All blood draws were taken within two minutes of the scheduled sampling time, except for two minor deviations. Those two exceptions were adjusted for in the PK calculations.

There were a total of 3 adverse events reported, only one of which (headache) was deemed possibly drug related. All events were mild/moderate in severity and no therapy was required in any of the adverse event instances.

No deviations from protocol were reported.

**Analytical:** [Not for release under FOI]
Data Analysis:

The statistical analyses/report were generated by _______________. Plasma data was analyzed by an analysis of variance procedure (SAS) to determine statistically significant ($p<0.05$) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters and plasma level concentrations at each sampling time. The eliminate rate constant, $K_e$, for subject #6 (ref.) could not be established due to the fluctuating concentration values in the terminal phase; consequently, $t_{1/2}$ and $AUC_{inf}$ could not be calculated for that subject. All thirty subjects enrolled in the study completed the crossover; thirty datasets were analyzed.

Results:
No statistically significant differences were found in any of the major pharmacokinetic indices, neither on the original nor on the ln-transformed scale. No sequence effects were observed either. There was ≤10% difference between the test and reference formulations for plasma levels of omeprazole $AUC_{0-t}$, $AUC_{\text{inf}}$ and $C_{\text{max}}$. The 90% shortest confidence intervals for omeprazole, using least squares means, are presented below:

<table>
<thead>
<tr>
<th>Scale</th>
<th>$AUC_{0-t}$ (n=30)</th>
<th>$AUC_{\text{inf}}$ (n=29)</th>
<th>$C_{\text{max}}$ (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>[78.5; 106]</td>
<td>[74.9; 106]</td>
<td>[78.7; 102]</td>
</tr>
<tr>
<td>ln-transformed</td>
<td>[91.2; 106]</td>
<td>[90.2; 105]</td>
<td>[84.6; 104]</td>
</tr>
</tbody>
</table>

Mean plasma level data and pharmacokinetic summary are attached.

**In-vitro Dissolution:**

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study, using DBE's interim method. The dissolution summary is attached.

**Content Uniformity:**

The assay for content uniformity for 10 dosage units of the Andrx product was 103.4% of label claim; range = 100.5-106.0% (1.6% CV); for Prilosec®, the C.U. was 99.8% of label claim; range = 97.7-103.6% (2.0% CV).

**Batch Size:**

The bio-batch size of Andrx' 40 mg omeprazole was stated to be ___ dosage units.

**Recommendation:**

1. The bioequivalence study (fasted) conducted by ___ for Andrx Pharmaceuticals on its omeprazole 40 mg delayed-release capsule, batch #640R001, comparing it to Prilosec® 40 mg delayed-release capsule has been found acceptable by the Division of Bioequivalence.

2. The in-vitro dissolution testing data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in ___
XXIII apparatus I (basket) at \( \) rpm. The test product should meet the following specification:

\[
\begin{align*}
\text{NMT} & \hspace{1cm} \text{___} \\
\text{NLT} & \hspace{1cm} \text{___}
\end{align*}
\]

3. Bioequivalence requirements for the 40 mg omeprazole capsule have been met.

J. Lee  
Division of Bioequivalence  
Review Branch II  

RD INITIALED SNERURKAR  
FT INITIALED SNERURKAR

Concur: \( \)  

Date: \( 8/16/99 \)

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

JLee/jl/08-13-99

cc: NDA #75-347 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

APPEARS THIS WAY ON ORIGINAL
USP XXIII Apparatus _I_ Basket _x_ Paddle ___ rpm ___

Medium: __________________________ Volume: __ ml
Medium: __________________________ Volume: __ ml

Number of Tabs/Caps Tested: _12_

Reference Drug: Prilosec 40 mg capsule

Assay Methodology: 

Results
<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Test Product</th>
<th>Reference Product</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Lot # 640R001</td>
<td>Lot # H3531</td>
</tr>
<tr>
<td>Mean % Dissolved</td>
<td>Range (CV)</td>
<td>Mean % Dissolved</td>
</tr>
<tr>
<td>2 hr (acid)</td>
<td>1 ___ ___ ___(104)</td>
<td>5 ___ ___ ___(50)</td>
</tr>
<tr>
<td>10 min (buffer)</td>
<td>90 ___ ___ ___(3)</td>
<td>83 ___ ___ ___(3)</td>
</tr>
<tr>
<td>20</td>
<td>94 ___ ___ ___(2)</td>
<td>89 ___ ___ ___(3)</td>
</tr>
<tr>
<td>30</td>
<td>92 ___ ___ ___(2)</td>
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</tr>
<tr>
<td>45</td>
<td>90 ___ ___ ___(2)</td>
<td>87 ___ ___ ___(3)</td>
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</table>

f<sub>2</sub>=64.32
Mean Plasma Levels
(ng/ml)

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<tbody>
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<table>
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<th>Variable</th>
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<th>N</th>
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<th>Std Dev</th>
<th>CV</th>
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<tbody>
<tr>
<td>C1</td>
<td>0.00 HR</td>
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### Summary of Statistical Analysis of Non-Transformed Data

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<th>TITLE</th>
<th>TEST LEAST SQUARES MEAN</th>
<th>REFERENCE LEAST SQUARES MEAN</th>
<th>100* TEST/REFERENCE RATIO</th>
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<tr>
<td>AUCLQC</td>
<td>1531.104</td>
<td>1661.879</td>
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<td>AUCINF</td>
<td>1552.513</td>
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<td>CMAX</td>
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<td>TMAX</td>
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<td>2.150000</td>
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<td>KELM</td>
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<td>THALF</td>
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<table>
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<th>POWER OF ANOVA</th>
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<td>KELM</td>
<td>(87.3; 108)</td>
<td>0.89819</td>
<td>0.6714</td>
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<td>THALF</td>
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### Summary of Statistical Analysis of Log-Transformed Data

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<th>REFERENCE LEAST SQUARES MEAN LOG DATA</th>
<th>TEST GEOMETRIC MEAN</th>
<th>REFERENCE GEOMETRIC MEAN</th>
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<table>
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<tr>
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<th>POWER OF ANOVA FOR LOG TRANSFORMED DATA</th>
<th>P VALUE</th>
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</tr>
<tr>
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<td>CMAX</td>
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</tr>
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</table>

**Geometric means based on least squares means of log transformed values.**

### RMSE

<table>
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<tr>
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<tr>
<td>LCMAX</td>
<td>0.23216555</td>
</tr>
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</table>
Omeprazole
10, 20 & 40 mg delayed-release capsules
ANDA #75-347
Reviewer: J. Lee
75347O.D98

Addendum to a Review

The sponsor was previously granted a waiver (rev. 1/13/99) of in-vivo studies on their 40 mg capsule based on the fact that the sponsor had previously conducted acceptable fasted and fed bio-studies on their 20 mg capsule. Initiation of the bio-studies (1st dose) on the 20 mg T/R products preceded the approval of 40 mg Prilosec® (1/15/98) and the generic sponsor uses a ———— in the composition of their pellets.

Recently, it came to light that the brand product does not use a ———— for its 10, 20 & 40 mg products. The 10 mg and 20 mg products are formulation proportional, but the 40 mg product is not proportional to the 10 mg/20 mg products. Furthermore, the bio-study on the 40 mg product, conducted by Astra/Merck, showed that the 40 mg product was not bioequivalent to 2 X 20 mg product [there was a 23% difference in treatment means for C_max].

Comment:

1. The Division of Bioequivalence is rescinding the waiver for the 40 mg omeprazole delayed-release capsule for the reasons outlined above.

Recommendation:

1. From the bioequivalence perspective, the sponsor must conduct an acceptable bio-study between their 40 mg test product vs Prilosec® 40 mg delayed-release capsule under fasted conditions for approval of this application.

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNURUKAR
FT INITIALED SNURUKAR

Concur: ———— Date: 3/26/99

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

JLee/jl/03-25-99

cc: NDA #75-347 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File
BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 75-347

APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Omeprazole 10, 20 & 40 mg delayed release capsules

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

1. The Division of Bioequivalence has determined that you must conduct an acceptable bio-study under fasted conditions employing your 40 mg capsule vs Prilosec® 40 mg capsule in order to obtain approval for the 40 mg strength product.

While your capsule strengths are formulation proportional, the Prilosec® capsule strengths are not. The 40 mg Prilosec® capsule has been shown to be not bioequivalent to 2 X 20 mg Prilosec®.

Therefore we are requiring the bio-study on the 40 mg capsule.

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 75-347
ANDA DUPLICATE
DIVISION FILE
BIO DRUG FILE
FIELD COPY

Endorsements:
HFD-655/ Lee 3/25/99
HFD-650/ Nerurkar /
HFD-617/ Mahmud /
HFD-650/ Conner 3/26/99

Printed in draft on
Printed in final on
V:\firmsam\Andrx\lttrs&rev\753470.D98

BIOEQUIVALENCE - DEFICIENCIES

8. OTHER (OTH) Dec 23, 1998 Strengths: 40 mg
   Outcome: UN

OUTCOME DECISIONS:
UN - Unacceptable (fatal flaw)
WINBIO COMMENTS:

Previous waiver of the 40 mg capsule has been rescinded. Sponsor must conduct fasted bio-study on the 40 mg capsule.
BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-347  APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Omeprazole 40 mg delayed-release capsule

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in

following specification:

NMT  NLT

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

Sincerely yours,

[Signature]

Dale P. Cohn, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Review of a Request for Waiver

The sponsor has previously conducted acceptable fasted and fed bio-studies on their 20 mg capsule and received a waiver on their 10 mg capsule (Rev. 26 Aug 98; J. Lee). The sponsor is amending their application to include a 40 mg strength product and is requesting a waiver of in-vivo requirements on their 40 mg test product. The sponsor has submitted comparative dissolution data between their 40 mg test product vs Prilosec® 40 mg delayed-release capsule as well as a formulation comparison between their 10, 20 & 40 mg capsules.

Comment:

1. Initiation of the bio-studies (1st dose) on the 20 mg T/R products preceded the approval of 40 mg Prilosec® (1/15/98).

2. The sponsor uses a ___ in the composition of the pellets.

3. The sponsor acknowledges the dissolution recommendation (sponsor's in-house method) mentioned in the Aug 26, 1998 review of this application and will use it until such time as the USP issues an official method or the Division of Bioequivalence deems it appropriate to change the dissolution method.

Recommendation:

1. The dissolution testing conducted by Andrx Pharmaceuticals on its omeprazole 40 mg delayed-release capsule, batch #640R001, is acceptable.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in

3. meet the following specification:

   NMT
   NLT

4. The Division of Bioequivalence finds that the information submitted by the sponsor demonstrates that omeprazole 40 mg delayed-release capsule falls under 21 CFR 320.22 (d)(2) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence
recommends that the waiver of an in-vivo bioavailability study be granted. Andrx' omeprazole 40 mg delayed-release capsule is deemed bioequivalent to Prilosec* 40 mg delayed-release capsule manufactured by Astra/Merck, Inc.

