

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-032

MEDICAL REVIEW(S)



MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research

Date: December 4, 2007

From: Andrea Leonard-Segal, M.D.
Director, Division of Nonprescription Clinical Evaluation

Subject: NDA 22-032
Omeprazole 20 mg Tablets

Sponsor: Dexcel Pharma Technologies, Ltd.

This is an addendum to the review co-signed by myself and Dr. Daniel A. Shames yesterday to update the thinking regarding the need for pediatric studies for this application. That review recommended that studies should be deferred in children < 2 years of age.

During the day today there was much internal discussion between Dr. Lisa Mathis and Dr. Hugo Gallo-Torres regarding the need for pediatric studies for this NDA. The gastroenterology group, after reconsideration, determined that there is no need to conduct further studies for this product and that omeprazole is appropriately labeled for the indication for use in ages < 18 years. Thus, for this application, the PREA requirement is "fulfilled." Dr. Shames is in concert with this thinking. I am attaching the e-mail chain that reflects the change in thinking to this memorandum.

Recommendation:

This application should be approved. The pediatric requirements are fulfilled.

RE Omeprazole Dexcel e-mail on pediatric studies.txt

From: Shames, Daniel A
Sent: Tuesday, December 04, 2007 3:48 PM
To: Leonard Segal, Andrea
Subject: RE: Omeprazole Dexcel

Yes it is fine
Dan

-----Original Message-----

From: Leonard Segal, Andrea
Sent: Tuesday, December 04, 2007 3:46 PM
To: Shames, Daniel A
Subject: FW: Omeprazole Dexcel
Importance: High

Dan,
Something new happened today.

I'm going to revise the memo that we signed yesterday to state that after communications between Lisa Mathis and Hugo there is no need to conduct further studies and that omeprazole is appropriately labeled for this indication for use in ages < 18 years of age. In the interest of time I'm going to put this revision in under my sole signature and I will DFS the e-mail chain.
Are you okay with that?
Andrea

Andrea Leonard-Segal, M.D.
Director,
Division of Nonprescription Clinical Evaluation
FDA
301-796-0940
301-769-9899

-----Original Message-----

From: Christl, Leah A
Sent: Tuesday, December 04, 2007 3:33 PM
To: Olin, Keith; Leonard Segal, Andrea
Subject: Fw: Omeprazole

Fix the letter based on the info below.

Sent from my BlackBerry wireless handheld

----- Original Message -----

From: Mathis, Lisa
To: Christl, Leah A
Sent: Tue Dec 04 15:30:57 2007
Subject: RE: Omeprazole

Yes ma'am!

Lisa L. Mathis, M.D.
CDR, USPHS
OND Associate Director
Pediatric and Maternal Health Staff
Office of New Drugs
White Oak Complex, Bldg 21, Rm 1633

RE Omeprazole Dexcel e-mail on pediatric studies.txt
10903 New Hampshire Ave.
Silver Spring, MD 20993
(301) 796-1704
fax (301) 796-9744
>email: Lisa.Mathis@fda.hhs.gov
>(Note this is a new e-mail address)
>

-----Original Message-----

From: Christl, Leah A
Sent: Tuesday, December 04, 2007 3:31 PM
To: Mathis, Lisa
Subject: Re: Omeprazole

So for the language you recommended below, we would say it is appropriately labeled for under the age of 18 and no additional studies are needed?

Sent from my BlackBerry wireless Handheld

----- Original Message -----

From: Mathis, Lisa
To: Christl, Leah A
Sent: Tue Dec 04 15:28:19 2007
Subject: RE: Omeprazole

You don't need to handle this. Just use the previous decision for OTC indication. It is fulfilled. Call if you need...

Lisa L. Mathis, M.D.
CDR, USPHS
OND Associate Director
Pediatric and Maternal Health Staff
Office of New Drugs
White Oak Complex, Bldg 21, Rm 1633
10903 New Hampshire Ave.
Silver Spring, MD 20993
(301) 796-1704
fax (301) 796-9744
>email: Lisa.Mathis@fda.hhs.gov
>(Note this is a new e-mail address)
>

-----Original Message-----

From: Christl, Leah A
Sent: Tuesday, December 04, 2007 3:27 PM
To: Mathis, Lisa; Addy, Rosemary; Carmouze, Grace N; Olin, Keith
Cc: Gallo Torres, Hugo E
Subject: Re: Omeprazole

since the Rx is not labeled down below the age of 2, how do we handle that?

Sent from my BlackBerry wireless Handheld

----- Original Message -----

From: Mathis, Lisa
To: Christl, Leah A; Addy, Rosemary; Carmouze, Grace N; Olin, Keith
Cc: Gallo Torres, Hugo E
Sent: Tue Dec 04 15:21:34 2007

RE Omeprazole Dexcel e-mail on pediatric studies.txt
Subject: RE: Omeprazole

All,
For the omeprazole, the PREA will be "fulfilled.". Studies of the prescription product have been performed, and additional studies are not necessary. This is the language for your action letter. Since no studies are necessary, use this language instead of the language Rosemary sent you.

This drug/biological product is appropriately labeled for use in ages INSERT AGE to INSERT AGE years for this/these indication(s). Therefore, no additional pediatric studies are needed in this age group.

Also, all pediatric plans, assessments, waivers and deferrals must be reviewed by the PerC. Because this approval doesn't involve any of these, it does not need to come to PerC.

Hope this helps.

Lisa
Lisa L. Mathis, M.D.
CDR, USPHS
OND Associate Director
Pediatric and Maternal Health Staff
Office of New Drugs
White Oak Complex, Bldg 21, Rm 1633
10903 New Hampshire Ave.
Silver Spring, MD 20993
(301) 796-1704
fax (301) 796-9744
email: Lisa.Mathis@fda.hhs.gov
(Note this is a new e-mail address)

From: Gallo Torres, Hugo E
Sent: Tuesday, December 04, 2007 3:06 PM
To: Mathis, Lisa
Cc: Christl, Leah A; Addy, Rosemary; Carmouze, Grace N
Subject: RE: Omeprazole

Lisa: I most certainly agree with the assessment that for children, especially younger children, GERD can or should be self diagnosed. I agree with the concept that the symptoms displayed in these young patients, such as apnea and bradycardia, are not pathognomonic of GERD and may be signs and symptoms of other serious congenital cardiac or pulmonary conditions. I also agree with the statement that these young patients should be evaluated by a physician, and parameters such as growth and development should be closely evaluated even in instances of endoscopically-proven reflux esophagitis.

I agree with the PIT. I believe the material above provides a medical/regulatory justification to grant a waiver.

Please let me know how can I help.

Hugo

From: Mathis, Lisa

RE Omeprazole Dexcel e-mail on pediatric studies.txt
Sent: Tuesday, December 04, 2007 2:48 PM
To: Gallo Torres, Hugo E
Cc: Christl, Leah A; Addy, Rosemary; Carmouze, Grace N
Subject: Omeprazole
Importance: High

Hugo,

Looks like the reason for the waiver on the suitability petition (which was at the time said to be the same as was done for the already OTC product, and thus consistent with this product specific to OTC) was that for children, Gastroesophageal reflux is not a condition that can or should be self diagnosed. Especially in younger children, the symptoms displayed are not pathognomonic for GERD and may be signs and symptoms of other serious conditions (e.g. congenital cardiac and pulmonary). Patients should be evaluated by a physician, and parameters such as growth and development should be closely monitored even if the diagnosis of GERD is definitively made.

Do you still agree with this assessment? The Pediatric Implementation Team reviewed this for the suitability petition and agreed with the waiver. I will try and assess the specific pediatric age group that was waived, and then we will recommend that OTC states that studies above that age group have been fulfilled (even if they are for Rx indications - we don't want further study).

Thanks so much for meeting with me earlier today, and for your help with this!

Lisa

Lisa L. Mathis, M.D.
CDR, USPHS
OND Associate Director
Pediatric and Maternal Health Staff
Office of New Drugs
White Oak Complex, Bldg 21, Rm 1633
10903 New Hampshire Ave.
Silver Spring, MD 20993
(301) 796-1704
fax (301) 796-9744
email: Lisa.Mathis@fda.hhs.gov
(Note this is a new e-mail address)

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

/s/

Andrea Segal

12/4/2007 04:13:09 PM

MEDICAL OFFICER



MEDICAL OFFICER'S SAFETY UPDATE REVIEW

Department of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation

NDA:	22-032
Drug name:	Omeprazole Delayed Release Tablet 20 mg
Sponsor:	Dexcel Pharma Technologies, Ltd.
Pharmacologic Category:	Proton-Pump Inhibitor
Proposed Indication:	Treatment of frequent heartburn
Subject:	NDA Resubmission Safety Update
Submission Date:	October 5, 2007
PDUFA Goal Date:	December 4, 2007
Reviewer:	Lolita A. Lopez, M.D.
Team Leader:	Daiva Shetty, M.D.

I. Introduction

This review addresses the safety update information submitted by the sponsor in response to the tentative approvable letter issued on June 14, 2007. This safety update covers the period from December 1, 2006 to September 25, 2007.

II. Background

On February 10, 2006, Dexcel Pharma Technologies, Ltd. submitted NDA 22-032, seeking approval to market Omeprazole Delayed Release Tablet 20 mg for over-the-counter (OTC) use in adults 18 years and older. The indication and dosing regimen will be similar to the already approved Prilosec OTCTM. This NDA was submitted under a 505(b)(2) application and relied on the Agency's previous finding of safety and efficacy for omeprazole. In support of this NDA, the sponsor conducted bioavailability studies (AA24171 and AA28531) under fasting and fed conditions comparing a single dose of the proposed Omeprazole Delayed Release Tablet and Prilosec OTCTM Delayed Release Tablet (RLD¹), 20 mg, in healthy adult subjects. Safety information was also submitted which included safety update for omeprazole (including sponsor's product), literature review and postmarketing adverse events. See this Medical Officer review of NDA 22-032 filed in DFS on November 9, 2006.

¹ Reference Listed Drug

On December 8, 2006, an approvable letter was issued to the sponsor; the deficiencies that needed to be resolved before being approved were issues raised during the DSI inspection (see approvable letter entered in DFS for details). On December 18, 2006, the sponsor submitted a document that they identified as a complete response to the approvable letter. See this Medical Officer's Review of safety update filed in DFS on June 4, 2007. On June 14, 2007, a tentative approval letter was issued to the sponsor for this NDA due to patent infringement issues.

On October 28, 2007, the sponsor submitted another complete response to the *tentatively* approved letter issued June 14, 2007 including a safety update and an updated label.

III. Safety Update

The sponsor reports that there have been no new trials conducted since the NDA submission and that there have been no regulatory actions taken by either the regulatory authorities or by the Marketing Authorization Holder (MAH) for safety related reasons. Below is a safety update on omeprazole 20 mg strength formulation.

Postmarketing (Sponsor's Database)

The sponsor reports that the total number of omeprazole 20 mg sold in the United Kingdom _____ and Israel _____ from December 1, 2006 to August 30, 2007 was _____. There were approximately _____ patients exposed to the drug during this reporting period assuming that the drug is taken once a day for 4 weeks.

b(4)

A total of five cases reporting adverse events were listed in the sponsor's safety database during this reporting period. The duration of use in patients from these reports was for up to one year and the dose ranged from 10 mg to 40 mg once daily. There was one patient who was on omeprazole 40 mg initially for 3 weeks and was subsequently switched to a 20 mg strength (the proposed OTC dose). After 2 weeks, she experienced vomiting, decreased saliva, dry mouth and esophagus.

Since 1998, it is estimated that there were approximately over _____ patients exposed to omeprazole formulations marketed by Dexcel Pharma Technologies in both the U.K. and Israel. To date, postmarketing spontaneous reports on the use of omeprazole 20 mg for a duration up to 2 weeks consisted of 10 reports of lack of effect, 1 report of vomiting, 1 report of decreased saliva, 1 report of dry mouth and esophagus, and 1 report of diarrhea.

b(4)

Literature Review

A review of the literature was performed for this reporting period from June 18, 2006 to September 24, 2007. There were four cases reported in the literature of adverse events occurring in adult patients receiving orally administered omeprazole 20 mg daily for a period not exceeding 2 weeks. These events were drug hypersensitivity, gynecomastia, toxic epidermal necrolysis (sulfasalazine considered primary suspect drug) and autoimmune hemolytic anemia; the last two events required hospitalization and were considered serious. These adverse events have been reported with the use of omeprazole (see omeprazole prescribing information).

FDA AERS Database

Updated information from the FDA AERS database for the second quarter of 2006 through the first quarter of 2007 was reviewed for oral omeprazole as a primary suspect drug when dosed at 20 mg per day for duration of not longer than 2 weeks. A total of 7 adverse events in 2 patients and 1 drug ineffectiveness were identified. The following is a short narrative of these cases:

- A 52-year old woman took omeprazole 20 mg for one day for upper abdominal pain, she was hospitalized; reported adverse events were hypersensitivity, arthritis, pyrexia, decreased platelet count, petechiae and abnormal liver function tests.
- A 57-year old female took omeprazole 20 mg for one day for gastroesophageal reflux disease and reported drug ineffectiveness.
- A 63-year old man took omeprazole 20 mg for 6 days for cough and gastrointestinal disorder and was hospitalized due to abnormal hepatic enzymes.

The above adverse events, with the exception of arthritis, have been reported with the use of omeprazole. Joint pain is included in the list of adverse events reported with the use of omeprazole but not arthritis (see omeprazole prescribing information). The clinical information available was limited to determine the relationship of the events to the use of omeprazole.

IV. Comments and Conclusion

Omeprazole has been proven safe and effective in the U.S. for over 16 years even at high doses (prescription use up to 120 mg three times a day) for the treatment of acid-related gastrointestinal disorders. This drug has been marketed worldwide since 1988 and in the United States since 1989. A 20 mg omeprazole magnesium (Prilosec OTC™) tablet has been available for OTC use since June 2003 for the treatment of frequent heartburn occurring two or more days a week, the duration of treatment is two weeks. The sponsor has marketing authorization for omeprazole in the United Kingdom (U.K.) since February 2002 and in Israel since September 1998.

The safety update from the review of the literature, FDA/AERS and sponsor's database submitted in response to the tentative approval letter that covers the period from December 1, 2006 to September 25, 2007 did not identify any new safety concerns or deaths for omeprazole delayed release tablet 20 mg when used for a duration of 2 weeks as proposed in this application.

V. Recommendation

From a clinical safety standpoint, Dexcel's proposed omeprazole 20 mg delayed release tablet indicated for the relief of frequent heartburn occurring two or more days a week for 14 days remains to have an acceptable safety profile for OTC marketing and therefore should be approved. For final approval, the sponsor needs to address the patent infringement issue identified in their tentative approval letter dated June 14, 2007.

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

/s/

Lolita Lopez
11/21/2007 12:53:00 PM
MEDICAL OFFICER

Daiva Shetty
11/21/2007 12:54:49 PM
MEDICAL OFFICER



MEDICAL OFFICER'S SAFETY UPDATE REVIEW

Department of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation

NDA:	22-032
Drug name:	Omeprazole Delayed Release Tablet 20 mg
Sponsor:	Dexcel Pharma Technologies, Ltd.
Pharmacologic Category:	Proton-Pump Inhibitor
Proposed Indication:	Treatment of frequent heartburn
Subject:	NDA Resubmission Safety Update
Submission Date:	December 18, 2006
PDUFA Goal Date:	June 18, 2006
Reviewer:	Lolita A. Lopez, M.D.
Team Leader:	Daiva Shetty, M.D.

I. Introduction

On February 10, 2006, Dexcel Pharma Technologies, Ltd. submitted NDA 22-032, seeking approval to market Omeprazole Delayed Release Tablet 20 mg for the treatment of frequent heartburn in adults 18 years and older for over-the-counter (OTC) use. The proposed dosing and indication for this product is similar to the already approved OTC omeprazole *magnesium* delayed release tablet, 20.6 mg (Prilosec OTC™), equivalent to 20 mg of omeprazole. In support of this NDA, the sponsor conducted one bioequivalence study (AA24171) comparing the pharmacokinetics of a single dose of the proposed Omeprazole Delayed Release Tablet 20 mg and Prilosec OTC™ Delayed Release Tablet 20 mg (reference listed drug) in healthy subjects. A food effect study (AA28531) was also conducted to determine the effect of food on the relative bioavailability of the sponsor's omeprazole product. This NDA was submitted under a 505(b)(2) application and relies on the Agency's previous finding of safety and efficacy for omeprazole. Safety information submitted with the NDA were the sponsor's safety update for omeprazole (including their product); literature review and postmarketing adverse events from the sponsor's database from November 2000 to June 2006; and AERS information February 2002 to first quarter of 2006.

On December 8, 2006, an approvable letter was issued to the sponsor; the deficiencies that needed to be resolved before being approved were issues raised during the DSI inspection (see approvable letter entered in DFS for details). In addition, the sponsor was also required to submit revised draft labeling and a safety update.

On December 18, 2006, Dexcel Pharma submitted a document that they identified as a complete response to the approvable letter, the subject of this review. This review addresses the safety update information submitted by the sponsor in response to the approvable letter. This safety update covers the period from June 2006 to November 2006.

II. Background

Omeprazole has been proven safe and effective in the U.S. for over 16 years even at high doses (up to 120 mg three times a day). This drug has been marketed worldwide since 1988 and in the United States since 1989. A 20 mg omeprazole magnesium (Prilosec OTC™) tablet has been available for over-the-counter use since June 2003. The sponsor has marketing authorization for omeprazole in the United Kingdom (U.K.) since February 2002 and in Israel since September 1998.

III. Safety Update

The formulation under review is not approved elsewhere. The proposed omeprazole delayed release 20 mg tablet formulation differs from the U.K. and Israel formulation in the enteric film coat. The safety assessment of the formulation under review was based on the adverse events from the two pharmacokinetics trials conducted in healthy volunteers (see Medical Officer's Review of NDA 22-032 entered in DFS on 11-9-06). There are no new adverse events reported for the pharmacokinetic studies conducted using this formulation. Below is a safety update on the omeprazole formulation marketed in the U.K. and Israel.

The sponsor reports that the total number of omeprazole 20 mg sold in the United Kingdom (U.K.) and Israel from June 2006 to November 2006 was _____. There were approximately _____ patients exposed to the drug during this reporting period assuming that the drug is taken once a day for 4 weeks. There were five adverse event reports involving eight patients:

- 6 patients for lack of effect
- 1 report for diarrhea
- 1 report for an incorrect dose (1 tab 4x/day instead of once a day), no adverse event occurred

It is also reported that as of November 30, 2006, there were approximately over 11 million patients exposed to Dexcel's omeprazole 20 mg in both the U.K. and Israel. To date, postmarketing spontaneous reports have consisted of lack of effect in 10 patients and diarrhea in 1 patient. The sponsor reports that there have been no regulatory actions taken by either the regulatory authorities or by the Marketing Authorization Holder (MAH) for safety related reasons.

b(4)

Medical Officer Comments: There were neither deaths nor serious adverse events reported. Diarrhea is a known side effect of omeprazole. Therefore, there are no new safety issues identified in this safety update.

IV. Conclusion

This safety update submitted by the sponsor in response to the approvable letter that covers the period from June 2006 to November 2006 did not identify any new safety concerns for omeprazole delayed release tablet 20 mg for OTC use.

V. Recommendation

From a clinical safety standpoint, Dexcel's proposed omeprazole 20 mg delayed release tablet indicated for the relief of frequent heartburn occurring two or more days a week for 14 days has an acceptable safety profile for OTC marketing and therefore should be approved. For final approval, the sponsor needs to address all the deficiencies identified in their approvable letter dated December 18, 2006.

APPEARS THIS WAY ON ORIGINAL

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

/s/

Lolita Lopez
6/4/2007 03:03:34 PM
MEDICAL OFFICER

Daiva Shetty
6/4/2007 03:26:35 PM
MEDICAL OFFICER



**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research**

MEMORANDUM: ADDENDUM

DATE: 12/8/06

FROM: Joyce A Korvick, MD, MPH
DGP/ODE III

SUBJECT: Deputy Division Director Action Recommendations

APPLICANT: Dexcel Pharma Technologies Ltd.

DRUG: NDA 22-032,
Omeprazole Delayed-Release Tablet 20 mg OTC®

DIVISION RECOMMENDATION (Addendum):

We support that the action letter to the sponsor should be an "approvable" action.

Deficiencies:

- The sponsor needs to provide an adequate complete response to the bioequivalence data deficiencies reported in the FDA 483 audit report by DSI. (this deficiency was identified in my original review)
- The sponsor needs to supply the data covering changes to the analytical procedure for this product and provide revised specifications to include known impurities. (this recommendation is new based upon final CMC review recommendations)

Additional Labeling Recommendations:

We agree with Dr. Leonard-Seigal's recommendation that the action letter contain the following information:

- It is important to convey to the sponsor, on Friday, that the agency is reconsidering the drug interaction warnings for OTC products containing omeprazole. We will have additional discussions between the Divisions and the Sponsor prior to finalizing the label.

