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RESEARCH**

*APPLICATION NUMBER:*  
**22-032**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

<b>NDA #:</b> 22-032	<b>Submission Date(s):</b> 04/04/2007
<b>Brand Name</b>	Omeprazole Delayed-Release Tablets
<b>Generic Name</b>	Omeprazole
<b>Reviewer</b>	Abimbola Adebowale, Ph.D.
<b>Team Leader</b>	Sue-Chih Lee, Ph.D.
<b>OCP Division</b>	Division of Clinical Pharmacology 3
<b>OND division</b>	Office of Nonprescription Products (ONP)
<b>Sponsor</b>	Dexcel Pharma Technologies Limited, Israel
<b>Submission Type; Code</b>	Amendment to a Pending Application; Standard
<b>Formulation; Strength(s)</b>	Delayed-Release Tablets; 20 mg
<b>Indication</b>	Treatment of frequent heartburns occurring 2 or more days a week

**Executive Summary**

This amendment is in response to the following comment included in the approvable letter (dated 12/18/2006) sent to the applicant.

“We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

1. During a recent inspection of one \_\_\_\_\_ facility for this application, our field investigator issued a 483 Notice of Findings to the facility’s representative. Satisfactory resolution of these deficiencies is required before this application may be approved.”

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The deficiency in the 483 Notice of findings issued by DSI was as follows:

DSI Recommendation (see DSI review for more details):

— failed to justify the exclusion of omeprazole concentration results from analytical batch 12DAU (Item 1 below). Thus, the original results for subjects 30-32 from batch 12DAU in Study AA24171 (fasting) should have been used for the bioequivalence determination. We recommend that the biopharmaceutics reviewer evaluate the impact of using the original concentration results for these subjects on the study outcome.

b(4)

**Item 1 was as follows:** The results from the original run (batch 12DAU) for subjects 30-32 in Study AA24171 were not reported although the run met the acceptance criteria. The firm’s investigation fails to justify the exclusion of the entire results from the original run. There was no SOP in place to address this issue.

**Information included in this submission:**

Prior to the Agency issuing the approvable letter (12/18/06), the applicant submitted an FDA 483 response (12/6/2007) that included a summary table of the results of the bioequivalence assessment comparing the results previously submitted (i.e. based on re-assayed samples for subjects 30-32 from batch 12 DAU) and, the results obtained with the original concentrations for subjects 30-32 from batch 12DAU. A copy of this summary table is included in the Appendix (entitled "Supportive Documentation"). The applicant was unable to provide more detailed analysis results that supported this summary table before the action due date.

In this submission, the applicant has included the pharmacokinetics and statistical data (A copy of this is included in the Appendix) that supports the summary table submitted in the FDA 483 response dated 12/6/2007.

**Review Comments:** The results from the original run (batch 12DAU) for subjects 30-32 were provided. The results of the bioequivalence determination obtained using this data was also provided. The results demonstrated that the use of the original plasma concentration for subjects 30-32 from analytical batch 12 DAU in Study AA24171 did not have any impact on the final bioequivalence conclusions. Basically, this data also demonstrated that omeprazole DR tablets, 20 mg were bioequivalent (90 % CI for C<sub>max</sub> and AUC were within the acceptance criteria of 80-125 %) to Prilosec, OTC 20 mg tablets.

**Recommendations:**

The clinical pharmacology and biopharmaceutics information included in this submission is acceptable.

Reviewer: \_\_\_\_\_

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Senior Clinical Pharmacology Reviewer  
Division of Clinical Pharmacology 3  
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Team leader: \_\_\_\_\_

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Appendix

Supportive Documentation

Project No. : AA24171

b(4)

Analytes : Omeprazole

Issue: PK evaluation with concentration data from a rejected batch (Batch 12DAU).

Comment:

Pharmacokinetic and statistical analyses were performed with concentration data from a rejected batch (Batch 12DAU). The results of the bioequivalence assessment for omeprazole in plasma are presented in the tables below.