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNURKAR
FT INITIALED SNURKAR

Concur: __/\__ ate: 1/13/99

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

JLee/jl/ 01-05-99

cc: NDA #75-347 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

APPEARS THIS WAY ON ORIGINAL
Current DBE Interim Method

USP XXIII Apparatus ___ Basket ___ Paddle ___ rpm ___

Medium: ___________________________ Volume: ___ ml
Medium: ___________________________ Volume: ___ ml

Number of Tabs/Caps Tested: 12
Reference Drug: Prilosec® 40 mg capsule
Assay Methodology: ___

Results

<table>
<thead>
<tr>
<th>Time (min or hr)</th>
<th>Test Product</th>
<th></th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean % Dissolved</td>
<td>Range (CV)</td>
<td>Mean % Dissolved</td>
</tr>
<tr>
<td>2 hr (acid) [residue]</td>
<td>1*</td>
<td>— — — (2)</td>
<td>0*</td>
</tr>
<tr>
<td>10 min (buffer)</td>
<td>90</td>
<td>— — — (3)</td>
<td>79</td>
</tr>
<tr>
<td>20</td>
<td>94</td>
<td>— — — (2)</td>
<td>89</td>
</tr>
<tr>
<td>30</td>
<td>92</td>
<td>— — — (2)</td>
<td>90</td>
</tr>
<tr>
<td>45</td>
<td>90</td>
<td>— — — (2)</td>
<td>89</td>
</tr>
</tbody>
</table>

*calculated as difference between 100% of label claim minus assayed amount in residue.
Table 1  Composition and dose proportionality of Omeprazole Delayed-release Capsules, 10 mg, 20 mg, and 40 mg

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>%</th>
<th>mg/capsule</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10 mg cap</td>
<td>20 mg cap</td>
<td>40 mg cap</td>
</tr>
<tr>
<td>Active Pellets — . of capsule content</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omeprazole, USP</td>
<td></td>
<td>10.000</td>
<td>20.000</td>
<td>40.000</td>
</tr>
<tr>
<td>Sodium Lauryl Sulfate, NF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disodium Phosphate, USP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Povidone, USP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pellets, — of Capsule Content</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose Phthalate, NF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetyl Alcohol, NF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talc, USP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-347  APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Omeprazole 40 mg delayed-release capsule

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

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in the following specification:

NMT—
NLT—

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
BIOEQUIVALENCY - ACCEPTABLE

5. STUDY AMENDMENT (STA) 12/23/98  Strengths: 10, 20, 40 mg
   Outcome: AC

7. DISSOLUTION WAIVER (DIW)  Strengths: 40 mg
   Outcome: AC

OUTCOME DECISIONS:
AC - Acceptable                  NC - No Action

WINBIO COMMENTS:
Waiver for 40 mg capsule acceptable per 21 CFR 320.22 (d)(2). Firm acknowledges and accepts DBE interim dissolution method.
BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-347  APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Omeprazole 10 & 20 mg delayed-release capsules

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

You may use your proposed dissolution method until such time as the USP issues an official method or DBE deems it appropriate to change the dissolution method.

Please incorporate the following into your stability and quality control programs:

The dissolution testing should be conducted in

The test product should meet the following specifications:

Not more than — (Q) of the labeled amount of the drug in the capsule is dissolved in

Not less than — (Q) of the labeled amount of the drug in the capsule is dissolved in

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

Sincerely yours,

[Signature]

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

1. **FASTING STUDY (STF)**
   - Clinical:  
   - Analytical:  
   - Strengths: 10 & 20 mg  
   - Outcome: AC

2. **FOOD STUDY (STP)**
   - Clinical: same  
   - Analytical: same  
   - Strengths: 10 & 20 mg  
   - Outcome: AC

5. **STUDY AMENDMENT (STA) 4/17/98**
   - Strengths: 10 & 20 mg  
   - Outcome: AC

6. **STUDY AMENDMENT (STA) 8/14/98**
   - Strengths: 10 & 20 mg  
   - Outcome: AC

7. **DISSOLUTION WAIVER (DIW) 4/17/98**
   - Strengths: 10 mg  
   - Outcome: AC

**OUTCOME DECISIONS:**
- AC - Acceptable
- NC - No Action

**WINBIO COMMENTS:**
Fasted & fed bio-studies are acceptable. Dissolution method proposed by sponsor will be adopted by DBE as the interim method for this drug product.

**APPEARS THIS WAY ON ORIGINAL**
OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 75-347 SPONSOR: Andrx Pharmaceuticals, Inc.
DRUG: Omeprazole
DOSAGE FORM: delayed-release capsule
STRENGTHS/(s): 10 & 20 mg
TYPE OF STUDY: Single—Multiple— Fasting—Fed—
STUDY SITE: _______________________

STUDY SUMMARY: Fed & Fed Studies meet 80-125 CE
WAIVER GRANTED FOR 10 mg DR-Capsule.

DISTRIBUTION: OK per sponsor's proposed method—

PRIMARY REVIEWER: Jenny Lee BRANCH: II
INITIAL: [S] DATE 8/20/98

TEAM LEADER: S. Nerurkar, Ph.D BRANCH: II
INITIAL: [S] DATE 8/24/98

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale Conner, Pharm.D
INITIAL: [S] DATE 8/26/98

DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: __________________ DATE __________________
Omeprazole
10 & 20 mg delayed-release capsules
NDA #75-347
Reviewer: J. Lee
75347SDIW.898

Andrx Pharmaceuticals, Inc.
Fort Lauderdale, Florida
Submission date:
March 17, 1998
April 17, 1998
August 14, 1998

Review of Fasted and Fed in-vivo Bioavailability Studies,
Dissolution Testing Data and a Request for Waiver

Objective:

To determine the relative bioavailability of 20 mg omeprazole delayed-release capsules after administration of single doses to healthy male subjects under both fasted and fed conditions.

Fasted Study

Study Design:

The clinical study (#97273) was conducted at , under the supervision of .

Thirty healthy male volunteers between the ages of 21-35 years and within 10% of ideal body weight for his height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history, physical examination, clinical laboratory tests [hematology, serum chemistry and urinalysis], and EKG.

Those with any of the following conditions were excluded:

History or presence of:

- chronic alcoholism or drug abuse
- major organ dysfunction
- malignancy, stroke, diabetes, cardiac, renal or liver disease
- conditions which might contraindicate or require caution be used in the administration of omeprazole
- any illness or medication requirement that would affect gastric pH
Rx and OTC medications were not allowed within 14 and 7 days, respectively, of the first drug administration and for the duration of the study. There was to be no alcohol or caffeine consumption for 48 hours prior to drug administration.

The study was designed as a randomized, open-label, two-way crossover study with a 7 day washout period between dosings. Treatments consisted of a single 20 mg dose of the following:

A. Omeprazole
   20 mg delayed-release capsule, batch #620R001
   Andrx Pharmaceuticals, Inc.
   expiry date: not given

B. Prilosec®
   20 mg delayed-release capsule, batch #D2678
   Astra/Merck, Inc.
   expiry date: January, 1998

Thirty subjects were dosed according to the following schedule:

<table>
<thead>
<tr>
<th></th>
<th>Period I</th>
<th>Period II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12/13/97</td>
<td>12/20/97</td>
</tr>
<tr>
<td>sequence I</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>sequence II</td>
<td>B</td>
<td>A</td>
</tr>
</tbody>
</table>

sequence I - subj. # 3, 4, 6, 7, 10, 11*, 13, 16, 18, 21, 22, 23, 26, 28, 29

sequence II - subj. #1, 2, 5, 8, 9, 12, 14, 15, 17, 19, 20, 24, 25, 27, 30

*Subject #11 did not report for period II dosing for undisclosed personal reason(s).

After an overnight fast, subjects were given a 20 mg dose of omeprazole with 240 ml of water. Fasting continued for 4 hours post-dose. Blood samples (10 ml) were drawn in pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8 and 10 hours. All blood draws were taken within two minutes of the scheduled sampling time.

Two subjects reported experiencing a total of 4 adverse events, only one of which (nausea, mild) was deemed probably drug related. All events were mild/moderate in severity and no therapy was required in any of the adverse event instances. The adverse events summary is summarized on page 114.

No deviations from protocol were reported.
Redacted

pages of

trade secret and/or

confidential

commercial

information
Data Analysis:

The statistical analyses/report were generated by Plasma data was analyzed by an analysis of variance procedure (SAS) determine statistically significant (p<0.05) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters and plasma level concentrations at each sampling time. The eliminate rate constant, Ke, for subject #4 (ref.) and subjects #3 & 13 (test) could not be established due to the fluctuating concentration values in the terminal phase; consequently, t½ and AUC_inf could not be calculated for those subjects. Of the original thirty subjects enrolled in the study, one did not complete the crossover; twenty-nine datasets were analyzed.

Results:

No statistically significant differences were found in any of the pharmacokinetic indices, neither on the original nor on the ln-transformed scale, except for AUCinf (p=0.0471). No sequence effects were observed for the major bioavailability parameters. There was 13% difference between the test and reference formulations for plasma levels of omeprazole AUC_0-t and AUC_inf. The Andrx product produced a 1% higher C_max than the Astra/Merck product. The 90% shortest confidence intervals for omeprazole, using least squares means, are presented below:

<table>
<thead>
<tr>
<th>Scale</th>
<th>Parameter</th>
<th>Value (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC_0-t</td>
<td>[102; 124]</td>
</tr>
<tr>
<td></td>
<td>AUC_inf</td>
<td>[102; 124]</td>
</tr>
<tr>
<td></td>
<td>C_max</td>
<td>[87.7; 121]</td>
</tr>
<tr>
<td>ln-transformed</td>
<td>AUC_0-t</td>
<td>[98.8; 113]</td>
</tr>
<tr>
<td></td>
<td>AUC_inf</td>
<td>[100; 115]</td>
</tr>
<tr>
<td></td>
<td>C_max</td>
<td>[83.9; 106]</td>
</tr>
</tbody>
</table>

Mean plasma level data and pharmacokinetic summary are attached.

Fed Study

Study Design:

The clinical and analytical facilities for this study were the same as that employed in the fasting study. The Inclusion and exclusion criteria for subject selection were also the same.
The study (#97274) was a randomized three treatment, three period, six sequence crossover. Treatments consisted of the same two batches of test and reference products (used in the fasted study). A 7 day washout period separated periods I and II; a 14 day washout separated periods II and III.