Discussion:

Since my review was finalized yesterday, we have received final comments and recommendations from CMC review. The DSI inspection resulted in the following

findings: The overall recommendation from the Office of Compliance regarding facility cGMP status is "Acceptable" for this NDA" and no 483 was issued by the FDA for CMC issues after the inspection was completed. However, there remain concerns regarding changes in the specifics of the analytical methods and revisions to specifications including known impurities. These uncertainties have lead the chemists to state that they are uncertain about the validity of the revised methods, and because the sponsor has not submitted a CMC amendment for these revisions, and perhaps other specifications, the recommend that the CMC section of the Application is not acceptable.

Specific deficiencies will be outlined in today's Action Letter.

APPEARS THIS WAY ON ORIGINAL

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

/s/

Joyce Korvick
12/8/2006 11:24:01 AM
MEDICAL OFFICER



MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation

Date: December 8, 2006

From: Andrea Leonard-Segal, M.D.
Director

Subject: NDA 22-032
Omeprazole 20 mg Tablets

Sponsor: Dexcel Pharma Technologies, Ltd.

Background:

This is an addendum to the division director review that I wrote on December 6, 2006 and entered into the Division File System yesterday morning on NDA 22-032 (Dexcel Pharma Technologies, Ltd. Omeprazole Delayed Release Tablets 20 mg for OTC use to treat frequent heartburn).

Chemistry:

Yesterday, December 7, 2006 at 02:47:31 PM, Drs. Ding and Rhee wrote an addendum to the chemistry review dated December 5, 2006. Refer to that addendum. They changed their recommendation on this application from "approve" to "approvable."

The overall recommendation from the Office of Compliance regarding facility cGMP status is "Acceptable" for this NDA and no 483 was issued by the FDA for CMC issues after the inspection was completed. However, after the inspection, there appears to have been verbal, but unwritten, communication between the inspectors and Dexcel to recommend that the sponsor report changes in analytical methods and revise specifications to include known impurities. An e-mail from John Faranolic, Manager, Lachman Consultant Services, Inc. (representing Dexcel Pharma Technologies, Inc.) to Keith Olin, Project Manager, DNCE dated November 28, 2006, reflects this type of discussion. This e-mail is appended to the chemistry addendum review.

The chemists state in their addendum that they are now uncertain as to the validity of the revised analytical methods because the sponsor has not submitted a CMC amendment for these revisions and perhaps "other CMC aspects."

Clinical Pharmacology:

Yesterday, the clinical pharmacologists concluded that the Dexcel omeprazole 20 mg tablet is bioequivalent to Prilosec OTC™ 20 mg based upon the data that they reviewed. However, at this time, they consider this bioequivalence data to be unacceptable to support an "approval" action because the applicant has not provided an adequate complete response to the clinical pharmacology deficiencies reported in the FDA 483 audit by the Division of Scientific Investigations.

For the food effect study the clinical pharmacology reviewers found that the Dexcel product demonstrated a decrease in the rate and extent of absorption as compared with the fasted state and there were no DSI deficiencies associated with this study. Prilosec OTC™ 20 mg for the treatment of frequent heartburn is to be taken on an empty stomach. This Dexcel product, if approved, would have the same labeling and the food effect would, thus, not be clinically relevant.

Conclusions:

Based upon the Chemistry addendum and the Clinical Pharmacology review, there are additional data needed before this NDA can be approved.

Recommendations:

- The action letter to the sponsor should be "approvable."
- The sponsor needs to provide an adequate complete response to the bioequivalence data deficiencies reported in the FDA 483 audit report by DSI.
- The sponsor needs to supply the data covering changes to the analytical procedure for this product and provide revised specifications to include known impurities.
- It is important to convey to the sponsor, no matter what the action on Friday, that the agency is reconsidering the drug interaction warnings for OTC products containing omeprazole.

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

/s/

Andrea Segal
12/8/2006 10:47:59 AM
MEDICAL OFFICER



MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation

Date: December 6, 2006

From: Andrea Leonard-Segal, M.D.
Director

Subject: NDA 22-032
Omeprazole 20 mg Tablets

Sponsor: Dexcel Pharma Technologies, Ltd.

Background:

Omeprazole magnesium delayed release tablets, 20.6 mg (Prilosec OTC TM) are proton-pump inhibitors that were approved as a nonprescription drug for the treatment of frequent heartburn in adults at least 18 years of age under NDA 21-229 in June, 2003. The product is used once a day, before breakfast, for a 14-day course of treatment and this treatment course may be repeated every 4 months, if needed.

Dexcel Pharma Technologies, Ltd. proposes to market Omeprazole Delayed Release Tablets 20 mg for OTC use for the same indication and treatment regimen as Prilosec OTC TM. The Dexcel tablet formulation has been marketed in the United Kingdom since 2002 and in Israel since 2000. A capsule formulation was approved in Israel in August, 1998 and was marketed until October, 1999 when it was removed from the market due to patent litigation.

Omeprazole (Prilosec®) has been marketed in the United States since 1989 as a prescription product to treat gastroesophageal reflux disease, erosive esophagitis, and peptic ulcer disease and worldwide for > 16 years. It has a wide therapeutic index and has been prescribed in doses up to 360 mg/day for hypersecretory disorders.

Chemistry:

Refer to the review dated December 5, 2006 by Dr. Shulin Ding. The reviewers after considering the data and the facility inspection results recommend that this NDA can be approved. They do not recommend a postmarketing commitment.

Pharmacology/Toxicology:

See the review by Dr. David Joseph. There are adequate preclinical data on omeprazole. However, the Agency requested toxicology information on two excipients in this Dexcel omeprazole formulation (sodium stearate and monoethanolamine) that are present at levels exceeding the maximum amounts listed in FDA's Inactive Ingredients Database. Dr. Joseph states that monoethanolamine is commonly referred to as ethanolamine.

Dr. Joseph stated in his review that based upon the known safety of sodium stearate and stearic acid as dietary components (GRAS for use as a direct human food ingredient) there is no safety concern about the ingestion of sodium stearate in this product. Data also supported the safety of monoethanolamine in this product. Dr. Joseph notes that the maximum approved dose of ethanolamine (a product for intravenous administration, Ethamolin® Injection, 5%) results in the release of 177.9 mg into the systemic circulation as compared to a total intake of — during the recommended 14-day treatment with the Dexcel omeprazole product. Dr. Joseph concludes that the oral administration of ethanolamine in rat reproductive toxicology studies, a 2-year oral toxicity study of a commercial dye mixture containing ethanolamine in dogs, a 2-year dietary toxicity study in dogs, and the human experience with intravenous exposure to Ethamolin® suggest that the daily oral intake of — ethanolamine in the Dexcel omeprazole product is a minimal safety risk with respect to systemic toxicity, even with long term administration. Thus, Dr. Joseph concluded that there are no unresolved toxicology issues with this Dexcel omeprazole 20 mg tablet formulation and recommended that the product can be approved based upon the pharmacology/toxicology data.

b(4)**b(4)****Clinical Pharmacology:**

The sponsor conducted two clinical pharmacology studies. One (AA24171) was an in-vivo relative bioavailability study and the other (AA28531) was a food effect study. The studies compared the pharmacokinetics of a single-dose Dexcel omeprazole 20 mg tablet with those of a single dose of Prilosec OTC™, the reference listed drug. Both studies were conducted in healthy adult volunteers using an open-label, randomized, crossover study design with the final formulation proposed for marketing. Study AA24171 enrolled 76 male and female subjects. The food effect study enrolled 18 healthy adult males. Both of these studies were conducted at — in 2005, and the FDA Division of Scientific Investigation inspected the clinical and analytical sites.

b(4)

The DSI inspection report dated December 5, 2006, included the following conclusions and recommendations.

- — failed to justify the exclusion of omeprazole concentration results from analytical batch 12DAU. Thus, the original results for subjects 30-32 from batch 12DAU in Study AA24171 (fasting) should have been used for the bioequivalence determination. Drs. O'Shaughnessy and Subramaniam recommended that the biopharmaceutics reviewer evaluate the impact of using the original concentration results for these subjects on the study outcome.
- The clinical portions of Studies AA24171 (fasting) and AA28531 (fed) can be considered for review.

b(4)

Ask a doctor or pharmacist before use if you are taking:

- *warfarin (blood-thinning medicine)*
- *prescription antifungal or anti-yeast medicines*
- *diazepam (anxiety medicine)*
- *digoxin (heart medicine)*

Since Prilosec OTC™ was approved, there have been two additional drugs added to the drug interaction section of prescription omeprazole labels. These are tacrolimus, the level of which is raised by concurrent administration of omeprazole and atazanavir, the plasma levels of which are lowered. It makes sense to consider adding these drugs to the warning section of OTC products containing omeprazole.

CYP2C19 is the major enzyme that metabolizes omeprazole and this enzyme is known to be deficient among a higher percentage of the Asian population (20%)^{1,2} relative to Caucasians (3%)³. In prior pharmacokinetic studies of omeprazole 20 mg, an increase in AUC of approximately four-fold was noted in Asian subjects when compared to Caucasians. Drs. Lopez and Rajpal both mention this in their reviews. The prescription Prilosec® label states that dose adjustment, particularly where maintenance of healing of erosive esophagitis is indicated, for the hepatically impaired and Asian subjects should be considered.” This information was known and considered in Dr. Robert Justice’s division director memorandum dated June 19, 2003 for NDA 21-229 Prilosec OTC™. He felt that the safety of a 14-day course of omeprazole 20 mg in slow metabolizers was supported by 14 years of postmarketing experience and the safety of doses of up to 120 mg t.i.d. (320 mg/day) in patients with Zollinger-Ellison syndrome who have received treatment continuously for periods of more than 5 years. He noted that overdoses with doses up to 2400 mg have been reported with only transient symptoms and no serious clinical outcomes. Prilosec OTC™ is not labeled with a warning about use in the Asian population.

The post marketing safety data for omeprazole 20 mg and for omeprazole magnesium 20 mg do not suggest that there is an increase in adverse events among the Asian population. Further, a study⁴ reviewed by Dr. Lopez which enrolled 119 Japanese patients with recurrent reflux esophagitis 103 of whom took omeprazole 20 mg/day and 18 of whom took 10 mg/day did not find a safety signal among poor metabolizers. One hundred of the patients in the study took the medication for 6 – 12 months; the incidences of adverse events, serious adverse events and adverse events leading to withdrawal did not differ among homozygous extensive metabolizers (n = 46), heterozygous extensive metabolizers (n = 53) or poor metabolizers (n = 20). The authors concluded that long-term treatment with omeprazole was well-tolerated in Japanese patients, irrespective of their cytochrome P450 2C19 metabolic genotype, indicating that dose adjustment depending on metabolic genotype is not required during treatment with omeprazole. This study provides reassurance that if poor metabolizers take 20 mg of omeprazole daily for 14 days, the recommended OTC treatment course, that they will tolerate the medication well.

Dr. Lopez wrote an addendum to her review (December 4, 2006) to further clarify her position on the poor metabolizer issue. She states that the current safety information does not warrant a change in the labeling of omeprazole OTC 20 mg for the proposed indication and duration of use (14 days of treatment) in the Asian population.

I agree with her that the Ohkusa study plus the post marketing data suggest that the OTC omeprazole label does not need to include a warning for populations more apt to be at risk for being poor metabolizers.

Pediatrics:

In 2003, the Agency determined that the nonprescription frequent heartburn indication should target a population at least 18 years old and, thus, Prilosec OTC™ is labeled for this population. The thinking has been that for patients less than age 18 years who may have frequent heartburn, it is appropriate for a physician to diagnose and treat this condition.

The sponsor requested a waiver for pediatric studies. Prilosec® Delayed Release Capsules are already labeled for use in children two years and older for prescription indications. In addition, there is already an existing alternative administration option for children who are unable to swallow the capsule (i.e. to sprinkle the capsule in applesauce). The Dexcel omeprazole will not offer meaningful therapeutic benefit over existing omeprazole formulations and therefore it makes sense that the waiver request be granted.

Pregnancy:

Omeprazole is currently listed as Pregnancy Category C because there are no adequate and well-controlled studies in pregnant women. The Prilosec OTC labeling addresses this issue by stating, *"If pregnant or breast feeding, ask a health professional before use."*

Labeling:

On November 21, 2006 the sponsor received a letter from the Agency listing deficiencies on the principle display Panel, the Drug Facts Label, and the Package Insert. Another communication was sent to the sponsor December 6, 2006 to request that they address two more labeling issues, one regarding the absence of a contact telephone number in the optional question box and the other to request that they remove the statement referring to Prilosec OTC™ on their label. These two labeling issues must be resolved before the drug can be approved on December 8, 2006.

Conclusions:

At the time of this review, two outstanding issues remain to be resolved before this NDA can be approved. The clinical pharmacologists have not completed their review of the bioequivalence studies, which are critical to the action on this NDA. At this time it appears that they are leaning toward recommending an approvable action because of a missing analysis. If the NDA is approvable, the remaining labeling issues do not need to be addressed at this time. If the clinical pharmacology group recommends that the

product be approved, the sponsor needs to accept the labeling changes that we are requesting for the NDA to be approved.

The new drug interaction warnings on prescription omeprazole products beg the need to reconsider the labeling for omeprazole-containing nonprescription products. This issue is currently being reviewed in the Division of Nonprescription Clinical Evaluation and recommendations for the need to modify OTC class labeling for omeprazole will be forthcoming. Dexcel should be informed that, post-approval, they may receive a request to modify the labeling warnings for their product.

Recommendations:

The final action hinges on the clinical pharmacology assessment of the interpretability of the data. If the clinical pharmacology reviewers recommend an "approvable action" because of insufficient data analyses, then I will accept that recommendation and if they recommend that the product can be approved, then I will accept that recommendation.

To be approved the sponsor needs to comply with the labeling recommendations that are being communicated by the agency today and any others that may arise prior to Friday, December 8, 2006 the date the action must occur.

It is important to convey to the sponsor, no matter what the action on Friday, that the agency is reconsidering the drug interaction warnings for OTC products containing omeprazole.

References:

1. Horai Y, Nakano M, Ishizak T, et al. Metoprolol and mephenytoin oxidation polymorphisms in Far Eastern Oriental subjects: Japanese versus Mainland China. *Clin Pharmacol Ther* 1989;46:198-207.
2. Kimura M, Ieiri I, Mamiya K, et al. Genetic polymorphism of cytochrome P450s, CYP2C19, and CYP2C9 in a Japanese population. *Ther Drug Monit* 1998;20:243-7.
3. Sagar M, Tybring G, Dahl M-L, et al. Effects of omeprazole on intragastric pH and plasma gastrin are dependent on the CYP2C19 polymorphism. *Gastroenterology* 2000;119:670-6.
4. Ohkusa T, Maekawa T, Arakawa T, et al. Effect of CYP2C19 polymorphism on the safety and efficacy of omeprazole in Japanese patients with recurrent reflux oesophagitis. *Aliment Pharmacol Ther* 2005;21:1331-1339.

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

/s/

Andrea Segal
12/7/2006 08:17:46 AM
MEDICAL OFFICER



**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research**

MEMORANDUM

DATE: 12/6/06

FROM: Joyce A Korvick, MD, MPH
DGP/ODE III

SUBJECT: Deputy Division Director Action Recommendations

APPLICANT: Dexcel Pharma Technologies Ltd.

DRUG: NDA 22-032,
Omeprazole Delayed-Release Tablet 20 mg OTC®

DIVISION RECOMMENDATION:

I concur with the medical review team regarding the efficacy evaluation for this product. We recommend the approval of Omeprazole Delayed-Release Tablet 20 mg OTC® for the indication of treatment of frequent heartburn (occurs 2 or more days a week) providing review of the final inspection report for the pharmacokinetics clinical site is found to be satisfactory. The OTC medical reviewer has recommended approval of this product after review of the safety data. Finalized labeling should resemble the innovator product, Prilosec OTC. Division of Non-Prescription Clinical Evaluation will take the lead on this.

The sponsor is requesting a waiver for pediatric studies; I concur with the review team and recommend that this request be granted. As stated by Dr. He in his review, "Prilosec Delayed Release Capsules are already labeled for use in children two years and older. Additional studies using the proposed Omeprazole Delayed-Release tablets will not offer meaningful therapeutic benefit over existing Omeprazole formulations. In addition, there is already an existing alternative administration option for children who are unable to swallow the capsule (i.e. to sprinkle the capsule in applesauce)." Finally, it has been our approach that OTC omeprazole should not be used in pediatric patients with undiagnosed "heartburn" for the following reason. A physician should be involved in the decision to place a pediatric patient on prescription omeprazole, based upon a diagnostic evaluation regarding the underlying cause of frequent heartburn (Gastro-Esophageal Reflux Disease). This requires a learned intermediary.

I. Regulatory History:

The sponsor submitted the NDA 22-032 under a 505(b)(2) application using Prilosec® OTC (Omeprazole Magnesium Delayed-Release Tablets) as the RLD and relies on the Agency's previous finding of safety and effectiveness for omeprazole. The sponsor conducted two bioequivalent studies comparing the PK of Dexcel Ltd. Omeprazole Delayed-Release 20 mg Tablets and Prilosec® OTC (Omeprazole Magnesium Delayed-Release 20 mg Tablets) in healthy adult subjects. Omeprazole is currently available over-the-counter (OTC) as omeprazole magnesium delayed release tablets indicated for the treatment of frequent heartburn at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg).

Omeprazole is also currently available by prescription in dosage strengths of 10 mg, 20 mg, and 40 mg for the following indications: treatment of active duodenal ulcer, *Helicobacter pylori* eradication (when used with clarithromycin and/or amoxicillin), treatment of gastric ulcer, treatment of gastroesophageal disorder (GERD), maintenance of healing of erosive esophagitis, and treatment for pathological hypersecretory conditions. Prescription Omeprazole is also currently indicated for treatment of GERD in pediatric patients 2 years of age and older.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

No new safety issues were raised in this review. Labeling will be similar to that of the already marketed OTC omeprazole products.

B. Chemistry and Manufacturing:

There is a site inspection report pending from the manufacture in Isreal. This will have to be sorted out by the Chemistry team to determine if this product can be approved. On 12/05/06 the Chemistry team communicated their recommendation, based upon the DSI inspection, finding the CMC site satisfactory.

C. Pre-Clinical Phamacology/Toxicology:

The pre-clinical review recommended approval, and has no outstanding toxicology issues.

D. Biopharmaceutics:

The sponsor submitted 2 clinical pharmacokinetics studies. The first was a relative bioavailability study (AA24171) comparing the maximum concentration (C_{max}) and area under the curve (AUC) of the Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg and the Prilosec OTC at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg). The second study was a food effect study.

Study AA24171 was an open-label, randomized, single-dose, 2-way crossover study. A total of 76 healthy adult subjects were enrolled with a 7 day or more washout period between treatment periods. The medication was administered with 240 mL of water in the fasting state. Blood samples

were collected at timed intervals through 12 hours post-dose. The results of Study AA24171 showed that Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg and Prilosec OTC at a dose of 20.6 mg equivalent to omeprazole dose of 20 mg) exhibited similar AUC_{∞} and C_{max} values. The 90% confidence intervals for the geometric mean ratios for AUC_{∞} and C_{max} , Dexcel Ltd. Omeprazole Delayed-Release Tablets versus Prilosec OTC, fell within the 80% to 125% equivalence window. The point estimate and 90% confidence interval for the geometric mean ratio, Dexcel Ltd. Omeprazole Delayed-Release Tablets versus Prilosec OTC, for AUC_{∞} was 104.2% (100.3% - 108.3%), and for C_{max} was 99.8% (93.0% - 107.1%). Thus, bioequivalence was demonstrated for this product.

It should be noted that since this was a pivotal study, a site inspection was performed, the report listed several deficiencies. Currently the Clinical Pharmacology team is reviewing these deficiencies. If they conclude the study is acceptable then the NDA may be approved.

The food effect study demonstrated that Dexcel Ltd. Omeprazole Delayed-Release Tablets exhibited a lower AUC_{∞} and lower C_{max} for fed subjects compared to fasting subjects. The point estimate and 90% confidence interval for the geometric mean ratio, fed versus fasting, for AUC_{∞} was 76.2% (60.8% - 95.9%), and for C_{max} was 98.5% (74.5.0% - 130.4%). The results indicated that administration of Dexcel Ltd. Omeprazole Delayed-Release Tablets with a high-fat meal resulted in a decrease in the rate and extent of absorption. In addition, T_{max} was found to be delayed by approximately 4 hours in fed subjects compared to fasting subjects. The median (range) T_{max} for the fed group and fasting group was 5.5 (2.0 - 23.5) hours and 1.5 (0.75 - 4.5) hours, respectively. This data supports the previous findings and the recommendation that this drug be taken on an empty stomach.