Ratios of Least-Squares Means (90% Confidence Intervals)

	Original Results
PK Parameter	Dexcel Ltd. (A) vs. P&G/AstraZeneca (B)
AUC 0-t	102.9% (99.0% – 107.0%)
AUCinf	104.2% (100.3% – 108.3%)
Cmax	99.8% (93.0% – 107.1%)

	Results with concentration data including Batch 12DAU
PK Parameter	Dexcel Ltd. (A) vs. P&G/AstraZeneca (B)
AUC 0-t	102.8% (98.9 – 106.9%)
AUCinf	104.5% (100.5 – 108.7%)
Cmax	100.4% (93.6 – 107.9%)

Bioequivalence conclusions for the Dexcel Ltd. study, — Project No. AA24171) remained unchanged when performing the pharmacokinetic and statistical analyses including the concentration data from Batch 12DAU.

b(4)

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Summary of analysis results using the original concentrations for subjects 30-32 from batch 12DAU

Table 1  
 Project No: AA24171  
 Summary of Results - Omeprazole in Plasma  
 Pharmacokinetic Parameters  
 (N = 72)

	ln AUC 0-t* (ng·h/mL)	ln AUCinf* (ng·h/mL)	ln Cmax* (ng/mL)	tmax (h)	Half-Life (h)	kel (1/h)
<b>Dexcel Ltd. (A)</b>						
Mean	440.381	449.415	313.3231	2.383	0.7258461	1.1058452
CV	93.5	95.3	69.3	44.8	47.4	33.0
n	72	69	72	72	69	69
<b>PfG/AstraZeneca (B)</b>						
Mean	428.319	438.722	311.9251	2.154	0.7323393	1.0860760
CV	99.5	100.4	74.2	44.2	45.3	32.5
n	72	70	72	72	70	70
<b>Least-Squares Means</b>						
Dexcel Ltd. (A)	440.381	452.051	313.3231			
PfG/AstraZeneca (B)	428.319	432.439	311.9251			
<b>Ratio of Least-Squares Means (A/B)X</b>						
	102.8	104.5	100.4			
<b>90% Confidence Intervals (A/B)X</b>						
lower limit:	98.9%	100.5%	95.6%			
upper limit:	106.9%	108.7%	107.9%			
<b>p-Value (ANOVA)</b>						
A vs B	0.2390	0.0621	0.9168			

\* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.  
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/s/

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Abi Adebawale  
6/1/2007 09:07:26 AM  
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Sue Chih Lee  
6/1/2007 10:07:01 AM  
BIOPHARMACEUTICS

## Clinical Pharmacology Review

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<b>NDA Number</b>	22-032
<b>Letter Date(s)</b>	February 8 <sup>th</sup> , 2006, June 20 <sup>th</sup> , 2006 and September 1 <sup>st</sup> , 2006
<b>Brand Name (Proposed)</b>	Omeprazole Delayed-Release Tablets
<b>Generic Name</b>	Omeprazole Delayed-Release Tablets
<b>Reviewer</b>	Abimbola Adebowale Ph.D.
<b>Acting Team Leader</b>	Sue-Chih Lee Ph.D.
<b>OCPB Division</b>	Division of Clinical Pharmacology 3 (DCP3)
<b>OND Division</b>	Office of Nonprescription Products (ONP)
<b>Applicant</b>	Dexcel Pharma Technologies Ltd, Israel
<b>Related IND(s)</b>	63,799
<b>Submission Type; Code</b>	505 (b) (2); 5S
<b>Formulation,; Strength (s)</b>	Delayed-Release Tablets; 20 mg
<b>Pharmacological Class</b>	Proton Pump Inhibitor
<b>Indication</b>	Treatment of frequent heartburns occurring 2 or more days a week
<b>Reference Listed Drug (RLD)</b>	Prilosec, OTC <sup>TM</sup> (Omeprazole Magnesium Delayed-Release Tablet, 20.6 mg (equivalent to 20 mg Omeprazole )

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### 1 Executive Summary

This application is a 505 (b)(2) application for Omeprazole Delayed Release (DR) Tablets, 20 mg for over-the-counter (OTC) use in adults 18 years and older. The proposed dosing regimen is oral administration of one tablet per day for a 14-day course of treatment. The reference listed drug (RLD) for this application is approved (NDA 21-229, approved June 20<sup>th</sup>, 2003) Prilosec, OTC<sup>TM</sup> (omeprazole magnesium delayed release tablet, 20.6 mg, equivalent to 20 mg of omeprazole). The proposed indication and dosing regimen for omeprazole DR tablet, 20 mg is the same as that approved for Prilosec OTC<sup>TM</sup>. However, unlike Prilosec OTC, omeprazole DR, 20 mg tablets utilizes omeprazole base rather than omeprazole magnesium.