Eighteen subjects were dosed according to the following regimen:

<table>
<thead>
<tr>
<th>sequence I</th>
<th>period I (01/04/98)</th>
<th>period II (01/11/98)</th>
<th>period III (01/25/98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sequence II</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>sequence III</td>
<td>A</td>
<td>C</td>
<td>B</td>
</tr>
<tr>
<td>sequence IV</td>
<td>B</td>
<td>A</td>
<td>C</td>
</tr>
<tr>
<td>sequence V</td>
<td>C</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>sequence VI</td>
<td>C</td>
<td>B</td>
<td>A</td>
</tr>
</tbody>
</table>

sequence I - subj #1, 10' 15' 24'    sequence II - subj #4, 12, 14, 19
sequence III - subj #6, 9, 17, 20   sequence IV - subj #5, 7, 16, 23'
sequence V - subj #3, 8, 13, 22     sequence VI - subj #2, 11, 18, 21'

Treatment A: 1 x 20 mg omeprazole capsule (Andrx) following an overnight fast
Treatment B: 1 x 20 mg omeprazole capsule (Andrx) following a standard breakfast*
Treatment C: 1 x 20 mg Prilosec® capsule (Astra/Merck) following a standard breakfast*

*standard breakfast:
1 buttered English muffin
1 fried egg
1 slice of American cheese
1 slice of Canadian bacon
1 serving (2.45 oz) of hash brown potatoes
6 fl oz of orange juice
8 fl oz of whole milk

Of the 24 subjects enrolled in the study, four subjects (#5, 10, 23, 24) dropped from the study before initial dosing and were not replaced. Subjects #15 and 21 did not return to complete phase III of the study for personal reasons. Eighteen subjects completed all phases of the study.

After an overnight fast, subjects on treatment B or C were served a standard breakfast 15 minutes before dosing. Fasting continued for 4 hours post dose. The sampling schedule followed that used in the fasted study except for an additional 12 hour sampling. All blood draws were taken within 2 minutes of their target times.

There were a total of 3 mild clinical complaints reported [headache, stomach ache], all of which were judged possibly/probably related to the study drug. [see summary, p. 001215].
Analytical:

Data Analysis and Results:

Means, standard deviations and CV% were calculated for the PK indices. Subject #13 had only one sample with a quantifiable level (per III). His period III data was eliminated in the statistical analyses. There were a large number of subjects for which $AUC_{inf}$ could not be calculated due to the erratic elimination profiles for those subjects after dosing with the T/R products under fed conditions. $AUC_{inf}$ was not used in the bioequivalence determination in this study. Areas under the curve and $C_{max}$ showed no difference for T/R (fed). There was a 27% decrease in AUC and a 40% decrease in $C_{max}$ from the effect of a high-fat meal observed for $T_{(fed)}/T_{(fasted)}$; $T_{max}$ increased by more than 2-fold. Labeling indicates that the drug product be taken before meals. The results are summarized in appended tables.

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study, using the sponsor’s dissolution method:
(acid stage) USP XXIII Apparatus I (basket) @ 100 rpm
900 ml 0.1N HCl @ 37°C
for 2 hours [analyze residue]

(buffer stage) USP XXIII Apparatus I (basket) @ 100 rpm
900 ml pH 6.8 phosphate buffer @ 37°C
sampling at 10, 20, 30 and 45 minutes

Content Uniformity:

The assay for content uniformity for 10 dosage units of the Andrx product was 99.9% of label claim; range = 96.5-104.0% (2.3% CV); for Prilosec®, the C.U. was 99.0% of label claim; range = 96.5-101.0% (1.6% CV).

Batch Size:

The executed batch record for the bio-batch of Andrx' 20 mg omeprazole shows a reconciled yield of dosage units.

Waiver Request:

The sponsor has requested a waiver of in-vivo requirements for their 10 mg omeprazole capsule. A quantitative formulation comparison between the 10 mg and 20 mg capsule was submitted, and comparative dissolution testing results were provided between the company's 10 mg test product vs Prilosec® 10 mg capsule.

Comment:

1. The sponsor has conducted dissolution testing using their own method. There is currently no USP method available, but DBE has an interim method that it has been recommending and the sponsor was asked to conduct dissolution testing with the interim DBE method as follows:

   Apparatus: USP paddle @
   Media, volume:
   Sampling times:

   Tolerances: To be determined.

The results of both dissolution methods are attached.
.3 For the reasons listed above, the sponsor has proposed that their dissolution method or some modification be considered as the analytical method for the analysis of omeprazole delayed-release capsules.

4. The Division of Bioequivalence concurs that the sponsor’s dissolution method is more suitable for this drug product and will recommend this method as the new interim dissolution method until such time as the USP issues an official method.

Recommendation:

1. The bioequivalence studies (fasted & fed) conducted by \(\_
\) for Andrx Pharmaceuticals on its omeprazole 20 mg delayed-release capsule, batch #620R001, comparing it to Prilosec\textsuperscript{®} 20 mg delayed-release capsule has been found acceptable by the Division of Bioequivalence. The study demonstrates that Andrx' omeprazole 20 mg delayed-release capsule is bioequivalent to the reference product, Prilosec\textsuperscript{®} 20 mg delayed-release capsule manufactured by Astra/Merck, Inc.

2. The in-vitro dissolution testing data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in \(\_
\) XXIII apparatus I (basket) at \(\_
\). The test product should meet the following specification:

\[
\begin{align*}
\text{NMT} & \quad \_
\\
\text{NLT} & \quad \_
\end{align*}
\]

3. The Division of Bioequivalence finds that the information submitted by sponsor demonstrates that omeprazole 10 mg delayed-release capsule falls under 21 CFR 320.22
(d)2 of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. Andrx Pharmaceuticals’ 10 mg test product is deemed bioequivalent to Prilosec® 10 mg delayed-release capsule manufactured by Astra/Merck, Inc.

3. From the bioequivalence viewpoint the firm has met the requirements of in-vivo bioavailability and in-vitro dissolution testing and the application is acceptable.

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

Concur. Date: 8/26/98

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

JLee/jl/07-31-98

cc: NDA #75-347 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

APPEARS THIS WAY ON ORIGINAL
DBE Interim Method

USP XXIII Apparatus ___ II ___ Basket ___ Paddle ___ x ___ rpm ___

Medium: __________________________ Volume: ___ ml
Medium: __________________________ Volume: ___ ml

Number of Tabs/Caps Tested: 12

Reference Drug: Prilosec 10 & 20 mg capsule

Assay Methodology: __________________________

<table>
<thead>
<tr>
<th>Results</th>
<th>20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
<td>Test Product</td>
</tr>
<tr>
<td>Lot # 620R001</td>
<td>Lot # D2678</td>
</tr>
<tr>
<td>Mean % Dissolved</td>
<td>Range (CV)</td>
</tr>
<tr>
<td>2 hr (acid)</td>
<td>0</td>
</tr>
<tr>
<td>10 min (buffer)</td>
<td>37</td>
</tr>
<tr>
<td>20</td>
<td>47</td>
</tr>
<tr>
<td>30</td>
<td>49</td>
</tr>
<tr>
<td>45</td>
<td>49</td>
</tr>
<tr>
<td>60</td>
<td>49</td>
</tr>
<tr>
<td>65 (150 rpm)</td>
<td>74</td>
</tr>
<tr>
<td>70 (150 rpm)</td>
<td>82</td>
</tr>
<tr>
<td>Time (min)</td>
<td>Test Product</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------</td>
</tr>
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APPEARS THIS WAY ON ORIGINAL
**Sponsor’s Method**

USP XXIII Apparatus: [ ] Basket [x] Paddle [ ] rpm [ ]

Medium: __________________________ Volume: _____ ml
Medium: __________________________ Volume: _____ ml

Number of Tabs/Caps Tested: 12

Reference Drug: Prilosec 10 & 20 mg capsule

Assay Methodology: __________________________

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## Mean Drug Levels and PK Summary - Fasted Study

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### Mean Drug Levels - Fed Study

**ng/ml**

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Pharmacokinetic Summary - Fed Study

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**Trt C (ref-fed)**

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<td>Active Pellets, 25% of capsule content</td>
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<td>Povidone, USP</td>
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<td>Cetyl Alcohol, NF</td>
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<td></td>
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</tr>
<tr>
<td>Talc, USP</td>
<td></td>
<td></td>
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</table>
BIOEQUIVALENcy COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-347  APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Omeprazole 10 & 20 mg delayed-release capsules

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

You may use your proposed dissolution method until such time as the USP issues an official method or DBE deems it appropriate to change the dissolution method.

Please incorporate the following into your stability and quality control programs:

The dissolution testing should be conducted in

37°C using USP Apparatus I (basket) at The test product should meet the following specifications:

Not more than (Q) of the labeled amount of the drug in the capsule is dissolved in

Not less than (Q) of the labeled amount of the drug in the capsule is dissolved in

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

Sincerely yours,

[Signature]

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

1. Fasting Study (STF)  
   Clinical: ___________  
   Analytical: ___________  
   Strengths: 10 & 20 mg  
   Outcome: AC

2. Food Study (STP)  
   Clinical: same  
   Analytical: same  
   Strengths: 10 & 20 mg  
   Outcome: AC

5. Study Amendment (STA) 4/17/98  
   Strengths: 10 & 20 mg  
   Outcome: AC

6. Study Amendment (STA) 8/14/98  
   Strengths: 10 & 20 mg  
   Outcome: AC

7. Dissolution Waiver (DIW) 4/17/98  
   Strengths: 10 mg  
   Outcome: AC

Outcome Decisions:  
AC - Acceptable  
NC - No Action

WinBio Comments:  
Fasted & fed bio-studies are acceptable. Dissolution method proposed by sponsor will be adopted by DBE as the interim method for this drug product.
OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 75-347 SPONSOR: Andrx Pharmaceuticals, Inc.
DRUG: Omeprazole
DOSAGE FORM: delayed-release capsule
STRENGTHS/(s): 10 & 20 mg
TYPE OF STUDY: Single - Multiple - Fasting - Fed -
STUDY SITE: 

STUDY SUMMARY: Fed & Fed Studies meet 80-125 CI
WAIVER GRANTED FOR 10 mg OR- CAPSULE.

DISSOLUTION: OK per sponsor's proposed method-

PRIMARY REVIEWER: Jenny Lee BRANCH: II

INITIAL: [Signature] DATE 8/20/98

TEAM LEADER: S. Nerurkar, Ph.D BRANCH: II

INITIAL: [Signature] DATE 8/24/98

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale Conner, Pharm.D

INITIAL: [Signature] DATE 8/26/98

DIRECTOR, OFFICE OF GENERIC DRUGS:

INITIAL: __________ DATE __________
BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-347  APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Omeprazole 40 mg delayed-release capsule

The Division of Bioequivalence has completed its review of the bio-study administered with applesauce and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in

USP Apparatus I (basket) at The test product should meet the following specifications:

NMT  of the drug in the capsule is dissolved

in

NLT  of the drug in the capsule is dissolved

in

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues.

Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

[Signature]

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

ANDA: 75-347  DRUG PRODUCT: Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg

FIRM: Andrx Pharmaceuticals Inc.

DOSAGE: Capsules

STRENGTH: 10 mg, 20 mg and 40 mg

CGMP STATEMENT/EIR UPDATE STATUS:
CGMP: Certification provided on page 2459.
EIR: Acceptable as of 8/23/01.

BIO STUDIES/BIOEQUIVALENCE STATUS:
Acceptable 4/25/01.

METHODS VALIDATION:
Completed and found satisfactory by Atlanta labs.

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

<table>
<thead>
<tr>
<th>Stability Specs</th>
<th>Limits</th>
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<tbody>
<tr>
<td>Test</td>
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<tr>
<td>Moisture</td>
<td>NMT — (capsule content only)</td>
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<tr>
<td>Assay (LC-label claim)</td>
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</tr>
<tr>
<td>Dissolution</td>
<td>NMT — dissolved</td>
</tr>
<tr>
<td></td>
<td>: NLT dissolved in</td>
</tr>
<tr>
<td>Total Impurities</td>
<td>Individual known impurity: NMT</td>
</tr>
<tr>
<td></td>
<td>; Other unknown peaks: NMT</td>
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<tr>
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<tr>
<td>Physical appearance</td>
<td>10 mg— Light green cap/white body, capsule</td>
</tr>
<tr>
<td></td>
<td>containing</td>
</tr>
<tr>
<td></td>
<td>20 mg— Dark green cap/white body, capsule</td>
</tr>
<tr>
<td>Physical appearance</td>
<td>10 mg - Light green cap/white body, capsule containing</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>20 mg - Dark green cap/white body, capsule containing</td>
</tr>
<tr>
<td></td>
<td>40 mg - Dark green cap/light green body, capsule containing</td>
</tr>
</tbody>
</table>

**LABELING REVIEW STATUS:**
Acceptable. See review dated 10/1/01

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

**BATCH SIZES:**
Bio batch (identity #, drug substance source):
Two sources are indicated in the ANDA. They are: _and_ 

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

**PROPOSED PRODUCTION BATCH:**
- 10 mg _capsules_
- 20 mg _capsules_
- 40 mg _capsules_

**COMMENTS:**
None; approval recommended.

**CHEMISTRY REVIEWER:** Radhika Rajagopalan, Ph.D.
**DATE:** 9/28/01

**APPEARS THIS WAY ON ORIGINAL**

[Signature]

10/4/01
TELEPHONE MEMO

To: Diane Servello and got voice mail
I was later able to reach Janet Von (Andrx Pharmaceuticals, Inc.)
954-581-7500

CC: ANDA 75-347 Omeprazole Delayed-release Capsules, 10 mg, 20 mg
and 40 mg

From: Saundra T. Middleton

Date: March 15, 2001

Subject: Timely filed patents for omeprazole

The following patents for omeprazole were timely filed patents and you need to certify to them:

6150380 exp 11/10/18 drug substance
6147103 exp 10/9/18 drug substance
6166213 exp 10/9/18 drug substance

FROM THE DESK OF...

PROJECT MANAGER
CDER/FDA/OGD/DLPS
7500 STANDISH PLACE
ROCKVILLE MD 20855

301-827-5862
Fax: 301-594-1174
I called Ms. D. Servello, the manager of regulatory affairs for Andrx Pharmaceuticals and requested her to amend stability and release specs. As recommended by the Division of Bioequivalence. She agreed to send a telephone amendment.

<table>
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<th>DATE</th>
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<tbody>
<tr>
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<td>APPLICANT/ BY SPONSOR TELE.</td>
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<td>X FDA _ IN PERSON</td>
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<table>
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<tr>
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<tbody>
<tr>
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<table>
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</table>

<table>
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<th>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD</th>
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<table>
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<th>SIGNATURE</th>
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4/16/99

APPEARS THIS WAY ON ORIGINAL
FACSIMILE AMENDMENT

ANDA 75-347

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: Andrx Pharmaceuticals, Inc. PHONE: 954-321-5229
ATTN: Jacqueline Davis FAX: 954-567-1054

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

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 17, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg.

Reference is also made to your amendment(s) dated August 5 and September 28, 1998.

Attached are ___ pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301-827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. Further if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT.

SPECIAL INSTRUCTIONS:

Chemistry, bio and labeling comments attached 12/11/98

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

X:\new\ogd\admin\macros\faxfax.frm
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-347  Date of Submission: March 17, April 9, & September 28, 1998

Applicant's Name:  Andrx Pharmaceuticals, Inc.
Established Name:  Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg

Labeling Deficiencies:

1. CONTAINER  (7s, 30s and 1000s)
   a. We encourage you to differentiate your product strengths with the use of boxing, contrasting colors or some other means.
   b. 10 mg & 20 mg

Replace the "..." statement with "Rx only". We refer you to "A GUIDANCE FOR INDUSTRY" entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site http://www.fda.gov/cder/guidance/index.htm. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.

c. 40 mg

Delete the "..." statement on the side panel.

d. 7s - Include a statement that identifies this container size as a physician sample size.

e. 30s - Include the following on the main panel:

    Unit-of-Use
2. INSERT (Submitted September 28, 1998)

a. GENERAL

i. We acknowledge that you have filed a Paragraph IV Patent Certification with regard to indication for “Treatment of H. Pylori associated with duodenal ulcer”. However, we note that you have removed this information from your package insert labeling. Please retain this information (i.e., dual therapy with omeprazole/clarithromycin) in the insert labeling. Information regarding triple therapy (omeprazole/clarithromycin/amoxicillin) for “Eradication of H. Pylori in patients with duodenal ulcer disease” should remain excluded from the insert labeling. Please refer to the enclosed annotated copy of the labeling of reference listed drug (Prilosec®; Astra Merck; Approved June 30, 1998; Revised June 1998). In addition, please revise the following:

ii. We ask you make a distinction between “subsection” and “sub-subsection” headings in terms of prominence throughout the text.

b. TITLE

See comment b under CONTAINER.

c. DESCRIPTION

i. Revise “  ” to read “molecular formula”.

ii. Revise “  ” to read “lactose monohydrate”.

iii. You may delete “  ” and “  ” form the listing of inactive ingredients.

iv. Last sentence- Revise to read:

The capsule shells and imprinting ink have...
d. CLINICAL PHARMACOLOGY (Clinical Studies, Gastric Ulcer) - Second table (i.e., foreign study)

Revise to read "---" rather than "20 mg" in the center column.

e. HOW SUPPLIED

   a. We encourage the relocation of "Rx only" to the TITLE section.

   b. 40 mg

   Include the reference to the sample size (7 capsules) and/or 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/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Prilosec® labeling
Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

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.

NAME OF DRUG: Omeprazole Delayed-release Capsules, 10 mg and 20 mg

DATE OF APPLICATION: March 17, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 17, 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.

In addition, to be in compliance with 21 CFR 314.50(e)(2)(ii), you must provide four copies of the draft labels and labeling in the archival copy of the application. Please provide three additional copies draft package insert and container labels for the archival copy. In the future, please include four copies of the draft labels and labeling in both the archival and review copies of 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
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
April 16, 1999

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg

TELEPHONE AMENDMENT
SENT BY FAX TO 301-443-3839 – HARD COPY TO FOLLOW

Dear Mr. Sporn:

We refer to a telephone communication from Ms. Radhika Rajagopalan of your office on April 15, 1999. It was requested that we submit revised “Release” and “Stability” specifications reflecting the dissolution specifications described in our March 23, 1999 amendment. Accordingly, we have enclosed the following:

1. Stability/Release Specification Sheet for Omeprazole Delayed-release Capsules, 10 mg
2. Stability/Release Specification Sheet for Omeprazole Delayed-release Capsules, 20 mg

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

RECEIVED
APR 20 1999

GENERIC DRUGS
Review of Correspondence

The three strengths of DR capsules in this ANDA were found to be acceptable by the Division of Bioequivalence (DBE) (See Ms. Lee's review dated 8-16-99 under V:\FIRMS\Am\Andrx\Ltrs&rev\75347S.899). According to the review the following dissolution specifications were communicated to the firm.

- NLT of the drug in the capsule is dissolved in
- NLT of the drug in the capsule is dissolved in

Firm subsequently contacted the Division of Bioequivalence (DBE) via telephone to seek clarifications of the two dissolution related issues.

1st issue: The firm assumed that NLT dissolution in buffer stage contains the NLT dissolution in acid stage. In other words, if the acid stage dissolves of the drug, then dissolution of the drug in the buffer stage (which makes of drug dissolution in 2 stages) is acceptable.

Answer to the 1st issue: The firm's understanding is not correct. The percent dissolution is the buffer stage is independent of the percent dissolution in the acid stage. In other words, if the acid stage dissolves of the drug, then dissolution of the drug in the buffer stage (which makes of the drug dissolution in 2 stages) is required.

2nd issue: Is it possible for DBE to change the dissolution specification in buffer stage from NLT in to NLT in ?

Answer to the 2nd issue: Based on the dissolution data in the DBE files, DBE will not change the dissolution specification. The time for dissolution will not be reduced from minutes to .

Omeprazole DR Capsules
10 mg, 20 mg, and 40 mg
ANDA # 75-347
Reviewer: S. G. Nerurkar
V:\firmsam\Andrx\Ltrs&rev\75347OT.100

Andrx Pharmaceuticals Inc.
Fort Lauderdale, Fla
Submission Date:
January 20, 2000
DBE requested the firm to confirm in writing its understanding of the DBE answers. With this communication the firm has done so. **There is no need to communicate with the firm on this issue and for this submission.**

2/3/2000

S. G. Nerurkar,  
Review Branch 2  
Division of Bioequivalence

Concur:  
Date 3/17/00

Dale P. Conner  
Director, Division of Bioequivalence

CC: ANDA 75-347 original, HFD-630, HFD 604, (OGD, Hare), HFD 22, (Hooton)  
HFC 130 (Jallen), HFD 655 (Nerurkar), Drug File

SGN/sgn/ 75347/2-2-2000
VIA AIRBORNE EXPRESS

September 28, 1998

Douglas L. Sporn
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: AMENDMENT: ANDA 75-347 (Omeprazole Delayed-release Capsules)

Dear Sir:

Please refer to Andrx's Abbreviated New Drug Application for Omeprazole Delayed-release Capsules, 10 mg & 20 mg, which was submitted on March 17, 1998.