E. Clinical/Statistical:

Efficacy:

There were no clinical studies required for this submission besides the demonstration of bioequivalence (see above).

Safety:

The safety evaluation for this NDA is conducted by Dr. Lolita Lopez, Medical Officer, in the Office of Non-Prescription Products (ONP). Please see her review for details.

As noted in Dr. Lopez's review, the current prescription drug label states "that in pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians. Dose adjustment, particularly for the maintenance of healing esophagitis should be considered." Dr. Lopez states in her safety review, that given the broad usage that omeprazole has

had in the population at large for the prescription drug, there are no safety signals among the Asian population. Further, she states that the limited time of exposure would lessen her concern regarding a safety issue. I agree with her review and position. No new recommendations regarding this issue were made regarding the OTC label.

F. Pediatric Use:

Waiver granted, see recommendation above.

G. Labeling Recommendations:

The Division of Non-Prescription Clinical Evaluation is taking the lead. The label will be similar to the currently marketed omeprazole OTC product.

III. Phase IV Commitments:

None recommended.

APPEARS THIS WAY ON ORIGINAL

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

/s/

Joyce Korvick
12/6/2006 04:06:37 PM
MEDICAL OFFICER



ADDENDUM TO OTC MEDICAL OFFICER'S REVIEW

Department of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation

NDA:	22-032
Drug name:	Omeprazole OTC Delayed Release Tablet 20 mg
Sponsor:	Dexcel Pharma Technologies, Ltd.
Pharmacologic Category:	Proton-Pump Inhibitor
Proposed Indication:	Prevention of frequent Heartburn
Submission Date:	February 10, 2006
PDUFA Goal Date:	December 10, 2006
Reviewer:	Lolita A. Lopez, M.D.
Team Leader:	Daiva Shetty, M.D.

This is an addendum to the Medical Officer's Review dated November 1, 2006. This addendum addresses the issue of omeprazole OTC use in Asian population. This can be found on page 33 of my Medical Officer's NDA review under section 8.3, Special Populations.

8.3 Special Populations

Race

In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians. Dose adjustment, particularly for the maintenance of healing esophagitis should be considered.

Medical Officer Comments: The above information is stated in the current prescribing information for omeprazole under the Clinical Pharmacology section, Pharmacokinetics and Metabolism subsection. The Division Director's Summary Review of Prilosec OTC¹ addressed this issue and recommended the approval of omeprazole 20 mg for OTC use. Consistent with Dr. Justice's review, it is the opinion of this Medical Officer that the safety of a 14-day course of omeprazole in Asian subjects is supported by more than 16 years of prescription postmarketing experience even at high doses up to 120 mg three times a day (360 mg/day) in patients with Zollinger-Ellison syndrome who have received treatment continuously for periods of more than

¹ See Division Director's Summary Review for NDA 21-229, Prilosec OTC 20 mg by Dr. Robert Justice (Division of Gastrointestinal and Coagulation Drug Products, now Division of Gastroenterology Products) entered in DFS on June 19, 2003.

5 years. Overdosages with doses up to 2400 mg have been transient and no serious clinical outcome has been reported². In addition, the safety of nonprescription use of omeprazole is supported by more than three years of postmarketing experience.

As part of the safety evaluation of this current submission, this Medical Officer searched the literature on the use of omeprazole, including its use in the Asian population³, and found no safety concerns regarding its use in this population. Therefore, this Medical Officer concludes that the current postmarketing and literature safety information available continue to support the 14-days use of omeprazole OTC 20 mg in the Asian population.

Recommendation:

The current safety information does not warrant a change in the labeling of omeprazole OTC 20 mg for the proposed indication and duration of use (14 days treatment) in the Asian population.

APPEARS THIS WAY ON ORIGINAL

² Prilosec Prescribing Information entered in DFS on 9-26-06.

³ Ohkusa T, Maekawa T, Arakawa T, et.al. Effect of CYP2C19 polymorphism on the safety and efficacy of omeprazole in Japanese patients with recurrent reflux oesophagitis. Aliment Pharmacol Ther 2005; 21: 1331-1339.

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

/s/

Lolita Lopez
12/4/2006 12:34:46 PM
MEDICAL OFFICER

Daiva Shetty
12/4/2006 12:54:23 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 12/22/2006

FROM: Ruyi He, MD
Medical Team Leader
Division of Gastroenterology Products/ODE III

TO: Brian Harvey, MD, Ph.D.
Director
Division of Gastroenterology Products/ODE III

SUBJECT: GI Team Leader AP Comments
NDA 22-032, Omeprazole Delayed-Release Tablet 20 mg OTC

APPLICANT: Dexcel Pharma Technologies Ltd.

DRUG: Omeprazole Delayed-Release Tablet 20 mg OTC

RECOMMENDATION

I concur with Dr. Anil Rajpal's recommendations that NDA 22-032 (Omeprazole Delayed Release Tablet, 20 Mg OTC) be approved for the indication of treatment of frequent heartburn (occurs 2 or more days a week).

However, on November 1, 2006, OND-IO informed the Division that the Office of Compliance has determined that BA/BE studies conducted by _____ may not be reliable. BA/BE studies in this NDA were conducted by _____. Results of the DSI inspection of _____ are pending. To get approval, the sponsor should obtain satisfactory DSI inspection.

b(4)

The sponsor is requesting a waiver for pediatric studies; I recommend that this request be granted. Prilosec Delayed Release Capsules is already labeled for use in children two years and older. Additional studies using the proposed Omeprazole Delayed-Release tablets will not offer meaningful therapeutic benefit over existing Omeprazole formulations. In addition, there is already an existing alternative administration option for children who are unable to swallow the capsule (i.e. to sprinkle the capsule in applesauce).

There is no recommendation on post-marketing actions.

Omeprazole is not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect. Omeprazole Delayed Release Tablet, 20 Mg OTC should be swallowed with a glass of water before eating in the morning, and taken once daily for 14 days. It is for adult OTC use only.

I. BACKGROUND

Omeprazole is a proton-pump inhibitor (PPI) approved for use in the United States since 1989. It suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺ adenosine triphosphatase (ATPase) enzyme system at the secretory surface of the gastric parietal cell therefore blocking the final step of acid production.

Omeprazole is currently available over-the-counter (OTC) as omeprazole magnesium delayed release tablets indicated for the treatment of frequent heartburn at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg). Omeprazole is also currently available by prescription in dosage strengths of 10 mg, 20 mg, and 40 mg. Omeprazole available by prescription currently has the following indications: treatment of active duodenal ulcer, *Helicobacter pylori* eradication (when used with clarithromycin and/or amoxicillin), treatment of gastric ulcer, treatment of gastroesophageal disorder (GERD), maintenance of healing of erosive esophagitis, and treatment for pathological hypersecretory conditions. Omeprazole available by prescription is also currently indicated for treatment of GERD in pediatric patients 2 years of age and older.

The sponsor submitted the NDA 22-032 under a 505(b)(2) application using Prilosec® OTC (Omeprazole Magnesium Delayed-Release Tablets) as the RLD and relies on the Agency's previous finding of safety and effectiveness for omeprazole. The sponsor conducted two bioequivalent studies comparing the PK of Dexcel Ltd. Omeprazole Delayed-Release 20 mg Tablets and Prilosec® OTC (Omeprazole Magnesium Delayed-Release 20 mg Tablets) in healthy adult subjects.

II. CLINICAL EVALUATION

Efficacy

There were no efficacy trials conducted for this NDA except for evaluation of pharmacokinetics (PK). The sponsor conducted a relative bioavailability study (AA24171) to compare maximum concentration (C_{max}) and area under the curve (AUC) of the Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg and the Prilosec OTC at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg).

Study AA24171 was an open-label, randomized, single-dose, 2-way crossover study. A total of 76 healthy adult subjects were enrolled with a 7 day or more washout period between treatment periods. The medication was administered with 240 mL of water in the fasting state. Blood samples were collected at timed intervals through 12 hours post-dose. The results of Study AA24171 showed that Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg and Prilosec OTC at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg) exhibited similar AUC_{∞} and C_{max} values. The 90% confidence intervals for the geometric mean ratios for AUC_{∞} and C_{max} , Dexcel Ltd. Omeprazole Delayed-Release Tablets versus Prilosec OTC, fell within the 80% to 125% equivalence window. The point estimate and 90% confidence interval for the geometric mean ratio, Dexcel Ltd. Omeprazole Delayed-Release Tablets versus Prilosec OTC, for AUC_{∞} was 104.2% (100.3% - 108.3%), and for C_{max} was 99.8% (93.0% - 107.1%).

Food effect was determined in study AA28531. Study AA28531 was an open-label, randomized, single-dose, 2-way crossover, 2-sequence study. A total of 18 healthy adult male subjects were enrolled. Subjects randomized to Treatment A received omeprazole 20 mg under fed conditions (standard high-fat breakfast). Subjects randomized to Treatment B received omeprazole 20 mg under fasting conditions. There was a 7 day washout interval between treatment periods. Blood samples were collected at timed intervals through 24 hours post-dose.

The results of Study AA28531 showed that Dexcel Ltd. Omeprazole Delayed-Release Tablets exhibited a lower AUC_{∞} and lower C_{max} for fed subjects compared to fasting subjects. The point estimate and 90% confidence interval for the geometric mean ratio, fed versus fasting, for AUC_{∞} was 76.2% (60.8% - 95.9%), and for C_{max} was 98.5% (74.5.0% - 130.4%). The results indicated that administration of Dexcel Ltd. Omeprazole Delayed-Release Tablets with a high-fat meal resulted in a decrease in the rate and extent of absorption. In addition, T_{max} was found to be delayed by approximately 4 hours in fed subjects compared to fasting subjects. The median (range) T_{max} for the fed group and fasting group was 5.5 (2.0 - 23.5) hours and 1.5 (0.75 - 4.5) hours, respectively.

By demonstrating that the two products have similar AUC and C_{max} , the trial provides a bridge from Dexcel Ltd. Omeprazole Delayed-Release Tablets to Prilosec OTC, and to FDA's previous finding of safety and efficacy for omeprazole.

Safety

The safety evaluation for this NDA is conducted by Dr. Lolita Lopez, Medical Officer, in the Office of Non-Prescription Products (ONP). Please see her review for details.

III. PEDIATRIC USE

Pediatric patients were not evaluated in this NDA. No data were submitted by the sponsor regarding this population.

The sponsor is requesting a waiver for pediatric studies; I recommend that the request be granted. Prilosec Delayed Release Capsules is already labeled for use in children two years and older. Additional studies using the proposed omeprazole tablets will not offer meaningful therapeutic benefit over the existing omeprazole formulations. In addition, there is already an existing alternative administration options for children who are unable to swallow the capsule (i.e. to sprinkle the capsule in applesauce) using the omeprazole delayed capsule formulation.

IV. LABELING RECOMMENDATIONS

I concur with Dr. Anil Rajpal's labeling recommendations listed in his review. Labeling for Dexcel Ltd. Omeprazole Delayed-Release Tablets should be same as the labeling of Prilosec OTC.

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

/s/

Ruyi He
11/22/2006 03:09:23 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA
Submission Number 22-032
Submission Code 000

Letter Date February 8, 2006
Stamp Date February 10, 2006
PDUFA Goal Date December 10, 2006

Reviewer Name Anil Rajpal, M.D.
Through Ruyi He, M.D.
Clinical Team Leader
Review Completion Date November 17, 2006

Established Name Omeprazole Delayed-Release Tablet
(Proposed) Trade Name Omeprazole Delayed-Release Tablet
Therapeutic Class Proton Pump Inhibitors (PPIs)
Applicant Dexcel Pharma Technologies Ltd.

Priority Designation S

Formulation Delayed-Release Tablet
Dosing Regimen 20 mg PO QD X 14 days
(14-day course may be repeated
every 4 months)
Indication Treatment of frequent heartburn
(occurs 2 or more days per week)
Intended Population Adults ($\geq$ 18 years old)

TABLE OF CONTENTS

TABLE OF CONTENTS	2
1 EXECUTIVE SUMMARY	4
1.1 RECOMMENDATION ON REGULATORY ACTION	4
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS	4
1.2.1 Risk Management Activity	4
1.2.2 Required Phase 4 Commitments	4
1.2.3 Other Phase 4 Requests	4
1.3 SUMMARY OF CLINICAL FINDINGS	4
1.3.1 Brief Overview of Clinical Program	4
1.3.2 Efficacy	5
1.3.3 Safety	6
1.3.4 Dosing Regimen and Administration	7
1.3.5 Drug-Drug Interactions	7
1.3.6 Special Populations	8
2 INTRODUCTION AND BACKGROUND	9
2.1 PRODUCT INFORMATION	9
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS	9
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES	9
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS	10
2.5 PRESUBMISSION REGULATORY ACTIVITY	10
2.6 OTHER RELEVANT BACKGROUND INFORMATION	11
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES	11
3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)	11
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY	11
4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY	12
4.1 SOURCES OF CLINICAL DATA	12
4.2 TABLES OF CLINICAL STUDIES	12
4.3 REVIEW STRATEGY	12
4.4 DATA QUALITY AND INTEGRITY	12
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES	13
4.6 FINANCIAL DISCLOSURES	13
5 CLINICAL PHARMACOLOGY	13
5.1 PHARMACOKINETICS	13
5.2 PHARMACODYNAMICS	14
5.3 EXPOSURE-RESPONSE RELATIONSHIPS	14
6 INTEGRATED REVIEW OF EFFICACY	14
6.1 INDICATION	14
6.2 METHODS	14
6.3 GENERAL DISCUSSION OF ENDPOINTS	14
6.4 STUDY DESIGN	15
6.5 EFFICACY FINDINGS	16
6.6 CLINICAL MICROBIOLOGY	16
6.7 EFFICACY CONCLUSIONS	17

7 INTEGRATED REVIEW OF SAFETY	17
8 ADDITIONAL CLINICAL ISSUES	17
8.1 DOSING REGIMEN AND ADMINISTRATION	17
8.2 DRUG-DRUG INTERACTIONS	18
8.3 SPECIAL POPULATIONS	18
8.4 PEDIATRICS	19
8.5 ADVISORY COMMITTEE MEETING	19
8.6 LITERATURE REVIEW	19
8.7 POSTMARKETING RISK MANAGEMENT PLAN	20
8.8 OTHER RELEVANT MATERIALS	20
9 OVERALL ASSESSMENT	21
9.1 CONCLUSIONS	21
9.2 RECOMMENDATION ON REGULATORY ACTION	21
9.3 RECOMMENDATION ON POSTMARKETING ACTIONS	22
9.3.1 Risk Management Activity	22
9.3.2 Required Phase 4 Commitments	22
9.3.3 Other Phase 4 Requests	22
9.4 LABELING REVIEW	22
9.5 COMMENTS TO APPLICANT	25
10 APPENDICES	26
10.1 LINE-BY-LINE LABELING REVIEW	26
REFERENCES	27

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer, based on the review of efficacy, recommends the approval of Omeprazole Delayed Release Tablet, 20 Mg OTC, for the indication of treatment of frequent heartburn (occurs 2 or more days a week). Omeprazole is not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect.

Omeprazole Delayed Release Tablet, 20 Mg OTC (1 tablet) should be swallowed with a glass of water before eating in the morning, and taken once daily for 14 days. A 14-day course may be repeated (if needed) every 4 months.

This reviewer's recommendation is contingent upon the pending Division of Scientific Investigations (DSI) inspection of ———. This reviewer's recommendation is also contingent upon the findings of other reviewers that include the clinical reviewer from the Office of Non-Prescription Products (ONP), the clinical pharmacology reviewer from the Office of Clinical Pharmacology (OCP), and the chemistry reviewer from the Office of New Drug Quality Assessment (ONDQA).

b(4)

To obtain approval, the sponsor must incorporate the labeling recommendations listed in this reviewer's Labeling Review and the team's labeling recommendations, and must obtain satisfactory DSI inspection.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None warranted at the present time.

1.2.2 Required Phase 4 Commitments

None warranted at the present time.

1.2.3 Other Phase 4 Requests

None warranted at the present time.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

On February 10, 2006, the sponsor submitted NDA 22-032 under a 505 (b) (2) application using

Omeprazole Delayed-Release Tablets

Prilosec OTC™ (Omeprazole Magnesium Delayed-Release Tablets, AstraZeneca LP, NDA 21-229) as the reference listed drug (RLD), and relies on the Agency's previous finding of safety and efficacy for omeprazole. The regulatory strategy of the sponsor is to demonstrate that the product is pharmaceutically similar to the RLD by a bioavailability/bioequivalence (BA/BE) study.

The Sponsor submitted results from two *in vivo* BA studies in healthy adult volunteers as described below. The first was a bioavailability/bioequivalence (BA/BE) study; the second was a food effect BA study.

1. AA24171: compared the pharmacokinetics (PK) of single-dose Dexcel Ltd. Omeprazole Delayed-Release Tablets, 20 mg, and Prilosec OTC™ (Omeprazole Magnesium Delayed-Release Tablets), 20.6 mg, in healthy adult volunteers under fasting conditions. (Omeprazole magnesium delayed-release tablet 20.6 mg is equivalent to 20 mg omeprazole.)
2. AA28531: compared the PK of fed and fasting regimens of single-dose Dexcel Ltd. Omeprazole Delayed-Release Tablets, 20 mg, in healthy adult male volunteers.

Omeprazole is currently available over-the-counter (OTC) as omeprazole magnesium delayed release tablets indicated for the treatment of frequent heartburn at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg). Omeprazole is also currently available by prescription in dosage strengths of 10 mg, 20 mg, and 40 mg. Omeprazole available by prescription currently has the following indications: treatment of active duodenal ulcer, *Helicobacter pylori* eradication (when used with clarithromycin and/or amoxicillin), treatment of gastric ulcer, treatment of gastroesophageal disorder (GERD), maintenance of healing of erosive esophagitis, and treatment for pathological hypersecretory conditions. Omeprazole available by prescription is also currently indicated for treatment of GERD in pediatric patients 2 years of age and older.

Omeprazole, like other proton-pump inhibitors (PPIs), is acid-labile and is rapidly degraded by gastric acid. The RLD, like many available oral omeprazole formulations, is delivered with an enteric coating as a protection from rapid degradation upon exposure to acid. This enteric coating gives the RLD its delayed-release characteristic.

1.3.2 Efficacy

There were no efficacy trials conducted for this NDA except for evaluation of pharmacokinetics (PK). The sponsor conducted a relative bioavailability study (AA24171) to demonstrate similar maximum concentration (C_{max}) and area under the curve (AUC) of the Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg and the Prilosec OTC™ at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg). By demonstrating that the two products have similar AUC and C_{max}, the trial provides a bridge from Dexcel Ltd. Omeprazole Delayed-Release Tablets to Prilosec OTC™, and to FDA's previous finding of safety and efficacy for omeprazole. Food effect was also determined in a separate study (AA28531).

Study AA24171 was an open-label, randomized, single-dose, 2-way crossover study comparing Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg with Prilosec OTC™ at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg). A total of 76 healthy adult subjects were enrolled with a 7 day or more washout period between treatment periods. The medication

was administered with 240 mL of water in the fasting state. Blood samples were collected at timed intervals through 12 hours post-dose.

The results of Study AA24171 showed that Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg and Prilosec OTC™ at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg) exhibited similar AUC_{∞} and C_{max} values. The 90% confidence intervals for the geometric mean ratios for AUC_{∞} and C_{max} , Dexcel Ltd. Omeprazole Delayed-Release Tablets versus Prilosec OTC™, fell within the 80% to 125% equivalence window. The point estimate and 90% confidence interval for the geometric mean ratio, Dexcel Ltd. Omeprazole Delayed-Release Tablets versus Prilosec OTC™, for AUC_{∞} was 104.2% (100.3% - 108.3%), and for C_{max} was 99.8% (93.0% - 107.1%).

Study AA28531 was an open-label, randomized, single-dose, 2-way crossover, 2-sequence, food effect study. A total of 18 healthy adult male subjects were enrolled. Subjects randomized to Treatment A received a single oral dose of one omeprazole 20 mg delayed-release tablet taken with 240 mL of water under fed conditions (standard FDA high-fat breakfast) 30 minutes prior to dosing. Subjects randomized to Treatment B received a single oral dose of omeprazole 20 mg delayed-release tablet taken with 240 mL of water under fasting conditions. There was a 7 day washout interval between treatment periods. Blood samples were collected at timed intervals through 24 hours post-dose.

The results of Study AA28531 showed that Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg exhibited a lower AUC_{∞} and lower C_{max} for fed subjects compared to fasting subjects. The point estimate and 90% confidence interval for the geometric mean ratio, fed versus fasting, for AUC_{∞} was 76.2% (60.8% - 95.9%), and for C_{max} was 98.5% (74.5.0% - 130.4%). The results indicated that administration of Dexcel Ltd. Omeprazole Delayed-Release Tablets with a high-fat meal resulted in a decrease in the rate and extent of absorption. In addition, T_{max} was found to be delayed by approximately 4 hours in fed subjects compared to fasting subjects. The median (range) T_{max} for the fed group and fasting group was 5.5 (2.0 - 23.5) hours and 1.5 (0.75 - 4.5) hours, respectively. Further discussion of the results of the food effect study may be found in the Clinical Pharmacology Review of Dr. Abimbola Adebawale, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP).