1.1 Recommendation (s):

The clinical pharmacology data demonstrated that Omeprazole delayed release tablet, 20 mg was bioequivalent to Prilosec, OTC, 20 mg Tablets (RLD). However, the final acceptability of this data is dependent on the results of the applicant's response to the deficiencies observed by the Division of Scientific Investigations (DSI) during the audit of the clinical and analytical sites. The DSI is still awaiting this response.

In a separate study, the administration of omeprazole delayed-release tablets with a high-fat meal resulted in a decrease in the rate and extent of absorption as compared to the fasted state. The applicant's labeling instructing patients to take the tablet before eating in the morning is consistent with that for the RLD. There were no DSI deficiencies associated with the data obtained from this study.

Therefore from a clinical pharmacology perspective, the bioequivalence data is not acceptable because the applicant has not provided an adequate complete response to the deficiencies reported in the FDA 483 audit report by DSI.

1.2 Phase IV Commitments: None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics (CPB) Findings:

In support of this application, the applicant conducted an in-vivo relative bioavailability study (AA24171) and a food effect study (AA28531). Both studies were conducted in healthy adult volunteers using an open-label, randomized, crossover study design. Both of these studies used the same formulation of the drug product as that proposed for marketing. A dissolution method with corresponding specifications was also proposed. A brief summary of the data is described below

Relative Bioavailability Study: The results of study # AA24171 indicated that omeprazole DR tablet, 20 mg were bioequivalent (90 % CI for Cmax and AUC were within the acceptance criteria of 80-125 %) to Prilosec, OTC 20 mg tablets following a single dose administration, to healthy subjects, in the fasted state. However, based on the DSI inspection results (see below), the sponsor will need to provide a re-analysis of the bioequivalence determination comparing the results of the original concentrations (run # 12) obtained for the three subjects (#'s 30-32) with that obtained for the repeat results (run # 27) that was included in this submission.

DSI Recommendation (see DSI review for more details):

*Failed to justify the exclusion of omeprazole concentration results from analytical batch 12DAU (Item 1 above). Thus, the original results for subjects 30-32 from batch 12DAU in Study AA24171 (fasting) should have been used for the bioequivalence determination. We recommend that the biopharmaceutics reviewer evaluate the impact of using the original concentration results for these subjects on the study outcome.*

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**Food Effect:** The results of study # AA28531 indicated that administration of omeprazole DR tablets with a high-fat meal resulted in a decrease in the rate and extent of absorption. The 90 % CI for Cmax and AUC were outside the acceptance criteria of 80 % to 125 %. The observed food effect is consistent with what was observed with the RLD and the same labeling (i.e. to be taken before meals in the morning) is being proposed for omeprazole delayed-release tablets.

**Dissolution Method and Specifications:** The proposed dissolution method and specifications are adequate to ensure in vivo performance of omeprazole DR tablets.

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Abimbola Adebawale, Ph.D.  
Clinical Pharmacology Reviewer  
Division of Clinical Pharmacology 3

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Sue-Chih Lee, Ph.D.  
Acting Team Leader  
Division of Clinical Pharmacology 3

## 2. QBR

### 2.1 General Attributes

Omeprazole is 5-methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole. The molecular formula is: C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S and the molecular weight is: 345.42. Omeprazole is a proton pump inhibitor. It is believed to suppress gastric acid secretion by specific inhibition of the H<sup>+</sup>/K<sup>+</sup> ATPase enzyme system at the secretory surface of the gastric parietal cell.

### 2.2 General Clinical Pharmacology

**Q. What were the design features of the clinical pharmacology and/or pivotal clinical studies used to support efficacy and safety?**

The applicant included two clinical pharmacology studies in this NDA. The design of the studies is reproduced in the table below:

Study #	Type of Study and the Objective of the Study	Study Design
AA24171	A relative bioavailability study to assess the single-dose relative bioavailability of Dexcel Ltd. 20 mg omeprazole DR tablets and Proctor & Gamble Co./Astra Zeneca LP (Prilosec OTC TM) 20.6 mg omeprazole magnesium DR tablets, under fasting conditions.	2-Way crossover study in 76 healthy subjects (42 males and 34 females).
AA28531	A food effect study to assess the effect of food on the bioavailability of Dexcel Ltd. 20 mg omeprazole DR tablets.	2-way crossover study in 18 healthy adult male subjects.