In accordance with 21 CFR 314.96, we are amending this application to include a new 40 mg strength. Please note that all three strengths have a common formulation and are made by the same manufacturing process. This amendment contains revised labeling, in vitro dissolution data, a request for waiver of in vivo bioequivalence studies, and manufacturing and controls information for the 40 mg strength.

The amendment consists of 1 volume. NOTE: THIS AMENDMENT CONTAINS AN ELECTRONIC SUBMISSION OF LABELING DATA – the revised draft package insert is provided in WordPerfect v.6.1 and MS Word 97 format on two 3.5" diskettes. The data contained in the electronic submission is the same as in the hardcopy submission.

Andrx Pharmaceuticals, Inc. certifies that in accordance with 21 CFR 314.94(d)(5), a field copy of this amendment has been submitted to the Florida District Office concurrently with this submission. That field copy is a true copy of the chemistry, manufacturing, and controls technical sections contained in the archival and review copies of the application.

Please direct any questions regarding this submission to Jacqueline Davis, Regulatory Affairs Manager, at 954-321-5229 (Tel.) or 954-587-1054 (Fax.).

Sincerely,

David A. Gardner
Vice President, Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054
VIA Facsimile

December 23, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347: Omeprazole Delayed-Release Capsules, 10 mg, 20 mg, & 40 mg

FACSIMILE AMENDMENT

Dear Sir/Madam:

Andrx Pharmaceuticals is amending its abbreviated new drug application for Omeprazole Delayed-Release Capsules to provide the additional information requested by facsimile on December 11, 1998. This amendment provides a complete response to all the minor deficiencies and comments listed in the FDA’s facsimile. It consists of one volume. An archival copy and two review copies (Chemistry and Bioequivalence) are provided.

In accordance with 21 CFR 314.96 (b), Andrx Pharmaceuticals certifies that a field copy of this amendment has been sent to the Florida District Office.

Should you have any questions concerning this submission, please contact the undersigned at (954) 321-5229 (tel.) or (954) 587-1054 (fax).

Sincerely,

Jacqueline Davis
Regulatory Affairs Manager

RECEIVED
DEC 24 1998
VIA FACSIMILE

March 23, 1999

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347: FACSIMILE AMENDMENT
Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg

Dear Sir/Madam:

Andrx Pharmaceuticals is amending its abbreviated new drug application for Omeprazole Delayed-release Capsules in response to the OGD’s facsimile deficiencies dated February 22, 1999. This amendment provides a complete response to all the deficiencies and comments listed. It consists of one volume.

In accordance with 21 CFR 314.96(b), Andrx Pharmaceuticals certifies that a field copy of this amendment has been submitted to the Florida District Office.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 321-5229 (telephone) or 954-587-1054 (facsimile).

Sincerely,

[Signature]
Jacqueline Davis
Regulatory Affairs Manager
July 28, 1999

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg

MAJOR AMENDMENT

Dear Mr. Sporn:

Andrx Pharmaceuticals is amending its abbreviated new drug application for Omeprazole Delayed-release Capsules in response to your letter dated May 18, 1999. This amendment provides a bioequivalence study for the 40 mg strength of this product. Please refer to our amendment dated June 14, 1999 for responses to the chemistry deficiencies cited in your May 18, 1999 letter.

In this regard, please find the following information:

- Three volumes containing a study entitled “A randomized, two-way crossover, single-dose, open-label study to evaluate the relative bioavailability of a test delayed release capsule formulation of Omeprazole (40 mg), compared to an equivalent dose of a commercially available reference drug product (Prilosec®, Merck & Co., Inc.) in 30 fasted, healthy, male subjects” (Protocol No. 99145). A diskette containing the study data, along with a hard copy of the files contained on the diskette are included in Volume 1 of the Archival Copy.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Diane Servello
Director, Regulatory Affairs
June 14, 1999

Douglas L. Sporn, Director  
Office of Generic Drugs, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

RE: ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg

MAJOR AMENDMENT/REQUEST FOR RECLASSIFICATION TO MINOR AMENDMENT

Dear Mr. Sporn:

Andrx Pharmaceuticals is amending its abbreviated new drug application for Omeprazole Delayed-release Capsules in response to your letter dated May 18, 1999. This amendment provides a complete response to all the deficiencies and comments listed. This submission also includes a request to reclassify this major amendment to a minor amendment for the 10 mg and 20 mg strengths. The major deficiency identified in your May 18, 1999 letter concerns a newly communicated requirement for a bioequivalence study on the 40 mg strength only. Our bioequivalence study on the 40 mg strength is underway, and will be submitted upon completion. We are requesting that the tentative approval for the 10 mg and 20 mg strengths not be delayed pending the review of the new bioequivalence study on the 40 mg.

The basis for our request that this amendment be reclassified is as follows:

1. The May 18, 1999 major deficiency letter refers to a letter issued by the Division of Bioequivalence on April 9, 1999 notifying Andrx that an additional bioequivalence study is required on the 40 mg strength of this product. As discussed in the attached response, this bioequivalence study is ongoing and will be submitted upon completion.

2. The bioequivalence deficiency does not pertain to the 10 mg and 20 mg strengths of this product. Since each strength is considered to be a separate product, we are requesting that the tentative approval for the 10 mg and 20 mg strengths not be delayed pending the Agency’s review of the 40 mg bioequivalence study.

3. Only one chemistry deficiency was cited in your May 18, 1999 letter. This was a CMC deficiency requiring a simple revision to the storage conditions in the labeling for the drug substance. From a CMC perspective, this response would clearly meet the criteria.
for a minor amendment, since it requires only the review of revised labeling for the drug substance.

In accordance with 21 CFR 314.96(b), Andrx Pharmaceuticals certifies that a field copy of this amendment has been submitted to the Florida District Office.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Diane Servello
Director, Regulatory Affairs
March 22, 2000

Pat Beers-Block, Approvals Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg

TELEPHONE AMENDMENT: CHEMISTRY MFG. & CONTROLS and PATENT INFORMATION

Dear Ms. Beers-Block:

Reference is made to our pending abbreviated new drug application for the above referenced drug product. Andrx Pharmaceuticals, Inc. ("Andrx") is amending its application to clarify the site of manufacture for the active drug substance. We are also reconfirming the Patent Certifications included in our original application.

1. We have enclosed a letter from ______ dated March 22, 2000. As mentioned in the attached letter, both lots of Omeprazole USP used in our biobatch were manufactured at ______ facility. The Certificate of Analysis that was included in our application for lot FX7246 mentioned corporate address in ______ However, as indicated in the attached letter no ______ takes place at the ______ facility. Furthermore, the "F" prefix in the lot number identifies the ______ manufacturing site.

2. Our original application contained the following patent certifications:
   - Paragraph III: Patent #4,255,431 (expires on 04/05/01),
   - Paragraph IV: Patent #s 4,636,499 (expires 05/30/05), 4,853,230 (expires 04/20/07), 4,786,505 (expires 04/20/07), 5,093,342 (expires 02/02/10), 5,599,794 (expires 02/04/14) and 5,629,305 (expires 02/04/14).

We acknowledge that because our application contains a paragraph III certification with respect to patent #4,255,431, expiring on April 5, 2001, this application can not receive final approval until this patent expires.

As indicated in our Patent Amendment dated May 28, 1998 the holders of the patents listed in our paragraph IV certification filed an action for patent infringement against Andrx. That litigation is pending.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Diane Sevello
Director, Regulatory Affairs
January 20, 2000

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Andrx Pharmaceuticals is amending its application to provide revised in-process and finished product specifications incorporating the dissolution specifications proposed by the Division of Bioequivalence on November 15, 1999.

This submission contains updated specifications for the enteric-coated pellets, the 10 mg, 20 mg, and 40 mg capsules. Three copies are provided – an archival copy, a chemistry review copy and a bioequivalence review copy.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions or comments concerning this submission, please contact Jacqueline Davis, Regulatory Affairs Manager, at (954) 327-4412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

[Signature]

Diane Servello
Director, Regulatory Affairs
August 6, 1999

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg, and 40 mg

TELEPHONE AMENDMENT

Dear Sir:

Reference is made to a telephone call from Jennifer Fan and Dr. Jenny Lee on August 5, 1999, requesting additional information for the test and reference products used in the 40 mg biostudy submitted on July 28, 1999. Accordingly, we are providing the following as a telephone amendment:

1. Comparative dissolution data for the 40 mg test and reference products (see attachment).

2. Potency and content uniformity results for the test and reference products:

<table>
<thead>
<tr>
<th></th>
<th>POTENCY, %</th>
<th>CONTENT UNIFORMITY, %</th>
</tr>
</thead>
</table>
| Test (Lot #640R001) | 103.5 | Avg.: 103.4  
% RSD (n=10) : 1.6  
Range: |
| Reference (Lot #H3531) | 99.8 | Avg.: 100.2  
% RSD (n=10) : 2.0  
Range: |

3. Batch size of 40 mg test product (Lot #640R001) = ____________ capsules.

Should you have additional questions, please contact the undersigned at (954) 327-4412 (Tel.) or (954) 587-1054 (Fax.).

Sincerely,

Diane Servello
Director of Regulatory Affairs
ANDA #: 75-347, Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg

December 15, 2000

Gary Buehler,
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: General Correspondence

Dear Sir:

This letter is to inform you that the administrative offices of Andrx Pharmaceuticals, Inc. have relocated to a new address. Please direct all future correspondences pertaining to the above referenced ANDA to the following address and/or contact persons:

Andrx Pharmaceuticals, Inc.
4955 Orange Drive
Fort Lauderdale, Florida 33314

Diane Servello, Director of Regulatory Affairs
Telephone: (954) 585-1412

Janet Vaughn, Manager of Regulatory Affairs
Telephone: (954) 585-1665

Facsimile: (954) 587-1054

Please note that the manufacturing site for the drug product has not changed. The new address for the administrative offices is contiguous with the manufacturing site.

Should you have any questions or comments concerning these changes, please contact Janet Vaughn at the above telephone number.

Sincerely,

[Signature]
Diane Servello
Director, Regulatory Affairs

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054
June 28, 2000

Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg

PATENT AMENDMENT

Dear Mr. Buehler:

We refer to the above referenced ANDA, which was tentatively approved on March 24, 2000. Upon a review of the paragraph IV patent notices for this application, it was noted that several patent notice-related documents were inadvertently not submitted to your office. The missing documents pertain to the 40 mg dosage strength of this product, which was submitted to this ANDA as an amendment on September 22, 1999. (The original ANDA submission, submitted on March 17, 1998 described only the 10 mg and 20 mg strengths.)