Overall, the results of the relative bioavailability study (Study AA24171) showed that Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg and Prilosec OTC™ at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg) had similar levels of exposure as determined by AUC_{∞} and C_{max} , and provide support of therapeutic equivalence for Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg and Prilosec OTC™ at a dose of 20.6 mg. Overall, the results of the food effect study (Study AA28531) indicated that administration of Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg with a high-fat meal resulted in a decrease in the rate and extent of absorption; thus, a food effect was observed.

1.3.3 Safety

The review of safety information in this NDA is in the Clinical Review of Dr. Lolita Lopez, Medical Officer, Office of Non-Prescription Products (ONP).

1.3.4 Dosing Regimen and Administration

The sponsor is seeking the indication and dose for Omeprazole Delayed-Release Tablet 20 mg that is already approved for Prilosec OTCTM.

Indication:

- Treatment of frequent heartburn (occurs 2 or more days a week)
- Not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect

Dose:

- Omeprazole Delayed Release Tablet, 20 mg (1 tablet) once a day
- Should be taken every day for 14 days (may be taken for more than 14 days if directed by a doctor)
- 14-day course may be repeated (if needed) every 4 months

Directions for use:

- Should be swallowed with a glass of water before eating in the morning
- Tablet should not be chewed or crushed

Dosage Adjustment: No dosage adjustment is needed in the elderly. Dose adjustment in Asian subjects should be considered. In PK studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects when compared to Caucasians. Further discussion of dosage adjustment may be found in the Clinical Review of Dr. Lolita Lopez, Medical Officer, Office of Non-Prescription Products (ONP).

1.3.5 Drug-Drug Interactions

Proton pump inhibitors (PPIs) inhibit the activity of some hepatic cytochrome P450 enzymes and may therefore decrease the clearance of benzodiazepines, phenytoin, warfarin, and many other drugs. There have been reports of increased prothrombin time and INR in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in prothrombin time and INR.

Although no interaction with propranolol or theophylline was found in normal subjects, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P450 system (e.g., benzodiazepines, cyclosporine, and disulfiram). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole.

Because of omeprazole's profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ampicillin esters, iron salts, and ketoconazole). Co-administration of clarithromycin and omeprazole has resulted in increases of plasma levels of clarithromycin, 14-hydroxy-clarithromycin, and omeprazole.

Omeprazole Delayed-Release Tablets

Further discussion of drug-drug interactions with regard to safety may be found in the Clinical Review of Dr. Lolita Lopez, Medical Officer, Office of Non-Prescription Products (ONP). Further discussion of drug-drug interactions with regard to pharmacokinetics and pharmacodynamics may be found in the Clinical Pharmacology Review of Dr. Abimbola Adebawale, Office of Clinical Pharmacology (OCP).

1.3.6 Special Populations

Since this NDA contains only PK studies conducted in healthy subjects, there are no new data regarding other patient populations (such as hepatic and renal failure patients), and the effects of gender, race or age on safety or efficacy. The studies submitted did not include individuals of Asian origin for safety reasons. CYP2C19 is the major enzyme that metabolizes omeprazole. It was found to be deficient in many subjects of the Asian population. In prior PK studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects when compared to Caucasians.

Pediatric

Pediatric patients were not evaluated in this NDA. No data were submitted by the sponsor regarding this population. Currently, omeprazole is not approved for over-the-counter (OTC) use in adolescents. It is approved for OTC use in adults 18 years of age and older.

The sponsor is requesting a waiver for pediatric studies for the Dexcel Ltd. Omeprazole Delayed-Release Tablets. The sponsor's rationale for the waiver is that the sponsor of the RLD product has previously addressed pediatric requirements for the drug product in AstraZeneca's PrilosecTM NDA as noted in the publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"). This reviewer recommends that this request should be granted.

The RLD product is currently available in a delayed-release tablet for OTC use and is not, according to the approved labeling, recommended for use in pediatric patients below 18 years of age. For patients less than 18 years of age it would be more appropriate to use the prescription product omeprazole delayed-release capsules which is labeled for use in children two years and older because it would require a physician's intervention for proper diagnosis and treatment for the accurate dosing based upon the child's weight. There is already an existing alternative administration option for children who are unable to swallow the capsule, i.e. to sprinkle the capsule in applesauce, using the omeprazole delayed-release capsule formulation.

Pregnancy Use

This application has no new information regarding pregnant women. Omeprazole is currently listed as Pregnancy Category C. There are no adequate or well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Omeprazole is a proton-pump inhibitor (PPI) approved for use in the United States since 1989. It suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺ adenosine triphosphatase (ATPase) enzyme system at the secretory surface of the gastric parietal cell therefore blocking the final step of acid production.

Omeprazole is currently available over-the-counter (OTC) as omeprazole magnesium delayed release tablets indicated for the treatment of frequent heartburn at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg). Omeprazole is also currently available by prescription in dosage strengths of 10 mg, 20 mg, and 40 mg. Omeprazole available by prescription currently has the following indications: treatment of active duodenal ulcer, *Helicobacter pylori* eradication (when used with clarithromycin and/or amoxicillin), treatment of gastric ulcer, treatment of gastroesophageal disorder (GERD), maintenance of healing of erosive esophagitis, and treatment for pathological hypersecretory conditions. Omeprazole available by prescription is also currently indicated for treatment of GERD in pediatric patients 2 years of age and older.

Omeprazole, like other proton-pump inhibitors (PPIs), is acid-labile and is rapidly degraded by gastric acid. The RLD, Prilosec OTCTM (Omeprazole Magnesium Delayed-Release Tablets, AstraZeneca LP), like many available oral omeprazole formulations, is delivered with an enteric coating as a protection from rapid degradation upon exposure to acid. This enteric coating gives the RLD its delayed-release characteristic.

2.2 Currently Available Treatment for Indications

The RLD, Prilosec OTCTM (Omeprazole Magnesium Delayed-Release Tablets, AstraZeneca LP), is currently available over the counter to treat frequent heartburn (more than two episodes per week) for 14 days. Other than omeprazole, the currently available medications available over the counter to relieve heartburn symptoms include the following: antacids (liquid and tablet), H₂-receptor antagonists (cimetidine, famotidine, nizatidine, and ranitidine), and a combination antacid/H₂-receptor antagonist (famotidine combined with calcium carbonate and magnesium hydroxide).

2.3 Availability of Proposed Active Ingredient in the United States

The RLD, Prilosec OTCTM (Omeprazole Magnesium Delayed-Release Tablets, AstraZeneca LP), was approved on June 20, 2003. Prilosec OTCTM is indicated for the short-term treatment of frequent heartburn (2 or more episodes per week).

Omeprazole was originally approved by the FDA in September 1989 for acute treatment only due to concern regarding long-term use. In December 1994, FDA approved the use of omeprazole for maintenance therapy of healing erosive esophagitis. In April 1996, a 14-day

regimen consisting of omeprazole and clarithromycin was approved for the treatment of *H. pylori*-associated duodenal ulcer; a 10-day regimen of omeprazole, amoxicillin, and clarithromycin was approved in June 1998. Generic omeprazole capsules were approved in November 2001. In July 2002, the FDA approved omeprazole use for children 2 years and older for the treatment of acid-related gastrointestinal diseases, including the treatment of symptomatic GERD, treatment of erosive esophagitis, and maintenance of healing of erosive esophagitis.

2.4 Important Issues With Pharmacologically Related Products

Proton pump inhibitors (PPIs) inhibit the activity of some hepatic cytochrome P450 enzymes and may therefore decrease the clearance of benzodiazepines, phenytoin, warfarin, and many other drugs. There have been reports of increased prothrombin time and INR in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in prothrombin time and INR.

Although no interaction with propranolol or theophylline was found in normal subjects, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P450 system (e.g., benzodiazepines, cyclosporine, and disulfiram). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole.

Because of PPI's profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ampicillin esters, iron salts, and ketoconazole). Co-administration of clarithromycin and omeprazole has resulted in increases of plasma levels of clarithromycin, 14-hydroxy-clarithromycin, and omeprazole. Concomitant administration of atazanavir and omeprazole (and most likely other PPIs) has been reported to reduce the plasma levels of atazanavir. Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Further discussion of issues with pharmacologically-related products with regard to safety may be found in the Clinical Review of Dr. Lolita Lopez, Medical Officer, Office of Non-Prescription Products (ONP). Further discussion of pharmacologically-related products with regard to pharmacokinetics and pharmacodynamics may be found in the Clinical Pharmacology Review of Dr. Abimbola Adebawale, Office of Clinical Pharmacology (OCP).

2.5 Presubmission Regulatory Activity

In a meeting on May 20, 2005, the Agency advised the sponsor on a number of issues regarding the planned 505 (b) (2) NDA using Prilosec OTC™ (Omeprazole Magnesium Delayed-Release Tablets, AstraZeneca, NDA 21-229) as the RLD. Key clinical responses to the sponsor's questions were as follows: (1) clinical safety and efficacy trials would not be required if the proposed product is found to be bioequivalent to the RLD; (2) if bioequivalence is shown to the RLD, the labeling for the proposed product may be the same as that of the RLD with the exception of the active and inactive ingredients; (3) if the labeling is identical to that of the RLD, then the sponsor

will not be required to conduct label comprehension studies; (4) a food effect BA study would be required; and (5) a safety update would be required.

On February 10, 2006, the sponsor submitted NDA 22-032 under a 505 (b) (2) application using Prilosec OTCTM as the RLD, and relies on the Agency's previous finding of safety and efficacy for omeprazole. The regulatory strategy of the sponsor is to demonstrate that the product is pharmaceutically similar to the RLD by a bioavailability/bioequivalence (BA/BE) study. The sponsor also submitted the results of a food effect bioavailability study. The sponsor submitted a safety update, a search of the FDA's Adverse Event Reporting System (AERS) database for the period April 1, 2003 to November 30, 2005. Review of safety information submitted by the sponsor for this NDA may be found in the Clinical Review of Dr. Lolita Lopez, Medical Officer, Office of Non-Prescription Products (ONP).

The proposed drug product is an enteric coating tablet with a delayed drug release profile. The to-be-marketed formulation is the same formulation that was used in the BA/BE study and the food-effect BA study.

The proposed drug product is packaged in unit-dose, child resistant blister trays. The blister tray has seven cavities and is designed to hold one tablet in each cavity.

2.6 Other Relevant Background Information

Since 1988, omeprazole has been marketed worldwide under various trade names. In 1989, omeprazole was first approved for marketing in the United States. Omeprazole is one of the most frequently prescribed medications on a worldwide basis; in excess of 380 million prescriptions worldwide have been written worldwide for omeprazole.

The reference listed drug, Prilosec OTCTM (Omeprazole Magnesium Delayed-Release Tablets, AstraZeneca LP, NDA 21-229) 20.6 mg (equivalent to 20 mg omeprazole) was approved for OTC marketing on June 20, 2003, for the treatment of frequent heartburn.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

CMC findings are discussed in the review from the Office of New Drug Quality Assessment (ONDQA).

3.2 Animal Pharmacology/Toxicology

This submission contains no new information on animal pharmacology/toxicology.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data utilized in this review were the sponsor's two *in vivo* BA studies in healthy adult volunteers as described below. The first was a bioavailability/bioequivalence (BA/BE) study; the second was a food effect BA study.

1. AA24171: compared the pharmacokinetics (PK) of single-dose Dexcel Ltd. Omeprazole Delayed-Release Tablets, 20 mg, and Prilosec OTC™ (Omeprazole Magnesium Delayed-Release Tablets), 20.6 mg, in healthy adult volunteers under fasting conditions. (Omeprazole magnesium delayed-release tablet 20.6 mg is equivalent to 20 mg omeprazole.)
2. AA28531: compared the PK of fed and fasting regimens of single-dose Dexcel Ltd. Omeprazole Delayed-Release Tablets, 20 mg, in healthy adult male volunteers.

4.2 Tables of Clinical Studies

Type of Study	Trial Name	Objective	Trial Design	Dosage strength	N
BA/BE	AA24171	Compare PK profiles of Prilosec OTC™ with Dexcel Ltd. Omeprazole Delayed-Release Tablets	Open-label, Randomized, Single-dose, 2-way Crossover Study (≥ 7 day washout)	20 mg*	76
Food Effect	AA28531	Compare PK of fed and fasting regimens	Open-label, Randomized, Single-dose, 2-way Crossover Study, 2-Sequence Study (7-day washout)	20 mg	18

* Prilosec OTC 20.6 mg dose administered (equivalent to omeprazole dose of 20 mg); Dexcel Ltd. Omeprazole Delayed-Release Tablets 20 mg dose administered.

4.3 Review Strategy

Two bioavailability studies submitted by the sponsor were utilized in this review. The first study was a BA/BE study comparing the PK of Prilosec OTC™ with that of Dexcel Ltd. Omeprazole Delayed-Release Tablets. The second study was a food effect BA study.

Although no efficacy trials were conducted for this NDA, the BA/BE study (AA24171) serves as a "bridging" study from the Dexcel Ltd. Omeprazole Delayed-Release Tablets to Prilosec OTC™ to FDA's previous finding of safety and efficacy for omeprazole.

The review of safety information in this NDA is in the Clinical Review of Dr. Lolita Lopez, Medical Officer, Office of Non-Prescription Products (ONP).

4.4 Data Quality and Integrity

A DSI inspection was requested and the results are pending at the time this NDA Review was written.

4.5 Compliance with Good Clinical Practices

Both Study AA24171 and Study AA28531 were conducted at _____
_____ Study AA24171 was conducted from May 26, 2005 to June 6, 2005. Study AA28531 was conducted from September 25, 2005 to October 3, 2005.

b(4)

The sponsor states that each of the protocols and informed consent forms (ICFs) were reviewed and approved by the Institutional Review Board (IRB) convening at _____ prior to study initiation. The sponsor further states that the IRB is constituted and operates in accordance with the principles and requirements described in the Canadian "Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans" (August 1998) and in the U.S. Code of Federal Regulations (21 CFR Part 56). The sponsor states that this research was conducted in accordance with the clinical research guidelines established by the Medical Research Council of Canada, the Basic Principles defined in the U.S. 21 CFR Part 312.20, the principles enunciated in the latest version of The Declaration of Helsinki referenced in the Protocol (Edinburgh, Scotland, October 2000) and the ICH harmonized tripartite guideline regarding Good Clinical Practice (GCP).

b(4)

On November 1, 2006, OND-IO sent an e-mail stating that the Office of Compliance (OC) has determined that BA/BE studies conducted by _____ may not be reliable. BA/BE studies in this NDA were conducted by _____. Results of the DSI inspection of _____ are pending. The findings in this review are contingent upon the satisfactory inspection findings of the DSI reviewer.

b(4)

4.6 Financial Disclosures

Dexcel Pharma Technologies LTD submitted an FDA Form 3454 certifying that as a sponsor of the submitted studies, it has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The sponsor also certified that each listed clinical investigator did not disclose any proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) and that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

5 CLINICAL PHARMACOLOGY

The review of clinical pharmacology information in this NDA is in the Clinical Pharmacology Review of Dr. Abimbola Adebawale, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP).

5.1 Pharmacokinetics

A review of pharmacokinetics is found in the Clinical Pharmacology Review of Dr. Abimbola Adebawale, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP).

5.2 Pharmacodynamics

A review of pharmacodynamics is found in the Clinical Pharmacology Review of Dr. Abimbola Adebowale, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP).

5.3 Exposure-Response Relationships

A review of exposure-response relationships is found in the Clinical Pharmacology Review of Dr. Abimbola Adebowale, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP).

6 INTEGRATED REVIEW OF EFFICACY

No new efficacy studies were conducted with this 505 (b) (2) application. Efficacy of this product is based on the pharmacokinetics data submitted from a relative bioavailability study (Study AA24171) and a food effect study (Study AA28531).

6.1 Indication

The indication proposed in this NDA for Omeprazole Delayed Release Tablet, 20 Mg OTC is the same indication that is already listed in the package insert for the RLD, Prilosec OTC™ (Omeprazole Magnesium Delayed-Release Tablets, AstraZeneca LP) as shown below.

Omeprazole Delayed Release Tablet, 20 Mg OTC:

- treats frequent heartburn (occurs 2 or more days a week)
- not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect

6.2 Methods

To support the above indication, the sponsor conducted two *in vivo* bioavailability studies in healthy adult volunteers. The first study was a relative bioavailability study (Study AA24171) that compared the pharmacokinetics (PK) of single-dose Dexcel Ltd. Omeprazole Delayed-Release Tablets, 20 mg, and Prilosec OTC™ (Omeprazole Magnesium Delayed-Release Tablets), 20.6 mg, in healthy adult volunteers under fasting conditions. (Omeprazole magnesium delayed-release tablet 20.6 mg is equivalent to 20 mg omeprazole.) Demonstration that the two products have similar AUC and Cmax in Study AA24171 provides a bridge from Dexcel Ltd. Omeprazole Delayed-Release Tablets to Prilosec OTC™, and to FDA's previous finding of safety and efficacy for omeprazole. The second study was a food effect BA study (Study AA28531) that compared the PK of fed and fasting regimens of single-dose Dexcel Ltd. Omeprazole Delayed-Release Tablets, 20 mg, in healthy adult male volunteers.

6.3 General Discussion of Endpoints

Efficacy was assessed by utilizing the data submitted by the applicant comprising studies comparing: (1) the PK of single-dose Dexcel Ltd. Omeprazole Delayed-Release Tablets, 20 mg, with that of the RLD in healthy adult volunteers (Study AA24171); and (2) the PK of fed and

Omeprazole Delayed-Release Tablets

fasting regimens of single-dose Dexcel Ltd. Omeprazole Delayed-Release Tablets, 20 mg, in healthy adult male volunteers (Study AA28531). The endpoints below were used.

Pharmacokinetic Endpoints (Study AA24171):

- Primary: The relative bioavailability of omeprazole after a single dose of each omeprazole formulation. This was determined from ratios of geometric means from analyses of the log-transformed AUC_{∞} , AUC_{0-t} , and C_{max} .
- Secondary:
 - AUC_{∞} , AUC_{0-t} , and C_{max} after a single dose of each omeprazole formulation
 - Other PK parameters (e.g. T_{max}) after a single dose of each omeprazole formulation

Pharmacokinetic Endpoints (Study AA28531):

- Primary: The food effect bioavailability of omeprazole after a single dose. This was determined from ratios of geometric means from analyses of the log-transformed AUC_{∞} , AUC_{0-t} , and C_{max} .
- Secondary:
 - AUC_{∞} , AUC_{0-t} , and C_{max} after a single dose in the fed and fasting state.
 - Other PK parameters (e.g. T_{max}) after a single dose in the fed and fasting state.

6.4 Study Design

Study AA24171:

Study AA24171 was an open-label, randomized, single-dose, 2-way crossover study comparing Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg with Prilosec OTC™ at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg). A total of 76 healthy adult subjects were enrolled with a 7 day or more washout period between treatment periods.

The medication was administered with 240 mL of water in the fasting state. Blood samples were collected at timed intervals through 12 hours post-dose.

Study AA28531:

Study AA28531 was an open-label, randomized, single-dose, 2-way crossover, 2-sequence, food effect study. A total of 18 healthy adult male subjects were enrolled.

Subjects randomized to Treatment A received a single oral dose of one omeprazole 20 mg delayed-release tablet taken with 240 mL of water under fed conditions (standard FDA high-fat breakfast) 30 minutes prior to dosing. Subjects randomized to Treatment B received a single oral dose of omeprazole 20 mg delayed-release tablet taken with 240 mL of water under fasting conditions. There was a 7 day washout interval between treatment periods. Blood samples were collected at timed intervals through 24 hours post-dose.

6.5 Efficacy Findings

Study AA24171:

The results of Study AA24171 showed that Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg and Prilosec OTC™ at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg) exhibited similar AUC_{0-t}, AUC_∞ and Cmax values. The 90% confidence intervals for the ratios of geometric means for AUC_{0-t}, AUC_∞, and Cmax, Dexcel Ltd. Omeprazole Delayed-Release Tablets versus Prilosec OTC™, fell within the 80% to 125% equivalence window. See table below.

Ratio of Geometric Means (90% Confidence Intervals)	
Parameter	Dexcel Ltd. (A) vs. P&G/AstraZeneca (B)
AUC _{0-t}	102.9% (99.0% - 107.0%)
AUC _∞	104.2% (100.3% - 108.3%)
Cmax	99.8% (93.0% - 107.1%)

Results in the table above are taken from the Sponsor's submission.