**Q. What are the Pharmacokinetic characteristics of Omeprazole DR Tablets?**

The single dose pharmacokinetics of omeprazole DR tablets obtained from Study # AA24171 and AA28531 under fasting conditions are reproduced in the table below:

PK Parameter	Mean (% CV) <sup>a</sup>	
	Study # 24171 (N=72) <sup>b</sup>	Study # AA28531 (N=17) <sup>c</sup>
AUC (0-t) ng*h/mL	440.34 (93.6)	514.83 (69.5)
AUC (inf) ng*h/mL	448.87 (94.5)	493.29 (71.3)
Cmax ng/mL	311.43 (70.0)	319.02 (60.2)
Tmax (h)	2.37 (45.3)	1.90 (46.8)
Half-life (t <sub>1/2</sub> ) (h)	0.73 (46.9)	1.0 (44.5)
Tlag (hrs)	Not Determined	1.5 (47.0)

<sup>a</sup>The antilog of the geometric mean is reported for AUC and Cmax and the arithmetic mean is reported for Tmax and half-life; <sup>b</sup> N=70 for AUCinf and half-life; <sup>c</sup> N=15 for AUCinf and half-life

**Q. What is the relative bioavailability of Omeprazole DR tablets compared to that of the RLD?**

The results of Study # AA 24171 indicated that omeprazole DR tablet is bioequivalent to Prilosec OTC™ DR tablet under fasting conditions. The 90% CI for the ratio of the geometric means of AUC 0-t, AUC inf and Cmax were within the bioequivalence acceptance criteria of 80-125 % (see table below).

**Table 11.4.3:1 Summary of Pharmacokinetic Results for Omeprazole**

Parameter	Dexcel Ltd. (A) vs. P&G AstraZeneca (B)
AUC 0-t	102.9% (99.0% – 107.0%)
AUCinf	104.2% (100.3% – 108.3%)
Cmax	99.8% (93.0% – 107.1%)

In addition, the mean (% CV) for the Tmax values obtained for Dexcel Ltd. and Prilosec™, OTC were similar (2.37 (45.3) hrs and 2.15 (44.2) hours, respectively).

*Reviewer's Comments: Based on the results of the DSI inspection with regards to the lack of justification for using the re-assayed repeat results instead of the original concentrations for three subjects for the bioequivalence determination, these results are inconclusive. The acceptability of this data is dependent on the outcome of the applicant's re-analysis of the data to determine the impact of using the re-assayed repeat results instead of the original concentrations for these three subjects.*

**2.3 Intrinsic Factors**

**Q. How does the systemic exposure change with differences in gender?**

**Gender:** The effect of gender on the pharmacokinetics of omeprazole following a single dose of omeprazole DR tablets and Prilosec OTC tablets was evaluated in 41 males and 31 female subjects (study # AA24171) under fasted conditions. Female subjects had both a higher rate and extent of absorption than males for both products and this was statistically significant ( $p < 0.05$ ). However, the omeprazole DR tablet was still bioequivalent to the Prilosec, OTC tablet regardless of the gender. Therefore the observed differences are unlikely to be clinically relevant provided the bioequivalence data are found to be acceptable.

Descriptive statistics of weight normalized AUC 0-t, AUCinf and Cmax values of omeprazole in male and female subjects are presented below for each Formulation.