Due to an oversight, Andrx Pharmaceuticals, Inc. ("Andrx") did not submit documentation of receipt by the patent/NDAs holder on June 3, 1999 of a second patent notice describing the new 40 mg strength product. A copy of documentation showing receipt of our second patent notice by Astra Pharmaceuticals LP ("Astra") is enclosed in Exhibit 1. In addition, a copy of cover page of the complaint initiated against Andrx by Astra on July 14, 1999 pertaining to the 40 mg strength was not submitted to your office. Please refer to Exhibit 2 for a copy of this document.

Please note that the court has consolidated Astra’s second complaint against Andrx for the 40 mg strength with the first complaint pertaining to the 10 mg and 20 mg strengths. Therefore, one court decision will be made on all three dosage strengths. However, we acknowledge that for regulatory purposes, a separate 30 month period was started on June 3, 1999, the date the second patent notice was received by Astra.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Diane Servello
Director, Regulatory Affairs
ANDA 75-347
Omeprazole Delayed-release Capsules
10 mg, 20 mg and 40 mg

March 16, 2001

Gary Buehler
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Amendment – Alternate Source of the Active Pharmaceutical Ingredient (API)

Dear Sir:

Please refer to Andrx Pharmaceuticals’ abbreviated new drug application (ANDA) for Omeprazole Delayed-release Capsules, ANDA 75-347. Pursuant to 21 CFR 314.96 (a), Andrx is herewith submitting an amendment providing for an alternate source of the active pharmaceutical ingredient (API), Omeprazole, USP  

Please note that the current source of the  

which was described in the tentatively approved ANDA, is  

or substituted. This amendment is only intended to provide an additional source of the API.

The proposed  

of Omeprazole, USP  

is  

The API is manufactured at  

manufacturing site located at the following address:

manufactures the API consistent with the procedures and controls described in their Type II Drug Master File (DMF  

which is currently on file with the FDA. A copy of a DMF authorization letter from  

that authorizes Andrx Pharmaceuticals, Inc. to reference DMF  

is provided in this amendment.

Omeprazole, USP (micronized) manufactured by  
(Andrx lot 0002028) has been tested and shown to meet the same acceptance criteria as those of the omeprazole used in the original bioequivalence (ANDA) test batches. Andrx has also manufactured an exhibit batch of the 40 mg strength of the drug product using omeprazole manufactured by the proposed alternate source. The batch was manufactured in compliance with Policy and Procedure Guide 22-90, using the same manufacturing procedure and in process controls described in the ANDA, and packaged in 7, 30 and 1000 count bottles. Please note however, that the batch records for the active and enteric-coated pellets were slightly modified to accommodate a change in equipment size, that is, from a  

to a  

A description of the modifications made and revised proposed commercial batch records that reflect the modifications are provided under Tab 6 of this amendment.
Accelerated (40°C/75% RH) stability data was generated on the exhibit batch (lot 640R003) and a comparative dissolution test performed versus the original 40 mg strength biobatch (lot 640R001). Please note that Andrx has adopted the dissolution procedure described in the Pharmacopeial Forum (PF) as the drug product is able to meet the PF criteria when this method is used. Revised release specifications and the revised standard test method are provided under Tab 8.

This amendment includes chemistry and manufacturing documentation that demonstrates that omeprazole, USP (micronized) from the proposed alternate source has no impact on the identity, strength, quality and purity of the final drug product. The exhibit batch, lot 640R003, meets the same release criteria as the original bioequivalence batches, has a similar in-vitro dissolution profile and remains stable for up to 3 months under accelerated stability conditions. A list of the chemistry and manufacturing documents included in this amendment is provided after the 356h form.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact Janet Vaughn, Regulatory Affairs Manager at (954) 585-1665 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director of Regulatory Affairs
December 20, 2000

Mr. Harvey Greenberg
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347 – Omeprazole Delay-release Capsules, 10 mg, 20 mg & 40 mg
Bioequivalence Amendment

Dear Mr. Greenberg:

As per your telephone request of December 20, 2000 with Diane Servello, I have enclosed a
signed original and copy of our 356h form for the above mentioned amendment.

Should you have any questions or comments concerning this submission, please contact the Diane
Servello, Director of Regulatory Affairs, at (954) 585-1412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Jamie A. Dorgan
Associate, Regulatory Affairs
December 18, 2000

Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg

BIOEQUIVALENCE AMENDMENT

Dear Mr. Buehler:

Andrx Pharmaceuticals, Inc. ("Andrx") has conducted an additional bioequivalence study on our Omeprazole Delayed-release Capsules, 40 mg to compare the Andrx product to Prilosec® 40 mg Capsules when the capsule contents are sprinkled over applesauce. A copy of the final study report, consisting of four (4) volumes, is enclosed as follows:

Study No. 00210: "A Randomized, Two-Way Crossover, Single-Dose, Open-Label Study to Evaluate the Relative Bioavailability of the Contents of a Test Delayed Release Capsules Formulation of Omeprazole (40 mg), on Applesauce, Compared to an Equivalent Dose of a Commerically Available Reference Drug Product (Prilosec®, Astra Zeneca LP) in 30 Fasted, Healthy Male Subjects"

This study was prepared in an effort to eliminate a stalling tactic used by innovator firms to delay generic competition for encapsulated pellet products. In the case of Tiazac, approval of Andrx’ ANDA was delayed by the NDA holder’s labeling supplement for this form of administration a few months before the Andrx ANDA was eligible for final approval.

With regard to this ANDA, we received tentative approval on March 23, 2000, and will be eligible for final approval upon the expiration of patent #4,255,431 (April 5, 2001), subject to a possible extension as a result of pediatric exclusivity. As we are concerned that Astra Zeneca will submit a similar labeling supplement to their NDA to permit administration by sprinkling over applesauce, Andrx is at this time submitting a bioequivalence study showing that the Andrx product is equivalent to Prilosec® when administered over applesauce.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 585-1412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Diane Servello
Director, Regulatory Affairs
March 27, 2001

Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg

BIOEQUIVALENCE TELEPHONE AMENDMENT

Dear Mr. Buehler:

Reference is made to our December 18, 2000 bioequivalence amendment to the above referenced ANDA. Reference is also made to a telephone communication between Jenny Lee and Nina Nwaba of the Division of Bioequivalence and Diane Servello of Andrx Pharmaceuticals, Inc. (“Andrx”).

During the March 23 telephone communication it was requested that Andrx submit dissolution and potency data on the reference and test products used in Study No. 00210, which compared Andrx Omeprazole Delayed-release Capsules, 40 mg (lot #640R001) to Prilosec® 40 mg (lot #K5536) when administered by sprinkling over applesauce. Accordingly, please find the requested information attached.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 585-1412 (telephone) or 954-587-1054 (facsimile).

Sincerely,

Diane Servello
Director, Regulatory Affairs
ANDA 75-347
Omeprazole Delayed-release Capsules

March 26, 2001

Gary Buehler, Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Patent Certification

Dear Mr. Buehler:

Reference is made to a March 15, 2001 telephone communication between Saudra Middleton of the Office of Generic Drugs and Janet Vaughn of Andrx Pharmaceuticals, Inc. (“Andrx”). In that communication Andrx was requested to submit patent certifications for the following patents:

<table>
<thead>
<tr>
<th>Patent Number</th>
<th>Expiration Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>6150380</td>
<td>11/10/18</td>
</tr>
<tr>
<td>6147103</td>
<td>10/09/18</td>
</tr>
<tr>
<td>6166213</td>
<td>10/09/18</td>
</tr>
</tbody>
</table>

In addition, we note that the following patent was listed on the March 19, 2001 Docket #95S-0117 (Patent Term Extension and New Patents):

6191148 10/09/18

Andrx does not believe that these patent listings are appropriate, and therefore we are amending this application under protest to provide a paragraph IV patent certification for the four patents listed above. A letter providing the reasons for our belief that these patent listings are inappropriate will be sent under separate cover.

Should you have any questions concerning this submission, please contact the undersigned at (954) 585-1412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs
ANDA #75-347
Omeprazole Delayed-release Capsules
10 mg, 20 mg, & 40 mg

November 9, 2001

Gary Buehler,
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347: Omeprazole Delayed-release Capsules, 10 mg, 20 mg & 40 mg

LABELING AMENDMENT

Dear Mr. Buehler:

Please refer to your October 31, 2001 facsimile requesting revisions to our package outsert for the above mentioned product (copy attached). The revision provides for the revision of the PRECAUTIONS, Information for Patients and the DOSAGE AND ADMINISTRATION sections of the package outsert to add information regarding the administration the enteric-coated pellets in applesauce for patients who may have difficult swallowing whole capsules.

Andrx Pharmaceuticals, Inc. has updated our labeling as requested in the facsimile. In this regard, we have enclosed the following:

1. Twelve (12) final printed package outserts.
2. A side-by-side comparison of our proposed labeling with our previous labeling, with all differences annotated and explained.

Should you have any questions concerning this submission, please contact the undersigned at (954) 585-1412 (telephone) or (954) 954-587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

Enclosure(s)
ANDA-75-347
Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg

September 11, 2001

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: TELEPHONE AMENDMENT

Dear Mr. Buehler:

Please refer to our ANDA for the above-mentioned drug product. Reference is also made to our July 30, 2001 minor amendment and to a September 10, 2001 telephone communication between Dr. Radika Rajagopalan of your office and Diane Servello of Andrx Pharmaceuticals, Inc.

This amendment includes stability data for the original ANDA test batches, lot numbers 610R002 (10 mg), 620R001 (20 mg), and 640R001 (40 mg) which were manufactured with omeprazole, USP from ____________, the Assay and related compounds test data at 43 months for the 10 mg and 20 mg capsules, and at 36 months for the 40 mg capsules, were obtained using the revised test method, STM #062, described in the July 30, 2001 minor amendment.

Andrx Pharmaceuticals, Inc. certifies that a Field Copy of this amendment was submitted to the Florida District Office. That field copy is a true copy of the information contained in this amendment.

Should you have any questions or comments concerning this amendment, please contact Janet Vaughn, Manager Regulatory Affairs, at (954) 585-1665 (Tel.) or 954-587-1054 (Fax.).

Sincerely,

Diane Servello
Director Regulatory Affairs

cc: Dr. Radika Rajagopalan
Chemistry Reviewer
Office of Generic Drugs
ANDA-75-347
Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg

July 30, 2001

Gary Buehler
Acting Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: MINOR AMENDMENT: CHEMISTRY

Dear Mr. Buehler:

Reference is made to your facsimile dated May 4, 2001 for the above referenced application (copy of facsimile attached). In accordance with 21 CFR 314.120, Andrx Pharmaceuticals, Inc. is submitting a minor amendment to this ANDA that provides a complete response to all the deficiencies listed in the facsimile.