Study AA28531:

The results of Study AA28531 showed that Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg exhibited a lower AUC_∞ and lower Cmax for fed subjects compared to fasting subjects. The results indicate that the rate and extent of absorption were decreased. Thus, a food effect was observed. (Further discussion of the results of the food effect study may be found in the Clinical Pharmacology Review of Dr. Abimbola Adebawale, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP). See table below.

Ratio of Geometric Means (90% Confidence Intervals)	
Parameter	Fed (A) vs. Fasting (B)
AUC _{0-t}	71.5% (58.2 %-87.8%)
AUC _∞	76.2% (60.8%-95.9%)
Cmax	98.5% (74.5%-130.4%)

Results in the table above are taken from the Clinical Pharmacology Review of Dr. Abimbola Adebawale.

In addition, Tmax was found to be delayed by approximately 4 hours in fed subjects compared to fasting subjects. See table below.

Tmax [Median (Range)]	Fed (A)	5.5 (2.0-23.5) h
	Fasting (B)	1.5 (0.75-4.5) h

Results in the table above are taken from the Clinical Pharmacology Review of Dr. Abimbola Adebawale.

6.6 Clinical Microbiology

This section is not applicable.

6.7 Efficacy Conclusions

The results of the relative bioavailability study (Study AA24171) showed that Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg and Prilosec OTC™ at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg) had similar levels of exposure as determined by AUC_{0-t}, AUC_∞ and C_{max}; and provide support of therapeutic equivalence for Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg and Prilosec OTC™ at a dose of 20.6 mg. The results of the food effect study (Study AA28531) indicated that administration of Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg with a high-fat meal resulted in a decrease in the rate and extent of absorption; thus, a food effect was observed. Because a food effect had also been observed with Prilosec OTC™, and because the labeling of both Prilosec OTC™ and Dexcel Ltd. Omeprazole Delayed-Release Tablets states that the product is to be taken before meals, the labeling for Dexcel Ltd. Omeprazole Delayed-Release Tablets with regard to efficacy is acceptable.

7 INTEGRATED REVIEW OF SAFETY

The review of safety information in this NDA is in the Clinical Review of Dr. Lolita Lopez, Medical Officer, Office of Non-Prescription Drug Products (ONP).

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor is seeking the indication and dose for Omeprazole Delayed-Release Tablet 20 mg that is already approved for Prilosec OTC™.

Indication:

- Treatment of frequent heartburn (occurs 2 or more days a week)
- Not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect

Dose:

- Omeprazole Delayed Release Tablet, 20 mg (1 tablet) once a day
- Should be taken every day for 14 days (may be taken for more than 14 days if directed by a doctor)
- 14-day course may be repeated (if needed) every 4 months

Directions for use:

- Should be swallowed with a glass of water before eating in the morning
- Tablet should not be chewed or crushed

Dosage Adjustment: No dosage adjustment is needed in the elderly. Dose adjustment in Asian subjects should be considered. In PK studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects when compared to Caucasians.

Further discussion of dosage adjustment may be found in the Clinical Review of Dr. Lolita Lopez, Medical Officer, Office of Non-Prescription Products (ONP).

8.2 Drug-Drug Interactions

Proton pump inhibitors (PPIs) inhibit the activity of some hepatic cytochrome P450 enzymes and may therefore decrease the clearance of benzodiazepines, phenytoin, warfarin, and many other drugs. There have been reports of increased prothrombin time and INR in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in prothrombin time and INR.

Although no interaction with propranolol or theophylline was found in normal subjects, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P450 system (e.g., benzodiazepines, cyclosporine, and disulfiram). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole.

Because of omeprazole's profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ampicillin esters, iron salts, and ketoconazole). Co-administration of clarithromycin and omeprazole has resulted in increases of plasma levels of clarithromycin, 14-hydroxy-clarithromycin, and omeprazole.

Further discussion of drug-drug interactions with regard to safety may be found in the Clinical Review of Dr. Lolita Lopez, Medical Officer, Office of Non-Prescription Products (ONP). Further discussion of drug-drug interactions with regard to pharmacokinetics and pharmacodynamics may be found in the Clinical Pharmacology Review of Dr. Abimbola Adebawale, Office of Clinical Pharmacology (OCP).

8.3 Special Populations

Since this NDA contains only PK studies conducted in healthy subjects, there are no new data regarding other patient populations (such as hepatic and renal failure patients), and the effects of gender, race or age on safety or efficacy. The studies submitted did not include individuals of Asian origin for safety reasons. CYP2C19 is the major enzyme that metabolizes omeprazole. It was found to be deficient in many subjects of the Asian population. In prior PK studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects when compared to Caucasians.

Pediatric

Pediatric patients were not evaluated in this NDA. No data were submitted by the sponsor regarding this population. Currently, omeprazole is not approved for OTC use in adolescents. It is approved for OTC use in adults 18 years of age and older.

Pregnancy Use

This application has no new information regarding pregnant women. Omeprazole is currently listed as Pregnancy Category C. There are no adequate or well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.4 Pediatrics

The sponsor is requesting a waiver for pediatric studies for the Dexcel Ltd. Omeprazole Delayed-Release Tablets. The sponsor's rationale for the waiver is that the sponsor of the RLD product has previously addressed pediatric requirements for the drug product in AstraZeneca's PrilosecTM NDA as noted in the publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"). This reviewer recommends that this request should be granted.

The RLD product is currently available in a delayed-release tablet for OTC use and is not, according to the approved labeling, recommended for use in pediatric patients below 18 years of age. For patients less than 18 years of age it would be more appropriate to use the prescription product omeprazole delayed-release capsules which is labeled for use in children two years and older because it would require a physician's intervention for proper diagnosis and treatment for the accurate dosing based upon the child's weight. There is already an existing alternative administration option for children who are unable to swallow the capsule, i.e. to sprinkle the capsule in applesauce, using the omeprazole delayed-release capsule formulation.

8.5 Advisory Committee Meeting

This section is not applicable.

8.6 Literature Review

The sponsor references a study by Goves et al., 1998.¹ This was a 4-week open label, randomized, multi-center study conducted in the UK in adult patients with dyspepsia (n=674). There were two arms as follows: (1) Omeprazole 10 mg QD [Losec (Astra)]; and (2) Antacid / alginate liquid 10 mL QID [Gaviscon].

Assessments by the Investigator were as follows: (1) Severity (overall symptoms): None, Mild, Severe; and (2) Frequency (in prior week): None, 0-1 day, 2-4 days, 5-6 days, 7 days. Definitions included the following: (1) Complete Relief = severity of "None" & frequency of "None"; (2) Sufficient Relief = severity at most "Mild" & frequency at most "0-1" day.

Results of that study were as follows:

7

b(4)

L

The figure above was taken from C

The table below summarizes the results of the percent of subjects with complete relief of heartburn by treatment group. Heartburn was the most common symptom at entry with $\geq 95\%$ having heartburn at entry.

b(4)

Values in the table above were taken from

The results of that study indicate that compared to antacid/alginate liquid 10 mL QID, omeprazole 10 mg QD is more effective in the management of heartburn symptoms.

A literature review with regard to safety information may be found in the Clinical Review of Dr. Lolita Lopez, Medical Officer, Office of Non-Prescription Products (ONP).

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan for this NDA.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

The results of the relative bioavailability trial conducted showed that Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg and Prilosec OTC™ at a dose of 20.6 mg (equivalent to omeprazole dose of 20 mg) had similar levels of exposure as determined by AUC_{0-t} , AUC_{∞} and C_{max} ; and provide support of therapeutic equivalence for Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg and Prilosec OTC™ at a dose of 20.6 mg. By demonstrating that the two products have similar AUC and C_{max} , the trial provides a bridge from Dexcel Ltd. Omeprazole Delayed-Release Tablets to Prilosec OTC™, and to FDA's previous finding of safety and efficacy for omeprazole.

The results of the food effect trial indicated that administration of Dexcel Ltd. Omeprazole Delayed-Release Tablets at a dose of 20 mg with a high-fat meal resulted in a decrease in the rate and extent of absorption; thus, a food effect was observed. Because a food effect had also been observed with Prilosec OTC™, and because the labeling of both Prilosec OTC™ and Dexcel Ltd. Omeprazole Delayed-Release Tablets states that the product is to be taken before meals, the labeling for Dexcel Ltd. Omeprazole Delayed-Release Tablets with regard to efficacy is acceptable.

Thus, this NDA supports the approval of Dexcel Ltd. Omeprazole Delayed Release Tablet, 20 Mg OTC for the indication of treatment of frequent heartburn (occurs 2 or more days a week). Omeprazole is not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect.

9.2 Recommendation on Regulatory Action

This Medical Officer recommends the approval of Dexcel Ltd. Omeprazole Delayed Release Tablet, 20 Mg OTC for the indication of treatment of frequent heartburn (occurs 2 or more days a week). Omeprazole is not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect.

Omeprazole Delayed Release Tablet, 20 Mg OTC (1 tablet) should be swallowed with a glass of water before eating in the morning, and taken once daily for 14 days. A 14-day course may be repeated (if needed) every 4 months.

This reviewer's recommendation is contingent upon the findings of other reviewers that include the clinical reviewer from the Office of Non-Prescription Products (ONP), the clinical pharmacology reviewer from the Office of Clinical Pharmacology (OCP), and the chemistry reviewer from the Office of New Drug Quality Assessment (ONDQA).

To obtain approval, the sponsor must incorporate the labeling recommendations listed in this reviewer's Labeling Review and the team's labeling recommendations, and must obtain satisfactory DSI inspection.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

No Phase 4 commitments are required at this time.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

Below are this Medical Officer's labeling recommendations. Deletions are in strikethrough; additions are in underlined text.

b(4)

2 Page(s) Withheld

 Trade Secret / Confidential (b4)

 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Clinical Review
Anil Rajpal, M.D.
NDA 22-032
Omeprazole Delayed-Release Tablets

9.5 Comments to Applicant

The sponsor should modify the label according to the above labeling recommendations.

APPEARS THIS WAY ON ORIGINAL

10 APPENDICES

10.1 Line-by-Line Labeling Review

See labeling review in section 9.4.

APPEARS THIS WAY ON ORIGINAL

REFERENCES

1. Goves J et al., *First line treatment with omeprazole provides an effective and superior alternative strategy in the management of dyspepsia compared to antacid/alginate liquid: a multicentre study in general practice.* Aliment Pharmacol Ther. 1998 Feb;12(2):147-57.

APPEARS THIS WAY ON ORIGINAL

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

/s/

Anil K Rajpal
11/20/2006 10:00:17 AM
MEDICAL OFFICER

Ruyi He
11/20/2006 11:24:53 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA
Submission Number 22-032
Submission Code 000

Letter Date February 8, 2006
Stamp Date February 10, 2006
PDUFA Goal Date December 10, 2006

Reviewer Name Lolita A. Lopez, M.D.
Review Completion Date November 1, 2006

Established Name Omeprazole Delayed Release Tablet
(Proposed) Trade Name Omeprazole Delayed Release Tablet
Therapeutic Class Proton Pump Inhibitor
Applicant Dexcel Pharma Technologies Ltd.

Priority Designation Standard

Formulation Delayed Release Tablets
Dosing Regimen 20 mg Tablet Once Daily for 14 Days
Indication Treatment of Frequent Heartburn
Intended Population Adults

Table of Contents

1	EXECUTIVE SUMMARY.....	4
1.1	RECOMMENDATION ON REGULATORY ACTION	4
1.2	RECOMMENDATION ON POSTMARKETING ACTIONS	4
1.2.1	Risk Management Activity	4
1.2.2	Required Phase 4 Commitments.....	4
1.2.3	Other Phase 4 Requests.....	4
1.3	SUMMARY OF CLINICAL FINDINGS.....	4
1.3.1	Brief Overview of Clinical Program.....	4
1.3.2	Efficacy.....	5
1.3.3	Safety	5
1.3.4	Dosing Regimen and Administration.....	6
1.3.5	Drug-Drug Interactions.....	6
1.3.6	Special Populations.....	6
2	INTRODUCTION AND BACKGROUND	8
2.1	PRODUCT INFORMATION	8
2.2	CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS.....	8
2.3	AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES	8
2.4	IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS.....	9
2.5	PRESUBMISSION REGULATORY ACTIVITY	9
2.6	OTHER RELEVANT BACKGROUND INFORMATION.....	10
3	SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES	11
3.1	CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)	11
3.2	ANIMAL PHARMACOLOGY/TOXICOLOGY	11
4	DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY.....	12
4.1	SOURCES OF CLINICAL DATA	12
4.2	TABLE OF CLINICAL STUDIES	12
4.3	REVIEW STRATEGY	12
4.4	DATA QUALITY AND INTEGRITY	12
4.5	COMPLIANCE WITH GOOD CLINICAL PRACTICES.....	13
4.6	FINANCIAL DISCLOSURES.....	13
5	CLINICAL PHARMACOLOGY	13
5.1	PHARMACOKINETICS	13
5.2	PHARMACODYNAMICS.....	16
5.3	EXPOSURE-RESPONSE RELATIONSHIPS	16
6	INTEGRATED REVIEW OF EFFICACY	16
7	INTEGRATED REVIEW OF SAFETY	17
7.1	METHODS AND FINDINGS	17
7.1.1	Deaths	17
7.1.2	Other Serious Adverse Events	17
7.1.3	Dropouts and Other Significant Adverse Events Overall profile of dropouts.....	17
7.1.4	Other Search Strategies.....	17
7.1.5	Common Adverse Events	18
7.1.6	Less Common Adverse Events	20
7.1.7	Laboratory Findings.....	20
7.1.8	Vital Signs	20

7.1.9	Electrocardiograms (ECGs).....	20
7.1.10	Immunogenicity	20
7.1.11	Human Carcinogenicity	20
7.1.12	Special Safety Studies.....	21
7.1.13	Withdrawal Phenomena and/or Abuse Potential.....	21
7.1.14	Human Reproduction and Pregnancy Data	21
7.1.15	Assessment of Effect on Growth.....	21
7.1.16	Overdose Experience	21
7.1.17	Postmarketing Experience.....	22
7.2	ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS	28
7.2.1	Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety	28
7.2.1	Description of Secondary Clinical Data Sources Used to Evaluate Safety.....	29
7.2.2	Adequacy of Overall Clinical Experience	29
7.2.3	Adequacy of Special Animal and/or In Vitro Testing	30
7.2.4	Adequacy of Routine Clinical Testing.....	30
7.2.5	Adequacy of Metabolic, Clearance, and Interaction Workup.....	30
7.2.6	Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study.....	30
7.2.7	Assessment of Quality and Completeness of Data	30
7.2.8	Additional Submissions, Including Safety Update	30
7.3	SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS	30
7.4	GENERAL METHODOLOGY	31
7.4.1	Pooling Data Across Studies to Estimate and Compare Incidence	31
7.4.2	Explorations for Predictive Factors	31
7.4.3	Causality Determination	31
8	ADDITIONAL CLINICAL ISSUES	31
8.1	DOSING REGIMEN AND ADMINISTRATION	31
8.2	DRUG-DRUG INTERACTIONS	32
8.3	SPECIAL POPULATIONS.....	33
8.4	PEDIATRICS.....	33
8.5	ADVISORY COMMITTEE MEETING	34
8.6	LITERATURE REVIEW	34
8.7	POSTMARKETING RISK MANAGEMENT PLAN	36
8.8	OTHER RELEVANT MATERIALS	36
9	OVERALL ASSESSMENT.....	36
9.1	CONCLUSIONS	36
9.2	RECOMMENDATION ON REGULATORY ACTION	37
9.3	RECOMMENDATION ON POSTMARKETING ACTIONS	37
9.3.1	Risk Management Activity	37
9.3.2	Required Phase 4 Commitments.....	37
9.3.3	Other Phase 4 Requests.....	37
9.4	LABELING REVIEW	37
9.5	COMMENTS TO APPLICANT.....	42
10	APPENDICES.....	42
10.1	REVIEW OF INDIVIDUAL STUDY REPORTS	43
10.2	LINE-BY-LINE LABELING REVIEW.....	43
10.3	REFERENCES	43

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The proposed Omeprazole Delayed Release Tablet 20 mg indicated for the relief of frequent heartburn occurring two or more days a week for 14 days has an acceptable safety profile for OTC marketing. Therefore, from a clinical safety standpoint, the application should be approved. Final approvability depends on the clinical efficacy evaluation, adequacy of the bioavailability studies conducted by the sponsor, and DSI inspection.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No special risk management activities are recommended for this NDA.

1.2.2 Required Phase 4 Commitments

No required phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

No other phase 4 requests are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Dexcel Pharma Technologies Ltd. is seeking approval to market Omeprazole Delayed Release Tablet 20 mg for over-the-counter (OTC) use in adults 18 years and older. The proposed dosing and indication for this product is similar to the already approved OTC omeprazole *magnesium* delayed release tablet, 20.6 mg (Prilosec OTC™), equivalent to 20 mg of omeprazole. This indication is for the treatment of frequent heartburn occurring two or more days a week; the dosage is one tablet a day (every 24 hours), every day for 14 days. This treatment course may be repeated every 4 months if necessary.

In support of this NDA, the sponsor conducted one bioequivalence study (AA24171) comparing the pharmacokinetics of a single dose of the proposed Omeprazole Delayed Release Tablet

20 mg and Prilosec OTC™ Delayed Release Tablet 20 mg, reference listed drug (RLD) in healthy subjects. A food effect study (AA28531) was also conducted to determine the effect of food on the relative bioavailability of the sponsor's omeprazole product. This NDA is submitted under a 505(b)(2) application and relies on the Agency's previous finding of safety and efficacy for omeprazole. Additional safety information submitted were the sponsor's safety update for omeprazole (including their product), literature review, postmarketing and AERS information.

1.3.2 Efficacy

There were no efficacy trials conducted for this 505(b)(2) application except for a pharmacokinetic (PK) evaluation. Efficacy of this product is extrapolated based on PK data from the single-dose relative bioavailability study assessing the sponsor's Omeprazole Delayed Release Tablet 20 mg and Prilosec OTC™ Delayed Release Tablet 20 mg. This bioequivalence study is an open label, randomized, single-dose, 2-way cross-over study in 76 healthy volunteers (42 male and 34 females) under fasting conditions, with a 7-day wash-out period. A food effect study was also conducted in 18 subjects.

Efficacy of this NDA will be reviewed by the Division of Gastroenterology Products and the relative bioavailability studies will be reviewed by the Office of Clinical Pharmacology (OCP).

1.3.3 Safety

The sponsor primarily relies on the safety information being referenced Prilosec OTC™ delayed release tablet and Prilosec® delayed release capsule.

Safety data submitted to this application include:

- Safety data from the sponsor's bioavailability studies
- Postmarketing adverse events from the sponsor's database from November 2000 to June 2006
- AERS database from February 2002 to first quarter of 2006
- Literature review (including ADISNEWS, Medline and EMBASE search) from January 2002 to June 2006

A total of 94 subjects were exposed to the proposed formulation in PK studies during the clinical development program. In the fasting bioequivalence study (AA24171) conducted, the most common adverse events reported for both treatments were headache (4/76, 5.3%), dizziness (3/76, 3.9%) and nausea (2/76, 2.6%). Headache was the only adverse event judged by the investigator as being related to study drug. In the food effect study AA28531, 3/18 (16%) subjects reported adverse events; upset stomach, headache and vomiting (one subject for each AE). These were all categorized as remotely or unrelated to the study drug and are consistent with the already well-characterized adverse event profile of omeprazole for OTC use.

Omeprazole has been proven safe and effective in the U.S. for over 16 years even at high doses (up to 120 mg three times a day). This drug has been marketed worldwide since 1988 and in the

United States since 1989. A 20 mg omeprazole magnesium (Prilosec OTC™) tablet has been available for over-the-counter use since June 2003. The sponsor has marketing authorization for omeprazole in the United Kingdom (U.K.) since February 2002 and in Israel since September 1998. The proposed formulation differs from the U.K. formulation [REDACTED] and from the Israel formulation. The sponsor reports that there have been no regulatory actions taken by either the regulatory authorities or by the Marketing Authorization Holder (MAH) for safety related reasons for either formulation.

b(4)

The combination of postmarketing data, previous clinical trials, literature review and adverse events information from the relative bioavailability studies conducted by the sponsor do not raise any new safety concern, and establish the safety of Omeprazole Delayed Release Tablet 20 mg for OTC use.

1.3.4 Dosing Regimen and Administration

The sponsor is seeking for the already approved OTC indications and dosing regimen for the currently marketed omeprazole magnesium 20 mg. The proposed indication will be the treatment of frequent heartburn occurring two or more days a week in adults 18 years of age and older. The tablet will be taken once a day for 14 days; the treatment course maybe repeated every 4 months if necessary.