Formulation	Gender	AUC 0-t (ng·h/mL per kg)			AUC inf (ng·h/mL per kg)			Cmax (ng/mL per kg)		
		Geometric			Geometric			Geometric		
		Mean	CV%	n	Mean	CV%	n	Mean	CV%	n
A	Males	5.090	94.6	41	5.187	96.0	40	3.421	64.7	41
	Females	8.693	96.9	31	8.810	98.4	30	6.576	72.2	31
B	Males	5.115	102.0	41	5.249	102.8	40	3.630	74.9	41
	Females	8.083	104.5	31	8.247	106.1	30	6.107	78.0	31

A: Dexcel Ltd; B: P&G/AstraZeneca

#### Summary of Pharmacokinetic Results for Omeprazole

Weight Normalized Parameter	Gender	Dexcel Ltd. (A) vs. P&G AstraZeneca (B)	P-value For Gender
AUC 0-t	Combined	102.9% (99.0% – 107.0%)	0.0200
	Male	99.3% (94.1% – 104.7%)	NA
	Female	108.4% (102.2% – 114.9%)	NA
Cmax	Combined	99.8% (93.0% – 107.1%)	0.0004
	Male	93.7% (85.2% – 103.1%)	NA
	Female	108.4% (97.4% – 120.6%)	NA
AUCinf *	Combined	105.0% (101.1% – 109.1%)	0.0211
	Male	100.2% (95.0% – 105.6%)	NA
	Female	110.7% (104.6% – 117.2%)	NA

\*Combined results, including the statistically significant interaction formulation\*gender

#### 2.4 Extrinsic Factors:

**Q.** *How does the systemic exposure change in the presence of foods?*

See food-effect study in Section 2.5.

#### 2.5 General Biopharmaceutics:

**Drug Product Composition:**

**Qualitative and Quantitative Composition for Omeprazole Delayed Released Tablets,  
20mg OTC**

Ingredients	Pharmaceutical Function	Amount mg/tablet	Percent/Tablet
b(4)			

**Q. What is the effect of food on the bioavailability (BA) of the drug from the dosage form?**

Food significantly affects the bioavailability of Omeprazole DR 20 mg tablets. The results of the food effect study (# AA28531) indicated that the rate and extent of absorption were decreased. The AUC 0-t and AUC inf were decreased by approximately 28.5 % and 23.8 %, respectively, under fed conditions. There was also a relatively small decrease (~1.5 %) in Cmax observed. However, the proposed product was not bioequivalent to the RLD in terms of Cmax because the 90% CI for the Cmax geometric mean ratio was not contained in the equivalence limits of 80-125% as shown in the table below:

Pharmacokinetic Parameter	Fed (A) vs. Fasting (B) Geometric Mean Ratio (90 % CI) <sup>a</sup>
AUC 0-t	71.5 % (58.2 % - 87.8 %)
AUC inf	76.2 % (60.8 % - 95.9 %)
Cmax	98.5 % (74.5 % - 130.4 %)

In addition Tmax was found to be delayed by approximately 4 hours in the fed state. The median (range) Tmax values for the fed and fasted states were 5.5 h (2.00-23.50 h) and 1.5 (0.75-4.50 h), respectively. Therefore the applicant proposed labeling the product to be taken before meals in the morning.

*Reviewer's Comments:*

This proposed labeling is acceptable and it is also consistent with what is currently in the label of the Prilosec OTC, the RLD. It should be noted that for the RLD the proposed label by OCP was for the Prilosec OTC. However, in the pivotal clinical studies for Prilosec OTC, the drug was to be taken before breakfast. Therefore the final label on the administration of Prilosec OTC with meals was consistent with how it was administered in the pivotal clinical trials.

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**Q. How do the dissolution conditions and specifications proposed ensure in vivo performance of the drug product?**

The dissolution data and specification proposed are adequate to ensure the in vivo performance of the product. The dissolution conditions and specifications proposed by the sponsor are as follows:

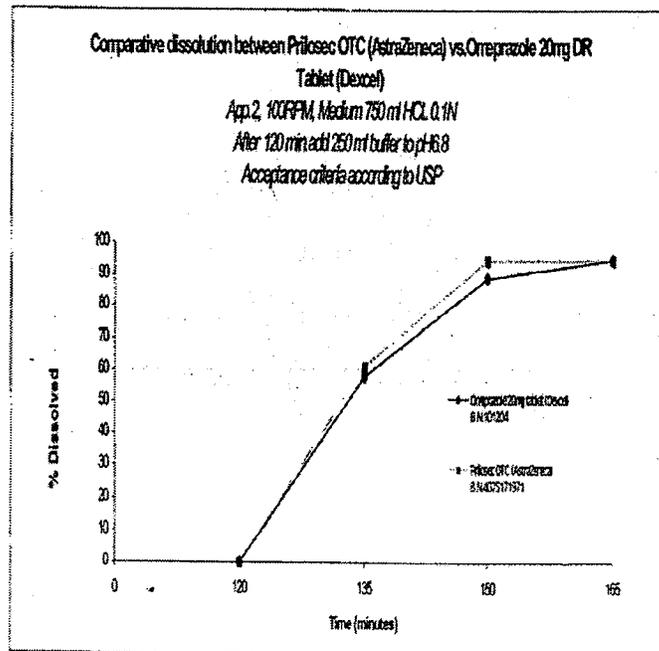
**Apparatus:** USP Apparatus 2 (paddles),  
**Agitation Speed:** 100 rpm  
**Medium:** *Acid Stage:* 750 ml, 0.1N HCl. *Buffer Stage:* (After 2 hours, add 250 ml of 0.2M Na<sub>3</sub>PO<sub>4</sub> solution, previously equilibrated to 37° C to the medium and adjust if necessary with 2M NaOH or 2N HCl to pH 6.8) 37° C +/- 5° C

**Specification:** NLT — (Q) of the labeled amount of omeprazole is dissolved in 30 min. (150 min total time). The quantity, Q, is the total amount of active ingredient dissolved in both the Acid and Buffer Stages, expressed as a percentage of the labeled content.

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Inserted below are the mean comparative dissolution data for omeprazole DR tablets and Prilosec, OTC tablets using the proposed method

Omeprazole 20mg		
Method: App. 2, 100 RPM, Medium: 750ml HCl 0.1N		
After 120 min. add 250ml buffer to pH 6.8, acceptance criteria according to USP		
Time (minutes)	Omeprazole 20mg DR tablet (Dexcel) B.N. 101204	Prilosec OTC (AstraZeneca) B.N. 4075171971
0	0	0
120	0	0
135	58	61
150	99	95
165	95	95



*Reviewer's Comments:*

- *The mean dissolution profiles of both the Omeprazole 20 mg Delayed Release tablets and Prilosec OTC tablets (RLD) are similar to each other, almost superimposable.*
- *Both products also meet the dissolution specifications proposed by the applicant.*
- *The data in both the graph and table above indicate that the dissolution method and specification is appropriate to ensure in vivo performance.*
- *However, the dissolution specifications may not be discriminating enough to ensure batch to batch product quality (Please see chemistry review for further details). Following discussions with the chemistry reviewer it was decided that this may not be a concern since this would not affect the in vivo performance of the product. In addition, the specification approved for Prilosec, OTC using a similar dissolution method was somewhat similar (Q was less by —) to that proposed for Omeprazole DR tablets.*

b(4)

**2.6 Analytical**

**Q. Were the analytical methods used for the determination of omeprazole in biological fluids adequately validated?**

Yes they were as shown in the table below:

<b>Method</b>	HPLC with Mass Spectrometric Detection
<b>Compound</b>	Omeprazole
<b>Internal Standard</b>	—
<b>Matrix</b>	Plasma
<b>Accuracy (% Theoretical)</b>	89.5 % to 103.5 %
<b>Within-Day</b>	91.4 % to 103.5 %
<b>Between-Day</b>	
<b>Precision (% CV)</b>	
<b>Within-Day</b>	2.5 % to 5.4 %
<b>Between-Day</b>	2.8 % to 5.9 %
<b>Standard curve range</b>	2.00 ng/mL to 2000 ng/mL ( $R^2 > 0.99$ )
<b>Sensitivity (LOQ)</b>	2.00 ng/mL (% CV= 5.9 % for n = 18)
<b>Selectivity</b>	N significant interference from endogenous components was observed at the retention time of Omeprazole.
<b>Recovery</b>	98.2 % to 104.7 %
<b>Stability</b>	< 13.2 % degradation was observed following long term storage @ -20° C for 290 days, 4 freeze-thaw cycles (-20° C) and ambient temperature for 99.5 hours.
<b>Conclusion</b>	Method validation is acceptable.

b(4)