A. Chemistry Deficiencies

1. Please provide a revised components and composition statement, since the level of Povidone, USP, has been changed.

Response
The revised components and composition statement, reflecting the change in the level of Povidone, USP, is provided under Tab 1.

2. Please provide Certificates of Analysis for the inactive ingredients employed in the manufacture of batch 640R003.

Response
Certificates of analysis for the lots of inactive ingredients employed in the manufacture of the exhibit batch lot 640R003, are provided under Tab 2.

3. Please update specifications for inactive ingredients as per USP/NF 24.

Response
The specifications for the inactive ingredients used in the exhibit batch are all in accordance with USP/NF 24. The USP supplements are continuously monitored for changes and the specifications are updated as soon as changes are made to the monograph. A copy of the current specification for each excipient is provided under Tab 2. Please note that in accordance with our current practice, the specifications refer to the “current” version of the USP as the test method used rather than specifying the exact USP version.

4. On page 159, ____________ are missing. Please submit.

Response
Redacted

3

pages of trade secret and/or confidential commercial information
ANANDA 75-347
MAJOR AMENDMENT

August 5, 1998

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

Dear Sir:

Please refer to Andrx’s ANDA 75-347, for Omeprazole Delayed-release Capsules, 10 mg and 20 mg, and to the FDA’s Not Approvable letter sent by facsimile on July 20, 1998.

This amendment provides a complete response to all the deficiencies listed in the Not Approvable letter. It consists of one volume, two copies of which are provided - an archival copy (blue binder) and chemistry review copy (red binder).

In accordance with 21 CFR 314.96(b), Andrx Pharmaceuticals certifies that a field copy of this amendment has been sent to the Florida District Office.

Please direct any questions regarding this submission to Jacqueline Davis, Regulatory Affairs Manager, by telephone at (954) 321-5229 or by facsimile at (924) 587-1054.

Sincerely,

David Gardner
Vice President, Regulatory Affairs/QA/QC

RECEIVED
AUG 07 1998

Andrx Pharmaceuticals, Inc.
4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054
ANDA 75-347
PATENT AMENDMENT

May 28, 1998

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

Dear Mr. Sporn:

As required by 21 CFR 314.107(f)(2), Andrx Pharmaceuticals, Inc. is amending its Abbreviated New Drug Application for Omeprazole Delayed-release Capsules to provide notice of legal action against it for patent infringement:

(i)  ANDA No.: 75-347

(ii)  Name of Applicant:  Andrx Pharmaceuticals, Inc.

(iii)  Established Name of Drug Product:
       Omeprazole Delayed-release Capsules, 10 mg and 20 mg

(iv)  Certification of Action for Patent Infringement:
       This certifies that an action for patent infringement (Case No. 98-6521, CIV-GRAHAM) has been filed by Astra Aktiebolag, Aktiebolaget Hassle, Astra Merck Enterprises, Inc., and Astra Merck, Inc. against Andrx Pharmaceuticals, Inc. alleging infringement of United States Patent No. 4,786,505 (the “505 patent”), Patent No. 4,853,230 (the “230 patent”), Patent No. 4,636,499 (the “499 patent”), Patent No. 5,599,794 (the “794 patent”), Patent No. 5,629,305 (the “305 patent”), Patent No. 5,093,342 (the “342 patent”), and Patent No. 4,255,431 (the “431 patent”). The complaint was filed in the United States District Court for the Southern District of Florida on May 21, 1998.

Please direct any questions regarding this submission to Jacqueline Davis, Regulatory Affairs Manager, by telephone at (954) 321-5229 or by fax at (954) 587-1054.

Sincerely,

David A. Gardner
Vice President, Regulatory Affairs/QA/QC
ANDA 75-347
BIOEQUIVALENCE TELEPHONE AMENDMENT

August 14, 1998

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

Dear Mr. Sporn:

Andrx Pharmaceuticals is amending its Abbreviated New Drug Application for Omeprazole Delayed-release Capsules, 10 mg and 20 mg, to provide additional information as requested by Ms. Lizzie Sanchez and Dr. Jennie Lee by telephone on July 31, 1998. Specifically, we are providing additional dissolution data for the test and reference products using the dissolution test parameters recommended in that telephone call (see Attachment 1).

In addition, we are providing clarification of the lot numbering system used by Andrx for its finished products – The finished product lot numbers are designated XXXAXXX(A), where, using the 20 mg product (Lot #620R001) as an example, the first three digits represent the product code (620); the letter R indicates that this batch is a R&D/biobatch; and the last three digits are a sequential number assigned to each lot, starting with the first lot manufactured for each year (001). The final letter represents the packaging configuration e.g. 620R001A is the packaging lot number for the 7 capsules/bottle configuration and 620R001B is the lot number for the 30 capsules/bottle package size. A more detailed explanation can be found in Section XVIII (Control Numbers) of the original ANDA submission, a copy of which is provided as Attachment 2.

Should you have any questions or comments regarding this amendment please contact Ms. Jacqueline Davis, Regulatory Affairs Manager, Tel. (954) 321-5229/Fax. (954) 587-1054.

Sincerely yours,

David A. Gardner
Vice President, Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054
ANDA 75-347
PATENT AMENDMENT

April 29, 1998

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

Dear Mr. Sporn:

Please refer to Andrx Pharmaceuticals' pending Abbreviated New Drug Application, ANDA 75-347, for Omeprazole Delayed-release Capsules, 10 mg and 20 mg.

In accordance with 21 CFR 314.95(b), Andrx Pharmaceuticals, Inc. certifies that notices of certification of invalidity or noninfringement of a patent have been provided by U.S. registered mail with return receipt requested to each person identified under 314.95(a) and that the notices met the content requirements under 314.95(c). The notices were sent on April 10, 1998, by James V. Costigan, patent counsel for Andrx Pharmaceuticals, Inc. In accordance with 21 CFR 314.95(e) a copy of the return receipt for each notice is provided in this amendment as documentation of receipt of notice.

This amendment consists of one volume. Two copies are provided - an archival copy (in a blue binder) and review copy (black binder). Please direct any questions regarding this submission to Jacqueline Davis, Regulatory Affairs Manager, by telephone at (954) 321-5229 or by fax at (924) 587-1054.

Sincerely,

David A. Gardner
Vice President, Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054
ANDA 75-347
BIOEQUIVALENCE AMENDMENT

April 17, 1998

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

Dear Mr. Sporn:

Please refer to Andrx Pharmaceuticals’ pending Abbreviated New Drug Application, ANDA 75-347, for Omeprazole Delayed-release Capsules, 10 mg and 20 mg.

Andrx Pharmaceuticals is amending this application to provide two replacement pages for an in vivo bioequivalence study report, Protocol No. 97273 (fasting study), submitted in the original application dated 3/17/98. We ask that pages 226 and 301 in volume 2 of the orginal application be replaced with the pages in this amendment. Two copies are provided - an archival copy (blue binder) and a bioequivalence review copy (orange binder).

Please direct any questions regarding this submission to Jacqueline Davis, Regulatory Affairs Manager, by telephone at (954) 321-5229 or by fax at (924) 587-1054.

Sincerely,

David A. Gardner
Vice President, Regulatory Affairs/QA/QC

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054
April 13, 1998

Jerry Phillips, Director
Division of Labeling and Program Support
Office of Generic Drugs (HFD-600)
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

RE: ANDA #75-347

Dear Mr. Phillips:

Please refer to our Abbreviated New Drug Application for Omeprazole Delayed-release Capsules, 10 mg and 20 mg, which was submitted on March 17, 1998.

As requested in your April 7, 1998 correspondence we are providing three additional copies of the draft container labels submitted in our original application for the archival copy of the ANDA. Please note that four copies of our revised package insert labeling were provided in both the archival and review copies of our 4/9/98 Labeling Amendment.

Should you have any questions or comments regarding this submission, please contact me by telephone at (954) 321-5229, or by fax at (954) 587-1054.

Sincerely,

Jacqueline Davis
Regulatory Affairs Manager
April 9, 1998

Douglas L. Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-347 Omeprazole Delayed-release Capsules, 10 mg & 20 mg
LABELING AMENDMENT

Dear Mr. Sporn:

Please refer to our Abbreviated New Drug Application for Omeprazole Delayed-release Capsules, 10 mg and 20 mg, which was submitted on March 17, 1998.

Andrx Pharmaceuticals hereby amends this application to provide revised package outsert labeling. The proposed labeling has been revised to delete all references to the use of omeprazole in as this use is under patent protection. As reflected in the revised labeling, Andrx’s Omeprazole Delayed-release Capsules will not be marketed for this use. This amendment consists of one volume. Two copies are provided - an archival copy (blue binder) and a review copy (red binder).

Please direct any questions or comments regarding this submission to Jacqueline Davis, Regulatory Affairs Manager at (954) 321-5229.

Sincerely,

[Signature]
David A. Gardner
V.P., Regulatory Affairs, QA/QC

RECEIVED
APR 13 1998

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054
March 17, 1998

Douglas L. Sporn, Director
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Abbreviated New Drug Application
OMEPRAZOLE DELAYED-RELEASE CAPSULES, 10 mg & 20 mg

Dear Mr. Sporn:

Pursuant to the requirements of Section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.94, Andrx Pharmaceuticals, Inc. ("Andrx") is submitting an original Abbreviated New Drug Application ("ANDA") for approval to market Omeprazole Delayed-release Capsules, 10 mg and 20 mg.

This ANDA contains information to demonstrate that Andrx's Omeprazole Delayed-release Capsules are the same as the reference listed drug, Prilosec® (Omeprazole) Delayed-release Capsules, manufactured by Astra Merck, Inc., in active ingredient, conditions of use, route of administration, dosage form, strength and labeling; and that the two products are bioequivalent. The ANDA also provides a detailed description of the manufacturing and controls of the Andrx product.

This ANDA consists of 9 volumes. Two copies are provided — an archival copy (in blue folders) and a review copy separated into the bioequivalence review section (in orange folders) and the chemistry review section (in red folders). A detailed description of the organization of this ANDA is provided on introductory page (v) - Executive Summary, Organization of the ANDA.

In accordance with 21 CFR §314.94(d)(5), Andrx Pharmaceuticals, Inc. certifies that concurrent with this submission, a field copy has been forwarded to the Orlando District Office. This field copy is a true copy of the technical sections contained in the archival and review copies of the application.

Please direct any correspondence regarding this application to me at the address below. I may also be contacted by telephone at (954) 581-7500 or by fax at (954) 327-5389.