1.3.5 Drug-Drug Interactions

There are no new significant drug-drug interactions that were evaluated in this submission that warrants a change in the label for omeprazole OTC. Drug interactions with omeprazole are addressed in the current omeprazole prescribing information and Prilosec OTC™ label which is similar to the sponsor's proposed label which states:

Ask a doctor or pharmacist before use if you are taking:

- *warfarin (blood-thinning medicine)*
- *prescription antifungal or anti-yeast medicines*
- *diazepam (anxiety medicine)*
- *digoxin (heart medicine)*

1.3.6 Special Populations

Since this NDA only contains PK studies conducted in healthy subjects, there are no new significant data regarding other patient population (such as hepatic and renal failure patients), and the effects of gender, race or age on safety or efficacy. The current label for omeprazole magnesium delayed release tablet for OTC use states "If pregnant or breastfeeding, ask a health professional".

Clinical Review

Lolita A. Lopez, M.D.

NDA 22-032

Omeprazole OTC Delayed Release Tablet 20 mg

Pediatrics

Pediatric patients were not evaluated in this NDA. No new significant data were submitted by the sponsor regarding this population for the proposed indication.

The sponsor is requesting a waiver to conduct pediatric studies; this request should be granted. The safety and effectiveness of omeprazole for OTC use for the indication of frequent heartburn have not been established for pediatric patients (<18 years old); therefore, omeprazole is not labeled for OTC use in children. For patients less than 18 years old, it is more appropriate to use omeprazole under the supervision of a physician for proper diagnosis and treatment.

APPEARS THIS WAY ON ORIGINAL

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Omeprazole is a proton-pump inhibitor (PPI) currently used for the treatment of acid-related gastrointestinal disorders. Like other PPIs, omeprazole is acid-labile and rapidly degraded by gastric acid; therefore, most oral omeprazole formulations available are delivered with enteric-coatings as a protection from rapid degradation upon exposure to acid. This gives the drug its delayed-release characteristic.

Omeprazole was approved as a prescription product in the United States in 1989 and subsequently as a non-prescription or over-the-counter (OTC) product in June 2003. As a prescription product, it is available in dosage strengths of 10 mg, 20 mg, and 40 mg and is indicated for the short-term treatment of active duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD), maintenance treatment of healing of erosive esophagitis (EE), treatment of pathological hypersecretory conditions and *H. pylori* eradication (when used with clarithromycin and/or amoxicillin). It is also approved in children two years and older for the treatment of GERD.

An OTC omeprazole *magnesium* delayed release tablet, 20.6 mg (Prilosec OTC™), equivalent to 20 mg omeprazole, is currently marketed for the treatment of frequent heartburn (occurring two or more days a week) in adults 18 years of age and older, used once a day for 14 days. This treatment course maybe repeated every 4 months if necessary.

Dexcel Pharma Technologies Ltd. is seeking approval to market Omeprazole Delayed Release Tablet 20 mg for OTC use. The proposed dosing and indication for this product is similar to the already marketed omeprazole magnesium (Prilosec OTC™) delayed release tablet for OTC use.

2.2 Currently Available Treatment for Indications

Omeprazole magnesium delayed release tablet (Prilosec OTC™) is the only PPI marketed for OTC use, and the only product indicated for the treatment of *frequent* heartburn (occurring two or more days per week). There are other OTC products available for the treatment of other acid-related gastrointestinal disorders such as H₂-receptor antagonists (ranitidine, cimetidine, famotidine and nizatidine), antacids (aluminum and/or magnesium hydroxide, calcium bicarbonate, sodium bicarbonate), etc.

2.3 Availability of Proposed Active Ingredient in the United States

The only omeprazole product available for OTC use is omeprazole magnesium delayed release tablet 20 mg (Prilosec OTC™) indicated for the treatment of frequent heartburn.

There are other omeprazole (both brand and generic) products marketed for *prescription* use available as 10 mg, 20 mg, and 40 mg doses.

2.4 Important Issues With Pharmacologically Related Products

Proton pump inhibitors (PPIs) are known to inhibit the activity of some hepatic cytochrome P450 enzymes and therefore may decrease the clearance of benzodiazepines, warfarin, phenytoin, and many other drugs that are metabolized by oxidation in the liver. A class labeling for PPIs has been incorporated in the label regarding potential drug interactions with these drugs.

There have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with PPIs and warfarin may need to be monitored for increases in INR and prothrombin time.

Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P450 system (eg, cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole.

Due to the profound and long lasting inhibition of gastric acid secretion from PPIs, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (eg, ketoconazole, ampicillin esters, and iron salts).

The most common adverse effects caused by PPIs are nausea, abdominal pain, constipation, flatulence, and diarrhea. Also reported are subacute myopathy, arthralgias, headaches, and skin rashes. There are conflicting data on the risk and clinical implications of enterochromaffin-like cell hyperplasia in patients on long-term proton pump inhibitor therapy. PPIs have a track record of more than 16 years of use worldwide, and no major new issues regarding safety have emerged. There is no reason to believe, therefore, that hypergastrinemia should be a trigger for discontinuation of therapy or that gastrin levels should be monitored routinely in patients on long-term proton pump inhibitor therapy. However, the development of a hypergastrinemic state may predispose the patient to rebound hypersecretion of gastric acid following discontinuation of therapy.

These important issues with pharmacologically related products are reflected in the current prescribing information and partly in the OTC label (for the most significant issues) for omeprazole.

2.5 Presubmission Regulatory Activity

The marketing of omeprazole was originally approved by the FDA for prescription use under NDA 19-810 (Prilosec®, Aztra-Zeneca) in September 1989 for the treatment of acid-related

On February 10, 2006, the sponsor submitted NDA 22-032 seeking the approval for an Omeprazole Delayed Release (DR) Tablet 20 mg formulation for OTC use. This is a 505(b)(2) application using Aztra Zeneca/Procter & Gamble's (AZ/P&G) Prilosec OTC™ Delayed Release Tablet 20 mg as the reference listed drug (RLD), and relies on the Agency's previous finding of safety and efficacy for omeprazole. The sponsor conducted two pharmacokinetics studies in support of their NDA: (1) a bioequivalence study (AA24171) comparing the PK of a single dose of the proposed Omeprazole Delayed Release Tablet 20 mg and Prilosec OTC™ in healthy adult subjects and (2) a food effect study (AA28531) to determine the effect of food on the bioavailability of the sponsor's proposed Omeprazole Delayed Release Tablet 20 mg. The proposed dosing and indication for this proposed product is similar to the already approved dosing and indication for Prilosec OTC™.

Dexel Pharma Technologies Ltd. has been marketing omeprazole products in Israel since 1998 and in the United Kingdom since 2002. See table 1 below for product approval history.

Product	Dosage Form	Market	Approval Date	Quantity Marketed	AE/ADR	Marketing Status
Omeprazole capsules	capsule	Israel	8/1998		None	Stopped due to injunction ¹
Omeprazole caplets	caplet	Israel	10/2000		None	On the market
Omeprazole Tablets	tablet	UK	02/2002		None	On the market

10

A bioequivalence study of two omeprazole 20 mg formulations in 40 healthy volunteers was conducted under fasting conditions (Study BES/023/99) for the approval of the 20 mg delayed release *caplet* formulation in Israel (October 2000) and for the approval of the delayed release *tablet* in the U.K. (February 2002). In this study, headache was experienced by three subjects, which was reported to be possibly related to the study drug; this adverse event was reported to be moderate in intensity and treated with paracetamol.

The proposed delayed release tablet formulation differs from the U.K. (tablet) formulation in the [redacted] and the Israel (caplet) formulation also differs slightly, both from the current formulation under review and from that marketed in the U.K. The sponsor reports that there have been no regulatory actions taken by either the regulatory authorities or by the Marketing Authorization Holder (MAH) for safety related reasons for either formulation. b(4)

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Omeprazole is susceptible to degradation not only in acidic environment but also under the influence of temperature, humidity and organic solvents. It degrades very rapidly in solutions at low pH values. The rate of degradation proceeds with a half-life of less than 10 minutes at pH values below 4. b(4)

During the development of the formula, the qualities to be maintained were:

-
-
-

The omeprazole (tablet) formulations marketed in the U.K. and Israel (caplet) have slight differences in their excipients. The sponsor is proposing to market Omeprazole Delayed Release Tablets 20 mg in the United States; the formulation proposed is similar to the U.K. formulation [redacted] the Chemistry Review of details on the quality of this product. b(4)

3.2 Animal Pharmacology/Toxicology

There are no additional new non-clinical studies conducted by the sponsor. The sponsor refers to the RLD's Pharmacology/Toxicology information. The Pharm/Tox reviewer Dr. David Joseph recommends that from a preclinical viewpoint, the application should be approved (see review entered in DFS).

² Sponsor's submission Module 2.3.P.2

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical data utilized in this review were the sponsor's bioequivalence study comparing Prilosec OTC™ (P&G/AZ) and Omeprazole (Dexcel) Delayed Release Tablets 20 mg, the prescription label of Prilosec® delayed release capsule, the non-prescription label of Prilosec OTC™ and the sponsor's safety data for omeprazole which includes the following:

- Literature review (including ADISNEWS, Medline and EMBASE search) from January 2002 to June 2006
- Postmarketing adverse events from the sponsor's database from November 2000 to June 2006
- AERS information February 2002 to first quarter of 2006
- Safety data gathered from the sponsor's two PK studies

4.2 Table of Clinical Studies

Table 2: Clinical Studies

Type of Trial	Trial	Objective	Trial Design	Treatment	N
PK	AA24171	Compare PK profiles of Prilosec OTC™ (P&G) and Omeprazole DR (Dexcel) Tabs	2-way Crossover, Healthy Subjects, Single dose	Prilosec OTC™ (P&G) and Omeprazole DR (Dexcel) Tabs qAM, 20 mg	76
PK	AA28531	To assess effect of food on the PK of Omeprazole DR (Dexcel) Tabs	2-way Crossover Single dose	Omeprazole DR (Dexcel), Tabs 20 mg	18

4.3 Review Strategy

This review covers the safety data only. Clinical efficacy is being reviewed by the Division of Gastroenterology Products. The Office of Clinical Pharmacology will review the submitted relative bioavailability studies in detail.

4.4 Data Quality and Integrity

A DSI inspection was requested for Studies AA24171 and AA28531. The results are pending at the time this NDA Review was written.

4.5 Compliance with Good Clinical Practices

The sponsor states that the two PK studies were conducted in accordance with the clinical research guidelines established by the Medical Research Council of Canada, the Basic Principles defined in the U.S. 21 CFR Part 312.20, the Principles enunciated in the latest version of the Declaration of Helsinki referenced in the Protocol (Edinburgh, Scotland, October 2000) and the ICH Harmonized Tripartite Guideline regarding Good Clinical Practice (GCP).

The sponsor states that the protocol and informed consent form (ICF) were reviewed and approved by an Institutional Review Board (IRB) convening at [REDACTED], prior to study initiation. The IRB is constituted and operates in accordance with the principles and requirements described in the Canadian "Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans" and in the U.S. Code of Federal Regulations (21 CFR Part 56).

b(4)

4.6 Financial Disclosures

The sponsor submitted an FDA form 3454 certifying that as a sponsor of the submitted studies, it has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The sponsor also certified that each listed clinical investigator did not disclose any proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) and that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

5 CLINICAL PHARMACOLOGY

The sponsor submitted a bioequivalence study comparing the pharmacokinetic profile of one dose of Prilosec OTC™ Delayed Release Tablets (P&G) and Omeprazole Delayed Release Tablets (Dexcel), 20 mg, conducted in 76 healthy adult subjects. A food effect study was also conducted for Dexcel's omeprazole in 18 healthy subjects. See Clinical Pharmacology review for details.

5.1 Pharmacokinetics

Omeprazole is administered orally and should be taken prior to meals, preferably in the morning due to the effect of food on its bioavailability. The pharmacokinetics of omeprazole are dose proportional up to 40 mg doses, however due to a saturable first-pass effect the pharmacokinetics of omeprazole are non-linear for doses greater than 40 mg. The drug is rapidly absorbed following oral administration and distributes throughout the body tissues, concentrating in the gastric parietal cells. Its absolute bioavailability is 30-40% due to pre-systemic metabolism after oral administration. It is not known if it crosses the placenta but it is excreted into breast milk. The drug's onset of action is 1 hour, and the duration of inhibition is greater than 72 hours. Omeprazole is 95% bound to plasma proteins. Extensive hepatic metabolism occurs, and the metabolites have minimal antisecretory activity. The plasma half-life in healthy patients is 0.5-1

hour. Secretory activity returns to normal 3-5 days after therapy is discontinued. Approximately 72-80% of a dose is excreted renally, and 18-23% is excreted in the feces.³

CPY2C19 is the major enzyme that metabolizes omeprazole. It was found to be deficient in many subjects of the Asian population. In studies of single 20 mg omeprazole doses, an approximate four-fold increase in AUC was noted in Asian subjects compared to Caucasians.⁴

The proposed indication for Dexcel's omeprazole delayed release tablet 20 mg is the treatment of frequent heartburn (occurring 2 or more days a week). The Clinical Pharmacology reviewer is reviewing study AA24171 to assess the bioequivalence of Dexcel's omeprazole delayed release tablets, 20 mg to the reference listed drug Prilosec OTCTM in 76 healthy adult subjects under fasting conditions. A food-effect relative bioavailability study conducted in 18 healthy subjects to demonstrate the effect of food on the PK of omeprazole formulation from Dexcel Ltd. (AA28531) is also being reviewed. See Clinical Pharmacology review for details.

Study AA24171 was a comparative, open label, randomized, single-dose, 2-way cross-over study in 76 healthy adult volunteers under (10 hours) fasting conditions. Subjects were divided into two groups. Subjects randomized to Treatment A received a single oral dose of one Dexcel's Omeprazole Delayed Release Tablet 20 mg taken with 240 mL of water under fasting conditions. Subjects randomized to Treatment B received a single oral dose of one Prilosec OTCTM taken with 240 mL of water under fasting conditions.

In each period, subjects were housed for at least 10 hours before dosing until after the 12-hour blood draw. See Study Events Flow Chart in Table 3 below. Single oral doses of Prilosec OTCTM and Omeprazole Delayed Release Tablet 20 mg were separated by a washout period of at least 7 days. All 76 subjects completed the clinical phase of the study. The following PK parameters were calculated for omeprazole: AUC_{0-t} , AUC_{inf} , AUC/AUC_{inf} , C_{max} , t_{max} , half-life and k_{el} .

APPEARS THIS WAY ON ORIGINAL

³ Pharmacology Online (<http://cpip.gsm.com/>) accessed on 9-21-06

⁴ Pharmacology Online (<http://cpip.gsm.com/>) accessed on 9-22-06

Table 3: Study Events Flow Chart (AA24171)

Study Phase Activity	Study Days in Period 1 and 2 ¹		
	Screening Within 28 days of dosing	Check-In Day -1 ²	Day 1
Informed Consent	X		
Medical History and Demographic Data	X		
Physical Exam	X		
ECG (12-lead)	X		
Vital Signs	X		
Hematology	X		
Urinalysis	X		
Serum Chemistry	X		
HIV/Hepatitis B & C screen	X		
Urine Drug Screen			
Cocaine, Cannabinoids	X	X	
Serum Pregnancy Test (for females only)	X	X	
Record of Concomitant Medication	X	X	X
Check-in Procedures		X	
Alcohol Screen		X	
Confinement in Study Unit		X	X
Drug Dosing			X
PK Blood Sampling ³			X
Adverse Events		X	X

Sponsor's Table

Table 4 below presents the results derived from the analyses of the ln-transformed AUC_{0-t} , AUC_{inf} and C_{max} pharmacokinetic parameters. The mean t_{max} value for the Dexcel Ltd. was 2.372 hours and 2.154 hours for P&G/AstraZeneca. The ratios of least-squares means (LSM) and the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC_{0-t} , AUC_{inf} and C_{max} for omeprazole in plasma were within FDA's requirements for bioequivalence of 80-125%.

Table 4: Summary of Pharmacokinetic Results for Omeprazole (AA24171)

Parameter	Dexcel Ltd. (A) vs. P&G/AstraZeneca (B)
AUC_{0-t}	102.9% (99.0% -107.0%)
AUC_{inf}	104.2% (100.3% - 108.3%)
C_{max}	99.8% (93.0% -107.1%)

The results of study AA24171 show that Dexcel's Delayed Release Tablet and Prilosec OTC™ have similar rate and extent of exposure under fasting conditions.

Study AA28531 was a comparative, open label, randomized, single dose, 2-way crossover food effect bioavailability study of Dexcel Omeprazole Delayed Release Tablet 20 mg in 18 healthy adult male volunteers; 17 subjects completed the study. Subjects were randomized to either treatment A or B. Treatment A received a single oral dose of one Omeprazole Delayed Release Tablet 20 mg taken with 240 mL of water under fed conditions; treatment B were dosed under fasting conditions. Doses were separated by 7 days wash-out period. Blood samples were collected prior to dosing up to 24-hours post-dose.

Table 5: Ratios of LSM% (AA28531)

Parameter	Dexcel Ltd. Fed (A) vs. Fasting (B)
AUC _{0-t}	71.5%
AUC _{inf}	76.2%
C _{max}	98.5%

The administration of food (standard high-fat breakfast) 30 minutes prior to dosing decreased Dexcel omeprazole's ln-transformed AUC_{0-t} by 28.5% and AUC_{inf} by 23.8% compared to the fasted state; C_{max} parameter was 98.5% (within 80-125%). In addition, the time to reach peak plasma concentrations was found to be delayed by approximately 4 hours as compared to the fasting state; this delay in t_{max} is expected based on the current literature and the RLD's data.

5.2 Pharmacodynamics

There are no new pharmacodynamic data submitted with this NDA.

5.3 Exposure-Response Relationships

There is no new exposure-response relationship data submitted with this NDA.

6 INTEGRATED REVIEW OF EFFICACY

No new efficacy studies were conducted with this NDA. Efficacy of this product is extrapolated based on PK data from the single dose bioequivalence study AA24171 conducted by the sponsor and the food effect study, AA28531. The efficacy review of this NDA will be addressed by the Division of Gastroenterology Products.

7 INTEGRATED REVIEW OF SAFETY

The safety of omeprazole 20 mg for OTC use for the indication of frequent heartburn has been reviewed in detail at the time of the original submission of Prilosec OTC™ Delayed Release Tablets, approved in June 2003.

7.1 Methods and Findings

All of the subjects in the trials conducted by the sponsor were healthy adults. Neither trial was conducted specifically to assess safety issues with the sponsor's omeprazole product; however, safety data were evaluated. In both trials, safety assessments consisted of physical examinations, vital signs measurements, clinical laboratory testing, and monitoring for adverse events (AEs).

7.1.1 Deaths

There were no reported deaths in the studies conducted.

7.1.2 Other Serious Adverse Events

There were no serious adverse events reported in the BE studies conducted.

7.1.3 Dropouts and Other Significant Adverse Events Overall profile of dropouts

There were no subjects reported withdrawn or discontinued from the fasting BE study AA24171. In the food effect study AA28531, one subject (no.18) was withdrawn by the Principal Investigator due to an adverse event, vomiting, in Period 1 (omeprazole taken under fasting condition).

7.1.3.1 Adverse events associated with dropouts

Subject no. 18 in the food effect study AA28531 was reported by the investigator to have vomited; this event was categorized as remotely related to the treatment, mild, non-serious and resolved with no treatment necessary.

7.1.3.2 Other significant adverse events

There were no other significant adverse events reported.

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

Historically, the most common drug-related associated with the use of omeprazole include the following:

- Headache
- Diarrhea
- Abdominal Pain
- Nausea
- Dizziness
- Vomiting
- Rash
- Constipation
- Asthenia

7.1.5.1 Eliciting adverse events data in the development program

Adverse events (AEs) were monitored throughout the study until resolution. AEs were described in terms of severity, seriousness, outcome, action, frequency and relationship to treatment.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor used MedRA Version 8.0 preferred terms to report adverse events, and categorized AEs according to severity (mild, moderate or severe), seriousness (serious or non-serious), outcome (resolved or unresolved) frequency (single, intermittent or continuous) and relationship (definite, probable, possible, remote or unrelated) to treatment. The adverse event categorization and preferred terms used in the study appears appropriate.

7.1.5.3 Incidence of common adverse events

The most common adverse events reported for both treatments in the AA24171 trial were headache (4/76, 5.3%), dizziness (3/76, 3.9%) and nausea (2/76, 2.6%). Headache was the only AE judged by the investigator as being related to study drug. In the food effect study AA28531, 3/18 (16%) subjects reported adverse events; upset stomach, headache and vomiting (one subject for each AE). These were all categorized as remotely or unrelated to the study drug.

7.1.5.4 Common adverse event tables

The table below lists the number and percentage of subjects with adverse events by treatment group and system organ class from Study AA24171.