Sincerely,

David A. Gardner
V. P., Regulatory Affairs/QA/QC

[RECEIVED]
MAR 17, 1998

GENERIC DRUGS
4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054
Office of Generic Drugs (HFD-600)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Re: ANDA 75-347 (Omeprazole Delayed-Release Capsules)  
Andrx Pharmaceuticals, Inc.

Dear Sirs:

This letter is submitted on behalf of AstraZeneca LP, which holds the approved new drug application for Prilosec, the reference listed drug referred to in the above-captioned abbreviated new drug application submitted by Andrx Pharmaceuticals, Inc.

In the tentative approval letter dated March 24, 2000, from FDA to Andrx concerning this ANDA (copy attached), FDA refers to patent litigation underway with respect to certain listed patents, including U.S. Patent No. 4,255,431 ("the '431 patent"). However, Andrx submitted a paragraph III certification for this patent, not a paragraph IV certification and, accordingly, Andrx has not been sued for infringement of this patent.

The purpose of this letter is to ensure that FDA correctly applies the statutory provisions relating to the effective date of the Andrx ANDA, with respect to the '431 patent. Because Andrx submitted a paragraph III certification with respect to this patent, the ANDA cannot be made effective before the expiration date of that patent, April 5, 2001, regardless of the disposition of litigation involving any of the other patents. In addition, omeprazole is the subject of a written request from FDA for pediatric information, and AstraZeneca anticipates qualifying for six months of pediatric exclusivity pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act. This would mean that the ANDA could not be approved before October 5, 2001.

The dates described in the preceding paragraph relate only to the paragraph III certification made with respect to the '431 patent and thus represent the earliest date on which the ANDA would be eligible for approval based on that certification. If any other applicable period resulting from other patents, litigation, or exclusivity expires after that date, or if the
ANDA otherwise were not eligible for approval, then the ANDA could not be subject to a final approval until the expiration of the last applicable date. See 21 C.F.R. § 314.107(b)(4).

Sincerely yours,

Bruce N. Kuhlik

Counsel for AstraZeneca LP

cc: Andrx Pharmaceuticals, Inc.
    Attention: Diane Servello

APPEARS THIS WAY ON ORIGINAL
BY HAND

Office of Generic Drugs (HFD-600)
Food and Drug Administration
Metro Park North 2, Room 286
7500 Standish Place
Rockville, MD 20855

Re: All ANDAs for Omeprazole Delayed-Release Capsules:
ANDAs 75-268, 75-347, 75-410, 75-576, 75-757, 75-785,
75-791, 75-832, 75-876

Dear Sirs:

This letter is submitted on behalf of AstraZeneca LP, which holds the approved new drug application for Prilosec® (NDA 19-810), the reference listed drug referred to in the above-captioned abbreviated new drug applications. Copies of this letter are being provided for each ANDA file.

The purpose of this letter is to ensure that the Office of Generic Drugs is aware of two recent developments affecting the timing of the approval of each of the omeprazole ANDAs.

First, AstraZeneca has recently listed four new patents with FDA in connection with the Prilosec NDA. On December 8, 2000, the CDER Central Document Room received information regarding U.S. Patents 6,150,380 and 6,147,103. On January 16, 2001, the CDER Central Document Room received information regarding U.S. Patent 6,166,213. On March 16, 2001, the CDER Central Document Room received information regarding U.S. Patent 6,191,148. AstraZeneca made these submissions within 30 days of the date of the issuance of the respective patents. Accordingly, each is deemed to have been listed on the date received by CDER (21 C.F.R. § 314.53(d)(4) and (5)). All four patents are now shown on FDA’s web site (<http://www.fda.gov/cder/orange/docket.pdf>). Each ANDA must be amended to provide a certification as to each of these patents (21 C.F.R. § 314.94(a)(12)). As of today, only one of the ANDA applicants (Andrx, ANDA No. 75-347) has provided notice of a paragraph IV certification to the first three of these patents, and none has provided notice with respect to the fourth patent. At the earliest, none of the ANDAs can be made effective
until the expiration of 45 days following receipt of such notice (21 C.F.R. § 314.107(b)(3) and (f)). Of course, if litigation is instituted within the 45-day period, or if an ANDA submits a certification under paragraph III rather than paragraph IV, later dates would apply.

Second, AstraZeneca has filed pediatric study reports in response to a written request from FDA for pediatric information pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act. Agency review of these reports is required no later than April 4, 2001, and the company expects to receive pediatric exclusivity as a result of that review. The award of pediatric exclusivity will add six months to all Prilosec patent and exclusivity periods for purposes of determining the dates on which the ANDAs can be approved. Of most immediate importance, for those applicants that certified under paragraph III to U.S. Patent No. 4,255,431, which expires on April 5, 2001, approval will be prohibited at least through October 5, 2001.

Each of the ANDA holders has made certifications to other patents listed for Prilosec and is the subject of infringement litigation brought within the applicable 45-day period. These certifications and lawsuits independently prohibit FDA approval of the ANDAs until specified dates. In addition, the 180-day exclusivity provision delays the approval of certain of the applications. The approval of any particular ANDA cannot be made effective until all of the applicable periods arising from the certifications, litigation, pediatric exclusivity, and 180-day exclusivity have expired (21 C.F.R. § 314.107(b)(4)).

Sincerely yours,

Bruce N. Kuhlik

Counsel for AstraZeneca LP

cc: ANDA 75-268 (Genpharm Inc.)
ANDA 75-347 (Andrx Pharmaceuticals, Inc.)
ANDA 75-410 (KUDCo)
ANDA 75-576 (Cheminor Drugs, Ltd.)
ANDA 75-757 (Lek Pharmaceutical & Chemical Co. d.d.)
ANDA 75-785 (Impax Laboratories, Inc.)
ANDA 75-791 (Eon Labs Manufacturing Inc.)
ANDA 75-832 (Zenith Goldline Pharmaceuticals, Inc.)
ANDA 75-876 (Mylan Pharmaceuticals Inc.)
March 27, 2001

VIA FACSIMILE AND
OVERNIGHT DELIVERY

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Re: Unlawful Patent Listings for Prilosec®

Dear Mr. Buehler:

Andrx objects to the listing by Astra Merck, Inc. (“Astra”) of four new patents, U.S. Patents No. 6,147,103, No. 6,150,380, No. 6,166,213 and No. 6,191,148, as covering the approved drug Prilosec® (omeprazole delayed-release capsules; NDA 19-810). Andrx believes that Astra is manipulating the patent listing provisions of the Hatch-Waxman amendments in an attempt to delay generic competition by Andrx’s tentatively approved bioequivalent product. Consistent with the provisions of 21 U.S.C. § 355(c)(2), C.F.R. § 314.53 and FDA’s longstanding limitation on patents that are listed in the Orange Book, Andrx requests that the agency require AstraZeneca to de-list the four newly-listed patents by next Monday, April 2, 2001.

In the first place, it would appear that at least the first three patents were not listed within the 30 days required by 21 C.F.R. § 314.53(d).

Second, the ’103, ’213, and ’148 patents are each entitled “Omeprazole Process and Compositions Thereof” and the ’380 patent also includes process claims, so they cannot be properly be listed under 21 CFR 314.53(b).

Third, to the extent any of the patents claim specific forms of omeprazole or compositions of omeprazole with specific levels of residual solvents or other chemicals, Andrx is unaware of any evidence
suggesting that Prilosec actually contains omeprazole in the form or composition claimed by the patents. The FDA is in a unique position to determine if Astra has amended its NDA to change the specification for the purity of the omeprazole that has been sold since at least 1990. If Astra has not notified the FDA of a change in its production process or products specification since the filing date of the four newly-listed patents and received all requisite approvals, the FDA has sufficient information in its own files to delist the newly listed patents.

Fourth, Andrx notes that the question of whether or not the patents are properly listed in the Orange Book is separate from the question of whether the listing can or should in any way delay FDA approval of Andrx’s ANDA under 21 U.S.C. § 355(j)(5)(B)(iii). There is no statutory basis for such a delay, and in fact any such delay would be contrary to the clear wording of the statute.

Andrx appreciates FDA’s attention to this matter, but must reserve all its rights. Our outside counsel, King & Spalding, will contact your office to follow-up on this letter.

Sincerely,

[Signature]

Scott Lodin
Executive Vice President & General Counsel

cc: Drug Information Services Branch (HFD-84)
    Mr. Donald B. Hare, Office of Generic Drugs (HFD-604)
    Kim E. Dettelbach, Esq., Office of the Chief Counsel (GCF-1)

    Eugene M. Pfeifer, Esq.
    Christina M. Markus, Esq.
    King & Spalding

[Stamp: CENTER FOR DRUG EVALUATION AND RESEARCH]

[Stamp: MAY 25, 2001]

[Stamp: OGD]
May 29, 2001

Gary Buehler,
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT
ANDA 75-347 – Omeprazole Delayed-release Capsules, 10 mg, 20 mg and 40 mg

Dear Mr. Buehler:

Andrx Pharmaceuticals, Inc. is amending the above referenced application to provide documentation of notification and receipt of notice, as follows:

Documentation of Notification /Receipt of Notices:

In accordance with 21 CFR 314.95(b), Andrx certifies that:

i. the required notices of certification of noninfringement of patents 6,147,103; 6,166,213 and 6,150,380 were provided on March 16, 2001 by Federal Express and U.S. Postal Service Express Mail, return receipt requested to each person identified under §314.95(b) (i.e.Astra Zeneca, LP; Merck & Co., Inc.; and Astra Aktiebolag). The Federal Express tracking documents indicate that the notices were received on March 19, 2001. The U.S. Postal tracking documents indicate that the notice to Merck was received on March 19, 2001 and the notice to Astra Aktiebolag was received on March 21, 2001. We have not received the return receipt from Astra Zeneca, LP.

ii. the required notices of certification of noninfringement of patent 6,191,148 were provided on March 22, 2001 by Federal Express and U.S. Postal Service Express Mail, return receipt requested to each person identified under §314.95(b) (i.e.Astra Zeneca, LP; Merck & Co., Inc.). The Federal Express tracking documents indicate the notices were received on March 27, 2001. The U.S. Postal tracking documents indicate that Astra Zeneca, LP received the notice on March 27, 2001 and Merck & Co., Inc. received the notice on March 26, 2001.

iii. the notices met the content requirements under §314.95(c).

Please see the attached summary table referencing the above information. Copies of the return receipt postcards and the delivery tracking reports are enclosed.

Based on the latest date (March 27, 2001) documented on the return receipts, the 45-day period, provided for in section 505(j)(4)(B)(iii) of the act, ended on May 11, 2001. As of today’s date, no litigation has been filed by the patent holder or the NDA holder. Should you have any questions regarding this amendment, please do not hesitate to contact Janet Vaughn at (954) 585-1665 (Tel.) or (954) 587-1054 (Fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

Enclosure(s)