Table 6: Incidence of Treatment-Emergent Adverse Events in Study AA24171

System Organ Class/ Preferred Term MedDRA Ver 8.0	Dexcel Omeprazole DR 20 mg (N=76)	Proctor & Gamble/ AstraZeneca Prilosec (omeprazole magnesium) 20.6 mg (N=76)	Total (N=76)
Number of subjects with adverse events	9 (11.8%)	4 (5.3%)	11 (14.5%)
Nervous system disorders	4 (5.3%)	4 (5.3%)	8 (10.6%)
Headache	2 (2.6%)	2 (2.6%)	4 (5.3%)
Dizziness	2 (2.6%)	1 (1.3%)	3 (3.9%)
Hypoaesthesia	0 (0%)	1 (1.3%)	1 (1.3%)
Paraesthesia	0 (0%)	1 (1.3%)	1 (1.3%)
Injury, poisoning and procedural complications	2 (2.6%)	0 (0%)	2 (2.6%)
Contusion	1 (1.3%)	0 (0%)	1 (1.3%)
Skin laceration	1 (1.3%)	0 (0%)	1 (1.3%)
General disorders and administrative site conditions	0 (0%)	2 (2.6%)	2 (2.6%)
Asthenia	0 (0%)	1 (1.3%)	1 (1.3%)
Catheter site pain	0 (0%)	1 (1.3%)	1 (1.3%)
Feeling cold	0 (0%)	1 (1.3%)	1 (1.3%)
Feeling hot	0 (0%)	1 (1.3%)	1 (1.3%)
Gastrointestinal disorders	2 (2.6%)	1 (1.3%)	2 (2.6%)
Nausea	1 (1.3%)	1 (1.3%)	2 (2.6%)
Vomiting	1 (1.3%)	1 (1.3%)	1 (1.3%)
Respiratory, thoracic and mediastinal disorders	1 (1.3%)	0 (0%)	1 (1.3%)
Pharyngeal hypoaesthesia	1 (1.3%)	0 (0%)	1 (1.3%)
Reproductive system and breast disorders	1 (1.3%)	0 (0%)	1 (1.3%)
Dysmenorrhoea	1 (1.3%)	0 (0%)	1 (1.3%)
Psychiatric disorders	0 (0%)	1 (1.3%)	1 (1.3%)
Nervousness	0 (0%)	1 (1.3%)	1 (1.3%)

Sponsor's submission Safety Update Report Vol.1.1 submitted 3-23-06

7.1.5.5 Identifying common and drug-related adverse events

There were 9/76 subjects (11.8%) who reported adverse events during the period of administration of the Dexcel's omeprazole product; and only two of these subjects had adverse events [vomiting (1/76, 1.3%) and headache (2/76, 2.6%)] that were judged by the investigator to be related to the study drug. Subject no.1 had vomiting and headache, and subject no. 41 had headache.

There were 4 subjects (5.3%) who reported adverse events during the period of administration of the comparator product Prilosec OTC™, and two of these subjects had adverse events that were judged by the investigator to be related to the study drug (nausea 1/76, 1.3%; headache 2/76,

2.6%; and vomiting 1/76, 1.3%). Subject no.1 had nausea and headache, and subject no. 27 had headache. See Table 6 in section 7.1.5.4 above.

There were no reported drug-related adverse events for Study AA28531.

7.1.5.6 Additional analyses and explorations

There were no additional analyses and explorations performed by the sponsor.

7.1.6 Less Common Adverse Events

The population and the number of adverse events in the bioequivalence study conducted are too small to assess the incidence of less common adverse events.

7.1.7 Laboratory Findings

Baseline hematology, serum chemistry, urinalysis, HIV/Hepatitis B & C screen were obtained at screening (within 28 days of dosing). Urine drug screen and serum pregnancy test were obtained at screening and 1 day prior to dosing. The sponsor did not evaluate each laboratory parameter since this was a bioequivalence study. Any abnormalities at screening were considered to be clinically insignificant.

7.1.8 Vital Signs

The sponsor measured the following vital signs during the screening period: blood pressure, pulse rate, respiratory rate, and temperature. No repeat vital signs were done thereafter according to the protocol. Any abnormalities at screening were considered to be clinically insignificant.

7.1.9 Electrocardiograms (ECGs)

Baseline 12-lead electrocardiogram was performed for each subject during the screening period. There were occasional ECG abnormalities noted, but no abnormality was regarded by the Investigator to be clinically significant.

7.1.10 Immunogenicity

There was no immunogenic evaluation conducted in this submission.

7.1.11 Human Carcinogenicity

No new animal or toxicology studies were submitted with this NDA. The sponsor relies on the reference listed drug for this information.

7.1.12 Special Safety Studies

There were no special safety studies requested or performed for this submission.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Omeprazole has no known withdrawal phenomena and/or abuse potential and is not regulated under the Controlled Substance Act. It is not likely to present a substantial risk for medical abuse, lead to addiction or misused for illegal purposes.

7.1.14 Human Reproduction and Pregnancy Data

This application has no new information warrants a change in the labeling of this product regarding pregnant women. Omeprazole is currently listed as Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women.

Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy.

Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The current omeprazole OTC Warning section of the label states, "*If pregnant or breast feeding, ask a health professional before use*".

7.1.15 Assessment of Effect on Growth

No information was submitted regarding the effect of omeprazole on growth. Omeprazole for OTC use is not indicated in children or individuals <18 years old.

7.1.16 Overdose Experience

The sponsor did not provide any new overdose data/information for omeprazole 20 mg.

Reports have been received for overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. Symptoms were transient, and no serious clinical outcome has been reported

when omeprazole was taken alone. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

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

The information is reflected in the current prescribing information for omeprazole.

7.1.17 Postmarketing Experience

Omeprazole (Prilosec®) has been marketed with a well-characterized safety profile in the United States since 1989, and has been marketed worldwide for at least 16 years. Omeprazole is a drug with a wide therapeutic index that has been prescribed at doses of up to 360 mg/day for hypersecretory conditions. Omeprazole for prescription use is available as 10 mg, 20 mg and 40 mg tablet for the treatment (for 4 weeks or more) of various acid-related disorders. For three years now, an OTC omeprazole magnesium (Prilosec OTC™) 20 mg has been marketed for the indication of treatment of frequent heartburn; treatment is for 2 weeks. An extensive safety database exists for omeprazole postmarketing experience.

Postmarketing data submitted to this NDA come from the sponsor's database (February 2002 to June 2006), and a review of FDA AERS database from January 2002 to the first quarter of 2006. Worldwide literature on the safety of omeprazole (including ADISNEWS, Medline and EMBASE search) from January 1, 2002 to June 18, 2006. The literature review can be found in section 8.6 of this NDA review.

Sponsor's Database

Dexcel Pharma Ltd. has marketing authorization for omeprazole tablet in the U.K. since February 2002 and for omeprazole caplet in Israel since 2000. A capsule formulation was also approved in Israel in August 1998 and was marketed until October 1999; marketing for the capsule formulation was stopped due to patent litigation. The sponsor markets omeprazole as a gastro-resistant coated *tablet* in 10, 20 and 40 mg doses and as a gastro-resistant coated *capsule* in 10 and 20 mg doses. There are no postmarketing data available for the current omeprazole formulation under review; however, postmarketing data were provided for two other omeprazole formulations marketed by the sponsor which differ slightly from the current formulation in the

██████████ In a Periodic Safety Update Report (PSUR) submitted in the U.K. which reviews the products from February 19, 2002 to November 30, 2005, it is stated that over ██████████ omeprazole 20 mg tablets/capsules were marketed with an estimate of ██████████ patients exposed in the U.K. In Israel, more than ██████████ omeprazole 20 mg tablets were marketed from October 2000 to December 2005.

b(4)

On October 23, 2006, per the clinical safety reviewing team's request, the sponsor submitted an addendum to the PSUR. This submission covers the interval reporting period from December 1, 2005 to June 18, 2006. During this interval, over [REDACTED] omeprazole 20 mg were sold in the U.K. and Israel with a calculated estimate of [REDACTED] patients exposed. There were 2 reports of lack of effect received for the 20 mg dose from health care practitioners and 2 reports of lack of effect received from consumers in U.K. during this reporting period.

b(4)

The sponsor states that no adverse drug reactions were reported during both reporting period that covers February 2002 to June 2006. No actions have been taken for safety reasons by any regulatory authority or Market Authorization Holder (MAH) during both reporting periods for safety related reasons.

Medical Officer Comments: This reviewer finds it unusual that there were no adverse events reported for a duration more than four years of marketing this product. The sponsor was repeatedly asked about any AEs reported and if there was a safety monitoring in place for both Israel and U.K. The sponsor certified that there were indeed no AEs reported for Dexcel's Omeprazole Delayed Release Tablets in U.K. (other than lack of efficacy reports) from February 2002 to June 2006, and in Israel from August 1998 to June 2006. The sponsor also certifies that there has been no withdrawal from any market for any safety reason for any Dexcel omeprazole products (capsule, caplet and tablet) since approval in Israel and the U.K.

A most recently approved changes to the prescribing information of omeprazole delayed release capsule (Prilosec®) is the addition of a language regarding its drug interaction with the anti-viral drug, atazanavir.

FDA AERS Database

The Adverse Event Reporting System (AERS) database was reviewed for omeprazole as a primary suspect drug when dosed at 20 mg orally per day for no longer than 2 weeks. There were 78 patients recorded with 293 adverse events terms from January 2002 to December 2005. The table below shows a summary of the adverse event terms reported in at least two patients. Most of the complaints were pharmaceutical product complaints or related to the drug's inefficacy.

APPEARS THIS WAY ON ORIGINAL

**Table 7: Summary of Adverse Event Terms Reported (N ≥ 2) From AERS
 for Omeprazole 20 mg Daily for Less than 2 weeks**

Adverse Event Term	Number of Patients Reporting	Adverse Event Term	Number of Patients Reporting
Pharmaceutical product complaint	26	Convulsion	2
Gastroesophageal reflux disease	10	Cytolytic hepatitis	2
Drug ineffective	9	Dialysis NOS	2
Condition aggravated	8	Drug eruption	2
Diarrhea	7	Drug interaction	2
Drug effect decreased	5	Drug intolerance	2
Dyspepsia	5	Dyspnea	2
Nausea	5	Generalized erythema	2
Pruritus	5	Hemodialysis	2
Renal failure acute	5	Hypersensitivity	2
Rhabdomyolysis	5	Insomnia	2
Disease recurrence	4	Loose stools	2
Hyponatremia	4	Platelet count decreased	2
Abdominal pain upper	3	Pulmonary edema	2
Hyperkalaemia	3	Septic shock	2
Nephritis interstitial	3	Toxic epidermal necrolysis	2
Abdominal pain	2	Toxic skin eruption	2
Blood CPK increased	2	Vomiting	2
Circulatory collapse	2	White blood cell count decreased	2
Collapse	2		

APPEARS THIS WAY ON ORIGINAL

A search of the AERS database for Prilosec OTCTM NDA 21-229 and omeprazole magnesium for the period of April 1, 2003 to November 30, 2005 was also conducted. The sponsor reports that a total of 134 reactions were reported, and 28 of these cases reported were SAEs. Table 8 below displays unique adverse event terms that occurred in 2 or more reports. The following adverse drug reactions were found to be most common: dyspnea (2.99%), fatigue (2.99%), urticaria (2.99%), dizziness (2.24%), hypersensitivity (2.24%), pruritus (2.24%), and swelling (2.24%).

Table 8: Adverse Events in the FDA AERS Database for Prilosec OTCTM (NDA 21-229) and Omeprazole Magnesium from April 1, 2003 to November 30, 2005 (N ≥ 2)

Reaction term	Number of Reported Terms
Dyspnoea	4
Fatigue	4
Urticaria	4
Dizziness	3
Hypersensitivity	3
Pruritus	3
Swelling	3
Anaphylactic shock	2
Angina Pectoris	2
Cerebrovascular accident	2
Chest pain	2
Cholangitis	2
Confusional state	2
Dysphagia	2
Erythema	2
Fall	2
Hepatic cirrhosis	2
Hepatic fibrosis	2
Hepatic steatosis	2
Fluctuation	2
Jaundice	2
Liver disorder	2
Muscle atrophy	2
Nausea	2
Rash	2
Swelling face	2
Syncope	2
Treatment non-compliance	2
Vasculitis	2

Sponsor's Table Amendment - Safety Update Report, March 23, 2006 p.8

Clinical Review

Lolita A. Lopez, M.D.

NDA 22-032

Omeprazole OTC Delayed Release Tablet 20 mg

Serious adverse events reports are summarized in the table below from April 1, 2003 to November 30, 2005.

Table 9: Serious Adverse Event Case Reports Identified in FDA AERS Database for Prilosec OTC™ and Omeprazole Magnesium from April 1, 2003 to November 30, 2005

ISR#	Age (years)	Gender	Indication	Reaction	Reason for SAE
Prilosec					
4137819	47	Male	Liver transplant	Ascites, diabetes mellitus	Hospitalization
4204221	60	Male	Dyspepsia	Dyspnea	Required intervention
4214878	11	Female	Gastritis	Fall, headache, loss of consciousness, visual disturbance	Required intervention
4216542	61	Female	GERD	Chest pain, pruritus generalized, rash, syncope, throat tightness	Required intervention
4216544	60	Male	Dyspepsia	Dysphagia, dyspnea, rash, swelling face, urticaria	Required intervention
4216546	46	Female	GERD	Back pain, fall, syncope, hypersensitivity	Required intervention
4268697	60	Female	GERD	Chest discomfort, chest pain, dysphagia, dyspnoea, hypersensitivity, nausea, oedema peripheral, pruritus generalised, rash, swollen tongue, syncope, throat tightness, urticaria, ventricular extrasystoles; wheezing	Required intervention
4284108	39	Male	Dyspepsia	Diabetes mellitus insulin-dependant, fungal infection, pancreatic disorder, urinary tract infection, weight decreased	Hospitalization
4287070	72	Female	Dyspepsia	Dizziness	Hospitalization
4287071	53	Male	Dyspepsia	Dizziness, hyperhidrosis	Hospitalization
4287072	Unknown	Female	GERD	Anaphylactic shock, erythema, swelling, urticaria	Hospitalization
Omeprazole Magnesium					
4098692	68	Female	Arthritis	Vitamin B12	Disability
4143862	86	Female	Chronic obstructive airway disease	Ischaemia, pancreatic necrosis, pancreatitis acute, pseudocyst	Hospitalization
4148759	60	Female	Depression, hypertension	Pulmonary embolism	Hospitalization, disability
4149811	57	Male	Rheumatoid arthritis	Hyperflexia, tremor	Required intervention

Clinical Review

Lolita A. Lopez, M.D.

NDA 22-032

Omeprazole OTC Delayed Release Tablet 20 mg

ISR#	Age (years)	Gender	Indication	Reaction	Reason for SAE
4168819	63	Male	Lung infection, pain, chronic obstructive airways disease, hypertension, multiple myeloma, duodenitis	Agitation, confusional state, consciousness fluctuating, hallucination visual	Disability
4159693	78	Male	Neurotoxicity	Calcinosis, cerebral haematoma, delirium, haemoglobin decreased, neutropenia, oedema, platelet count decreased, white blood cell count	Hospitalization
4267284	70	Male	Unknown	Abdominal distension, cardiac failure, weight increased	Hospitalization
4285037	78	Female	Pain, coronary artery disease, hypertension, hypercholesterolaemia, GERD, thrombosis prophylaxis	Aortic stenosis, balance disorder, dizziness, nausea, dyspnoea, stress symptoms, prescribed overdose	Other
4468693	66	Male	Back pain	Angina pectoris, blindness unilateral, cerebrovascular accident, chest pain, infarction	Death
4480187	76	Female	Exostosis	Blood pressure increased, cardiac disorder	Hospitalization
4546750	39	Male	Rheumatoid arthritis, renal disorder	Aplasia pure red cell, peritoneal dialysis, refractory anaemia	Hospitalization
4557633	62	Male	Osteoarthritis	Angina pectoris, condition aggravated	Hospitalization
4558918	67	Male	Collagen disorder, constipation	Amblyopia, retinal artery occlusion	Disability, Hospitalization
4635653	58	Female	Hypercholesterolaemia	Change of bowel habit, insomnia, INR fluctuation, mental disorder, mood altered, palpitations	Disability

AERS= adverse event reporting system

SAE=Serious Adverse Event

GERD=Gastroesophageal reflux disease

INR= international normalised ratio

Medical Officer Comments:

It is to be noted that there is inconsistency in the number of cases of serious adverse events referred to in this submission. The sponsor states that there were 28 cases of reported serious adverse events; however, in table 9 above which they provided, there are only 25 and not 28 cases. This reviewer searched the FDA AERS Database and reviewed each case with reported serious adverse events listed in table 8 above. A total of six (6) cases had SAEs which can possibly be attributed to an allergic reaction/hypersensitivity to omeprazole. There was one report of death in a 66 y/o male on omeprazole and several other medications for the treatment of underlying multiple medical problems including diabetes, hyperlipidemia, myocardial infarction, leg and back pain; the cause of death was attributed to a massive stroke. The rest of

the cases with SAEs were either due to a concomitant medication(s) taken, or to an underlying medical illness.

A review of the database for the first quarter of 2006 identified one case wherein omeprazole was a primary suspect drug when dosed at 20 mg per day for no longer than 2 weeks. A 75-year-old woman receiving 20 mg/day for one day reported anorexia, blood uric acid increased, dysgeusia, dysuria, increased eosinophil count, decreased hematocrit, decreased hemoglobin, interstitial nephritis, pollakiuria, polyuria, and rash. No further details were provided.

Medical Officer Comments: The postmarketing experience and the adverse reactions from case reports with the already approved omeprazole formulation do not reveal any new serious, unusual or significant safety concerns associated with the OTC use of omeprazole 20 mg.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The sponsor refers to FDA's finding of safety for both prescription and OTC omeprazole. There are no new safety issues identified in the pharmacokinetic studies conducted by the sponsor.

7.2.1.1 Study type and design/patient enumeration

In support of this NDA, the sponsor conducted bioequivalence study AA24171 under fasting conditions. This was a comparative, randomized, single-dose, two-way, crossover relative bioavailability study of Dexcel's Omeprazole Delayed-Release Tablets 20 mg and P&G/AZ omeprazole magnesium (Prilosec OTCTM) delayed release tablets 20.6 mg, equivalent to 20 mg omeprazole) in 76 healthy adults under fasting conditions. Study AA24171 will be the primarily discussed in this review.

Study 28531 was also conducted to detect the effect of food on the sponsor's proposed omeprazole product. This was a comparative, randomized, single-dose, two-way, crossover relative bioavailability study of Dexcel's 20 mg Omeprazole Delayed-Release Tablets in 18 healthy male adults under fasting and fed conditions.

7.2.1.2 Demographics

In study AA24171, the study population consisted of 76 subjects, 55% males and 45% females; 4% Black, 96% Caucasian; with a mean age of 37 years (range of 18-54 years) and mean weight of 69.3 kg (range of 45.9-94.5 kg). No subjects of Asian origin were included due to a higher possible exposure to the drug in this population (see Pharmacokinetic section). A demographic summary for all subjects for Study AA24171 is shown in the table below.

Table 10: Demographic Summary for All Subjects for Study AA24171

Trait		Female	Male	Overall
Gender	Female	.	.	34
	Male	.	.	42
Race	Black	.	3	3
	Caucasian	34	39	73
Frame Size	Small	7	9	16
	Medium	25	32	57
	Large	2	1	3
Age	Mean	37	36	37
	S.D.	10	10	10
	Minimum	18	18	18
	Maximum	51	54	54
	N	34	42	76
Weight (kg)	Mean	59.5	77.2	69.3
	S.D.	6.4	7.4	11.2
	Minimum	45.9	57.7	45.9
	Maximum	73.5	94.5	94.5
	N	34.0	42.0	76.0
Height (cm)	Mean	163	180	172
	S.D.	6	7	11
	Minimum	154	162	154
	Maximum	180	192	192
	N	34	42	76

Sponsor's submission Module 5 p. 409

7.2.1.3 Extent of exposure (dose/duration)

A total of 76 subjects received a single dose of each treatment, Dexcel's 20 mg Omeprazole Delayed Release Tablet, and P&G/AZ's Prilosec OTCTM Delayed Release Tablet, and all 76 subjects completed the fasting study. Subject no. 63 did not have a 0.5-hr blood draw in Period 1 due to difficulty with draw. A total of 18 subjects received two doses of Dexcel's Omeprazole Delayed Release Tablet 20 mg (under fasting and fed conditions) in Study 28531.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Postmarketing safety data is discussed in section 7.1.17 and safety data from published literature is discussed in section 8.6 of this review.

7.2.3 Adequacy of Overall Clinical Experience

Omeprazole has been proven safe and effective in the U.S. for over 16 years even at high doses (up to 120 mg three times a day); a 20 mg omeprazole tablet is available for over-the-counter use for the treatment of frequent heartburn (occurring two or more days a week) for more than three years now. This drug has been marketed worldwide since 1988 and in the United States since

1989. Therefore, there is an adequate clinical experience with omeprazole for both prescription and OTC use.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There are no new animal studies submitted with this NDA.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing which included vital signs, physical exam, EKG, urinalysis and laboratory evaluation including hematology and chemistry were adequate for this pharmacokinetic study.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new information on metabolic, clearance and interaction was submitted with this NDA.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

This section is not applicable.

7.2.8 Assessment of Quality and Completeness of Data

A consult to the Division of Scientific Investigation was requested and the result of their evaluation is still pending at the time this review was written.

7.2.9 Additional Submissions, Including Safety Update

An amendment to the Safety Report was submitted on March 23, 2006 and September 1, 2006. A 120-day Safety Update was submitted on October 23, 2006 that covers the period from December 1, 2005 to June 18, 2006. There are no new safety issues identified in this reporting period.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Not applicable.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

No pooled data analyses were done by the sponsor. The sponsor submitted one PK study comparing Prilosec OTC™ delayed release tablet to their own omeprazole delayed release tablet formulation.

7.4.2 Explorations for Predictive Factors

No explorations for predictive factors were done by the sponsor.

7.4.3 Causality Determination

This section is not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor is seeking for the already approved OTC indications and dosing regimen for Omeprazole Delayed Release Tablet 20 mg. The proposed indication will be the treatment of frequent heartburn occurring two or more days a week in adults 18 years of age and older. The following are the product's uses and directions for use:

Uses

- treats frequent heartburn (occurs 2 or more days a week)
- not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect

Directions

- adults 18 years of age and older
- this product is to be used once a day (every 24 hours), every day for 14 days
- it may take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours

14-Day Course of Treatment

- swallow 1 tablet with a glass of water before eating in the morning
- take every day for 14 days
- do not take more than 1 tablet a day
- do not chew or crush the tablets

- do not crush tablets in food
- do not use for more than 14 days unless directed by your doctor

Repeated 14-Day Courses (if needed)

- you may repeat a 14-day course every 4 months
- do not take for more than 14 days or more often than every 4 months unless directed by a doctor
- children under 18 years of age: ask a doctor

8.2 Drug-Drug Interactions

No new drug-drug interactions were evaluated in this submission. The current prescribing information for omeprazole reflects the information described below.

Proton pump inhibitors (PPIs) inhibit the activity of some hepatic cytochrome P450 enzymes and therefore may decrease the clearance of benzodiazepines, warfarin, phenytoin, and many other drugs. There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in INR and prothrombin time.

Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P450 system (eg, cyclosporine, disulfiram, and benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole. Concomitant administration of omeprazole has been reported to reduce the plasma levels of atazanavir, and may increase the serum levels of tacrolimus.

Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (eg, ketoconazole, ampicillin esters, and iron salts). Co-administration of omeprazole and clarithromycin has resulted in increases of plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin.

The current OTC label for omeprazole directs consumers to consult a doctor or pharmacist before use if taking the following drugs:

- warfarin (blood-thinning medicine)
- prescription antifungal or anti-yeast medicines
- diazepam (anxiety medicine)
- digoxin (heart medicine)

8.3 Special Populations

No new information regarding other patient populations was submitted with this NDA. The pharmacokinetic studies did not perform any analyses by ethnic group. The subjects predominantly comprised of Caucasians (96%); with few (4%) Black subjects.

Pregnancy Use

This application has no new information on the OTC use of omeprazole regarding pregnant women that warrants a change in the labeling for OTC use. Omeprazole is currently listed as Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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

Race

In pharmacokinetic studies of single 20 mg omeprazole doses, an increase in AUC of approximately four-fold was noted in Asian subjects compared to Caucasians. Dose adjustment, particularly for the maintenance of healing esophagitis should be considered.

8.4 Pediatrics

Pediatric patients were not evaluated in this NDA. No data were submitted by the sponsor regarding this population for the proposed indication. The sponsor is requesting a waiver to conduct pediatric studies; this request should be granted. The safety and effectiveness of omeprazole for OTC use for the indication of frequent heartburn have not been established for pediatric patients (<18 years old); therefore, omeprazole is not labeled for OTC use in children. For patients less than 18 years old, it would be more appropriate to use omeprazole under the supervision of a physician for proper diagnosis and treatment.

The safety and effectiveness of omeprazole have been established for prescription use in the age group 2 years to 16 years for the treatment of acid-related gastrointestinal diseases, including the treatment of symptomatic GERD, treatment of erosive esophagitis, and the maintenance of healing of erosive esophagitis. The safety and effectiveness of omeprazole have not been established for pediatric patients less than 2 years of age. Use of omeprazole in the age group 2

years to 16 years is supported by evidence from adequate and well-controlled studies of omeprazole in adults with additional clinical, pharmacokinetic, and safety studies performed in pediatric patients.

8.5 Advisory Committee Meeting

This section is not applicable.

8.6 Literature Review

Worldwide Literature on Safety of Omeprazole

A review of the ADISNEWS, MedLine and Embase literature databases was conducted by the sponsor from January 2002 to June 2006.

Below is a review of the literature from January 2002 to December 2005 on published case reports that identified an adverse event in a patient receiving omeprazole.

A summary of the case reports in patients receiving omeprazole included:

- Lack of effect in a patient with CYP2C19 extensive metabolizer polymorphism treated with omeprazole 40 mg OD for 6 weeks (8)
- Rhabdomyolysis in a 56 y/o male administered with IV omeprazole 20 mg BID for 5 days (10)
- Hyponatremia in a 43 y/o female with weakness, nausea, feeling twitchy after receiving third dose of omeprazole 20 mg BID (reported as serious) (9)
- Fever, vomiting, weight loss, severe abdominal pain, hyponatremia in a 64 y/o female after 4 months of treatment with omeprazole 40 mg/day (reported as serious) (16)
- Hyperkalemia in a 59 y/o male after 4 days of receiving IV omeprazole BID. (16)
- Acute hepatitis in a 15 y/o female 5 days after receiving IV omeprazole 40 mg/day for 2 days followed by 20 mg/day of orally. (5)
- Acute interstitial nephritis in a 66 y/o and 73 y/o female patients, treated with omeprazole 20 mg/day for 2 or 3 months (reported as serious). (18)
- Cough in a 42 y/o female the day after receiving omeprazole 20 mg/day. (19)
- Cutaneous leucocytoclastic vasculitis in a 71 y/o female after 4 weeks of receiving omeprazole 20 mg/day. (20)
- Cyanocobalamin deficiency in 3 patients on chronic omeprazole cases. (21)
- Iron deficiency anemia in a 49 y/o male receiving omeprazole 40 mg/day for 3 years. (22)
- Iron replacement therapy ineffective in 2 females, 51 and 83 y/o (1 case-omeprazole 20 mg/day, 1 case-dose not stated). (23)
- Drug Interactions:
 - Myopathy from omeprazole + methotrexate in a 13 y/o male on 20 mg/day of omeprazole (24)
 - Decreased atazanavir exposure when administered with omeprazole (25)

- Decreased clozapine concentrations-2 cases (40-60 mg/day mg/day) (26)
- Increased clozapine concentrations with/without seizures-3 cases, dose not stated. (27)

Medical Officer Comments: In majority of the cases listed, patients either received omeprazole at doses of >20mg/day (two cases received IV formulation) or treatment was administered for longer than the proposed duration of 14 days treatment, or both. Most of the adverse events listed from the case reports above are already reflected in the current prescribing information for omeprazole for which it is stated that in many instances, the relationship to omeprazole was unclear. The following case reports are not in the current list: rhabdomyolysis, hyperkalemia, cutaneous leucocytoclastic vasculitis, and drug reactions with clozapine and methotrexate. Additional information is needed in assessing the relationship of these adverse events to omeprazole treatment.

Clozapine, an atypical antipsychotic drug, is mainly metabolized by cytochrome P450 enzymes; the clozapine-omeprazole interaction can possibly be partly attributed to the pharmacokinetic interactions associated with cytochrome P450 enzymes during drug metabolism. It is known that there have been clinical reports of omeprazole interactions with other drugs metabolized via the cytochrome P450 system. Additional information is needed in assessing the relationship of this drug-drug interaction. Drug interaction with concomitant administration of omeprazole with atazanavir and tacrolimus has been incorporated in the prescribing information for omeprazole.

The proposed dose in this NDA is only 20 mg orally once a day for a shorter duration of treatment, i.e., 14 days for OTC use. With the exception of one case (cough in a 42 y/o female the day after receiving omeprazole 20 mg/day), none of the above serious adverse cases reported were related to the OTC regimen for omeprazole. Therefore, the above reported serious adverse events do not warrant a change in the labeling of omeprazole for the proposed indication and duration of use (14 days treatment).

There have been reports of cyanocobalamin (vitamin B₁₂) deficiency and iron deficiency anemia in patients who are on chronic acid suppression with proton-pump inhibitors such as chronically ill (especially pediatrics) patients, and the elderly with poor dietary intake.

Medical Officer Comments: This is already addressed in the Drug Interactions section of the prescribing information for omeprazole which states, "Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability...". This is more of a concern in patients who are receiving prescription omeprazole for chronic acid-suppression. The use of omeprazole OTC is limited for a duration of 14 days at a time and not more often than every 4 months (ie., 3x/year) unless directed by a doctor. Therefore, if omeprazole OTC is used according to the label, there should be no issues regarding cyanocobalamin or iron absorption.

The sponsor also included information regarding a study in pregnant women who took PPIs (omeprazole, lansoprazole and pantoprazole) for 3 weeks during the first trimester of pregnancy. Results of the study suggests that PPIs do not represent a major teratogenic risk in humans.⁵

Medical Officer Comment: The study is limited to the exposure to PPI during the first trimester of pregnancy and does not evaluate genetic or other anomalies. Additional information is needed before determining if omeprazole is indeed safe to use during pregnancy. This Medical Officer recommends the use of omeprazole during pregnancy under the supervision of a physician only if the potential benefit justifies the potential risk to the fetus. The proposed OTC label already directs pregnant women to consult a healthcare provider before use of the product.

A review of the literature from January 2002 to November 2005 for omeprazole 20 mg (within 2 weeks use) identified 3 events: myopathy (within 48 hours of rechallenge), cough, and hepatitis. The patients recovered upon discontinuation of the medication. See the Appendix section of this review for tabulated case reports. *Medical Officer Comments: These are already known adverse events for omeprazole. A review of the literature from December 2005 to June 2006 did not reveal any significant new toxicity associated with omeprazole.*

Overall, the adverse reactions from case reports and current literature did not reveal any new serious, unusual, significant or new safety concerns associated with the OTC use of omeprazole 20 mg for a duration of two weeks.

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan recommended for this NDA.

8.8 Other Relevant Materials

There are no other relevant materials submitted for the review.

9 OVERALL ASSESSMENT

9.1 Conclusions

A single dose of the sponsor's (Dexcel) Omeprazole Delayed Release Tablets 20 mg is considered to be bioequivalent to the single dose of the reference product, Prilosec OTC™ Delayed Release Tablets 20.6 mg (pending DSI inspection). Both treatments were well-tolerated, there were a few adverse events reported from the study which were consistent with the already known adverse events for omeprazole. There were neither deaths nor serious adverse events reported.

⁵ Diav-Citrin O, J Arnon, S Shechtman. The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study. *Aliment Pharmacol Ther* 2005; 21: 269-275.

The clinical experience with the already approved omeprazole for OTC use and the studies conducted by the sponsor do not identify any new safety concerns. From a clinical safety standpoint, this application should be approved.

9.2 Recommendation on Regulatory Action

From a clinical safety standpoint, Dexcel's proposed omeprazole 20 mg delayed release tablet indicated for the relief of frequent heartburn occurring two or more days a week for 14 days has an acceptable safety profile for OTC marketing and therefore should be approved. Final approvability depends on the adequacy of the bioequivalence study and DSI inspection.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No special risk management activities are recommended for this NDA.

9.3.2 Required Phase 4 Commitments

No required phase 4 commitments are recommended.

9.3.3 Other Phase 4 Requests

No other phase 4 requests are recommended.

9.4 Labeling Review

Below are the sponsor's proposed labels and product insert. A member of the Interdisciplinary Scientist (IDS) group in the Division of Nonprescription Regulation Development (DNRD) will be reviewing the proposed label. The sponsor is proposing a label and a package insert which are very similar to the already approved Prilosec OTC TM label (including the Drug Facts, Uses, Warnings, and Directions). Both the proposed label and the package insert are acceptable from a clinical perspective.

Below are the sponsor's proposed carton labels and package insert:

4 Page(s) Withheld

 Trade Secret / Confidential (b4)

 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

9.5 Comments to Applicant

None.

10 APPENDICES

Below are tabulated cases identified in the literature from January 2002 to November 2005 for omeprazole 20 mg daily.

Table A-1: Cases identified in the Literature from January 2002 to November 2005 for Omeprazole 20 mg daily.

CASE REPORTS FROM LITERATURE SEARCH (JANUARY 2002 TO NOVEMBER 2005) OMEPRAZOLE 20 MG DAILY							
Literature reference no.	Age (yrs)	Gender	Dose Frequency	Duration until AE onset	AE description	Outcome	Comments
Country							
6 France	13	Male	20 mg daily p.o.	Within one month and 48 hours after rechallenge	Painful myopathy	Recovered 72 hours upon discontinuation	Patient was rechallenged and re-occurred; possibly due to drug interaction with methotrexate. Patient had ALL and on methotrexate, purinethol, and sulfamethoxazole/trimethoprim. Muscle cramps, muscle weakness, myalgia, and leg pain listed in label.
10, 11 France	42	Female	20 mg daily p.o.	1 day	Chronic cough	Recovered upon discontinuation	Omeprazole was continued for 4 months before being discontinued; Cough is listed in label.
27, 28 USA	51	Female	20 mg daily p.o.	6 months	Decreased iron absorption	Recovered upon discontinuation	Drug interaction – interfered with absorption of ferrous sulfate in iron-deficient individuals. Mentioned in the label.
27, 28 USA	83	Female	unknown	6 months	Decreased iron absorption	Recovered upon discontinuation	Drug interaction – interfered with absorption of ferrous sulfate in iron-deficient individuals. Mentioned in the label.
35, 36 New Zealand	66	Female	20 mg daily p.o.	3 months	Interstitial nephritis	Discontinued omeprazole, and recovered in 3 months	Treated with reducing course of prednisolone. Serious. Listed in label.

Literature reference no.	Age (yrs)	Gender	Dose Frequency	Duration until AE onset	AE description	Outcome	Comments
Country 35, 36 New Zealand	73	Female	20 mg daily p.o.	2 months	Interstitial nephritis	Discontinued omeprazole and valproic acid and after 3 months had residual renal impairment	Treated with prednisolone for 3 months Serious Listed in label
44, 45 Israel	71	Female	20 mg daily p.o.	4 weeks	Cutaneous leucocytoclastic vasculitis	Recovered a few days after discontinuation	Patient was also on budesonide and amiodarone Serious Severe skin reactions listed but not this one in particular
73, 74 United Kingdom	15	Female	40 mg intravenous for 2 days then 20 mg daily p.o.	iv- 2 days; po - 3 days	Hepatitis	Recovered 6 days after discontinuation	Patient had mild jaundice, elevated liver function tests, and prolonged prothrombin time Listed in label

10.1 Review of Individual Study Reports

Not applicable.

10.2 Line-by-Line Labeling Review

See labeling review by the Interdisciplinary Scientist from the Division of Nonprescription Regulation Development (DNRD).

10.3 References

1. Clinical Pharmacology Online (<http://cpip.gsm.com/>)
2. Confino-Cohen R, Goldberg A. Anaphylaxis to omeprazole: diagnosis and desensitization protocol. *Annals of Allergy, Asthma & Immunology*, (2006 Jan) Vol. 96, No. 1 pp. 33-6.
3. Diav-Citrin O, Arnon J, Shechtman S, et al. The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study. *Aliment Pharmacol Ther*. 2005 Feb 1; 21(3): 269-75.
4. El-Matary W, Dalzell M. Omeprazole-induced hepatitis. *Pediatr Emerg Care*. 2005 Aug; 21(8): 529-30.
5. Gibbons TE, Gold BD. The use of proton pump inhibitors in children: a comprehensive review. *Paediatr Drugs* 2003; 5(1): 25-40.
6. Gold BD, Freston JW. Gastroesophageal reflux in children: pathogenesis, prevalence, diagnosis, and role of proton pump inhibitors in treatment. *Paediatr Drugs* 2002; 4(10): 673-85.

7. Kinoshita Y, Kobayashi T, Kato M, et al., The pharmacodynamic effect of omeprazole 10 mg and 20 mg once daily in patients with nonerosive reflux disease in Japan. *J Gastroenterol.* 2006 Jun; 41(6): 554-61.
8. Lay C-S, Lai Y-L, Lin J-R. Effect of omeprazole in one patient with peptic ulcer. *Mid-Taiwan Journal of Medicine* 2005, Vol. 10, No.2, pp. 107-111.
9. Morton, A, Mackintosh, J. Severe hyponatraemia associated with omeprazole. *Australian Prescriber* 2005, Vol. 28, p. 48-49.
10. Nozaki M, Suzuki T, Hirano, M. Rhabdomyolysis associated with omeprazole. *Journal of Gastroenterology*, (2004), Vol. 39, p.86.
11. Ohkusa T, Maekawa T, Arakawa T, Nakajima M, et.al., Effect of CYP2C19 polymorphism on the safety and efficacy of omeprazole in Japanese patients with recurrent reflux oesophagitis. *Aliment Pharmacol Ther.* 2005 Jun 1; 21(11): 1331-9.
12. Pascual J, Marcen R, Orea O E, et al. Interaction between Omeprazole and tacrolimus in renal allograft recipients; a clinical-analytical study. *Transplantation proceedings* (2005 Nov) 37 (9) 3752-3.
13. Reilly JP. Safety profile of the proton-pump inhibitors. *Am J Health Syst Pharm.* 1999 Dec 1; 56 (23 Suppl 4):S11-7.
14. Sinues B, Fanlo A, Bernal ML, et.al. Omeprazole treatment: genotoxicity biomarkers, and potential to induce CYP1A2 activity in humans. *Hum Exp Toxicol.* 2004 Mar; 23(3): 107-13.
15. Torregrosa E, Rovira RE, Calvo C, et.al. Acute interstitial nephritis associated with omeprazole therapy *Nefrologia* 2004; 24 Suppl 3:61-3.
16. Colls B, Menzies O. Hyponatraemia, fever, vomiting, severe abdominal pain, and weight loss associated with omeprazole. *New Zealand Medical Journal* 2005, Vol. 118, pp. 1-3.
17. Tashiro M, Yoshikawa I, Kume, K, et al. Acute hyperkalemia associated with intravenous omeprazole therapy. *American Journal of Gastroenterology* 2003, Vol. 98, pp. 1209-1210.
18. Delve P, Lau, M Yun, K, et al. Omeprazole-induced acute interstitial nephritis. *New Zealand Medical Journal* 2003, Vol. 116.
19. Howaizi M, Delafosse C. Omeprazole-induced intractable cough. *Annals of Pharmacotherapy* 2003, Vol. 37, pp.1607-1609.

20. Odeh M, Lurie M, Oliven A. Cutaneous leucocytoclastic vasculitis associated with omeprazole. *Postgraduate Medical Journal* 2002, Vol. 78, pp.114-115.
21. Andres E, Noel E, Abdelghani MB. Vitamin B(12) deficiency associated with chronic acid suppression therapy. *Annals of Pharmacotherapy* 2003, Vol. 37, p. 1730.
22. Khatib MA, Rahim O, et al. Iron deficiency anemia: induced by long-term ingestion of omeprazole. *Digestive Diseases and Sciences*, (2002), Vol. 47, pp. 2596-2597.
23. Sharma VR, Brannon MA, Carloss EA. Effect of omeprazole on oral iron replacement in patients with iron deficiency anemia. *Southern Medical Journal*, (2004), Vol. 97, pp. 887-889.
24. Natali F, Martin G, Zagnoli F, et al. Painful myopathy induced by omeprazole-methotrexate combination. *Douleurs* (2004) Vol. 5, No.3, pp. 128-131.
25. ADR news: Coadministration of omeprazole reduces atazanavir exposure levels. *REACTIONS* 12 Jan 2005.
26. Frick A, Kopitz J, Bergemann N. Omeprazole reduces clozapine plasma concentrations: a case report. *Pharmacopsychiatry* (2003), Vol 36, p. 121-123.
27. *Reactions Weekly: Volume (923)* 12 October 2002 p. 7
28. Prilosec OTC Product Monograph for Healthcare Professionals
(www.prilosecotc.com/hcp/tools2.jsp)

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

/s/

Lolita Lopez
11/9/2006 10:36:45 AM
MEDICAL OFFICER

Daiva Shetty
11/9/2006 02:59:23 PM
MEDICAL OFFICER