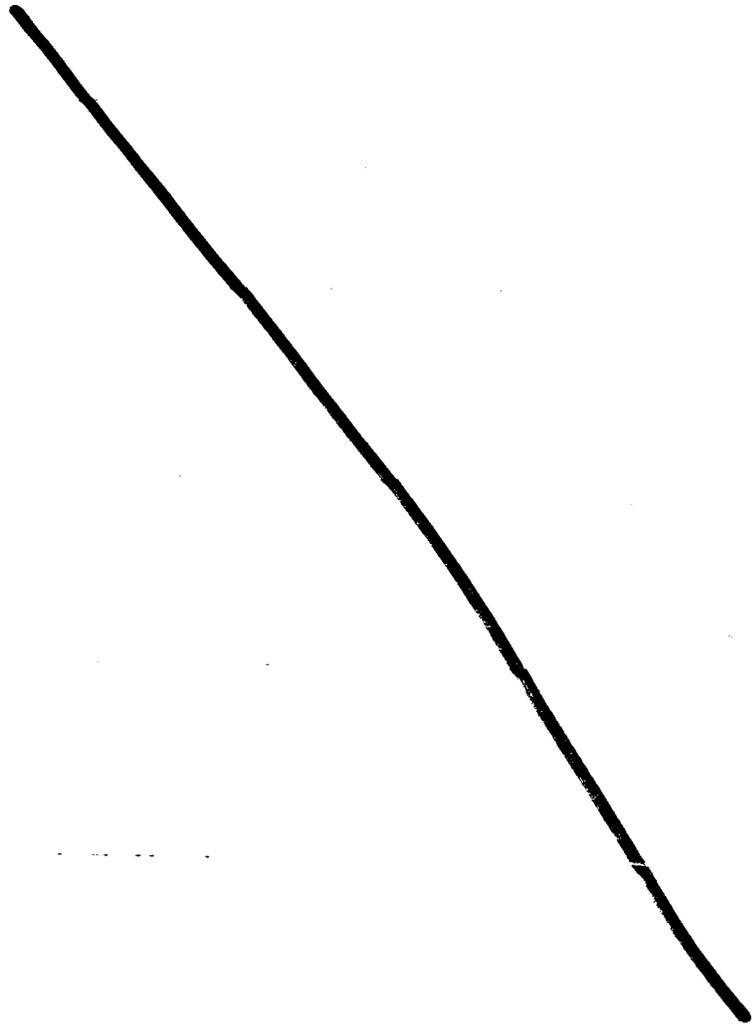
**3 Labeling Recommendations:**

There are no labeling recommendations.

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**Appendix**

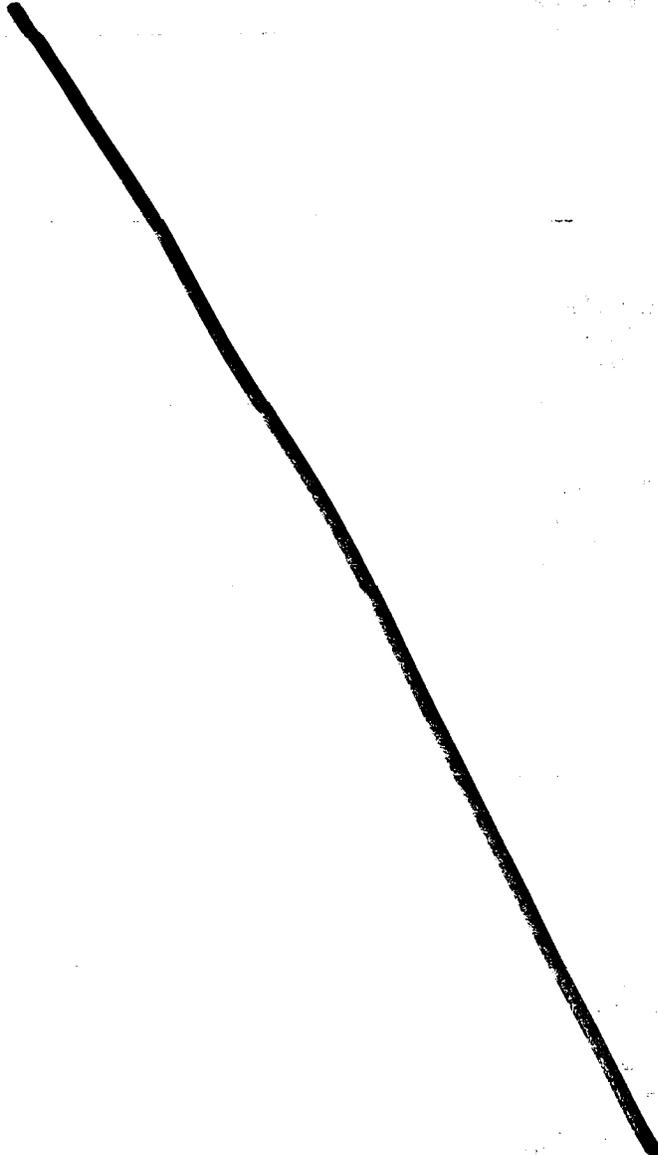
- 4.1 Pharmacometrics Consult: None required since there was no PK/PD or POPPK data submitted.
- 4.2 Proposed Package Insert:



b(4)



✓



b(4)

✓

4.3 Individual Study Reviews:  
SYNOPSIS: Study # AA24171

**Title:** Comparative, Randomized, Single-Dose, 2-way, Crossover Bioavailability Study of Dexcel Ltd. 20 mg Omeprazole Delayed-Release Tablets and Procter & Gamble Co./AstraZeneca LP (Prilosec OTC™) 20.6 mg Omeprazole Magnesium Delayed-Release Tablets (equivalent to 20 mg omeprazole) in Healthy Adult Volunteers under Fasting Conditions

**Objective:** The objective of this study was to assess the single-dose relative bioavailability of Dexcel Ltd. 20 mg omeprazole delayed-release tablets and Procter & Gamble Co./AstraZeneca LP (Prilosec OTC™) 20.6 mg omeprazole magnesium delayed-release tablets (equivalent to 20 mg omeprazole), under fasting conditions.

**Study Site:** \_\_\_\_\_

**Study Dates:** May 25<sup>th</sup>, 2005 to June 6<sup>th</sup>, 2005

**Study Design:** This was an open-label, randomized, single-dose, 2-way crossover relative bioavailability study performed on 72 healthy adult volunteers and 4 alternates (42 males and 34 females). Subjects were divided into two groups for dosing:

Group 1 (Subject Nos. 1 - 36, with alternate Subject Nos, 37 and 38) and Group 2 (Subject Nos. 39 - 74, with alternate Subject Nos, 75 and 76). All 76 subjects completed the clinical phase of the study. In each period, subjects were housed from at least 10 hours before dosing until after the 12-hour blood draw. Single oral doses (20 mg dose of omeprazole (batch # B0415) or 20.6 mg dose of omeprazole magnesium (equivalent to 20 mg of omeprazole) (batch # 4344171971) taken with 240 mLs of water were separated by a washout period of at least 7 days.

**Pharmacokinetic Sampling:** Blood samples (1 x 3 mL) were collected in blood collection tubes containing EDTA at Hour 0 (predose) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.667, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 12 hours postdose. A total of 40 blood samples (120 mL) were drawn during the study for drug analysis.

**Analytical Method:** Omeprazole in plasma was analyzed using a validated LC/MS/MS method developed at \_\_\_\_\_ The analytical range was 2.01 to 2010 ng/mL.

**Pharmacokinetic and Statistical Analysis:** The AUC 0-t, AUCinf, AUC/AUCinf, Cmax, tmax, half-life and kel pharmacokinetic parameters were calculated for plasma omeprazole. Analyses of variance (ANOVA) were performed on the ln-transformed AUC 0-t, AUCinf, and Cmax. The ANOVA model included group, sequence, period nested within group, formulation, and formulation\*group interaction as fixed effects, and subject nested within group\*sequence as a random effect. If the formulation\*group interaction was not statistically significant, at a 5% level, the interaction term was dropped from the final model.

The ratios of least-squares means (LSM) were calculated using the exponentiation of the LSM from the analyses on the ln-transformed AUC 0-t, AUCinf and Cmax. The 90% confidence intervals for the ratios were derived by exponentiation of the confidence intervals obtained for the difference between formulation LSM resulting from the analyses on the ln-transformed pharmacokinetic parameters AUC 0-t, AUCinf and Cmax. Statistical and pharmacokinetic analyses were performed on data from a total of 72 subjects. Subject Nos. 2-37 from Group 1 and Subject Nos. 39-74 from Group 2.

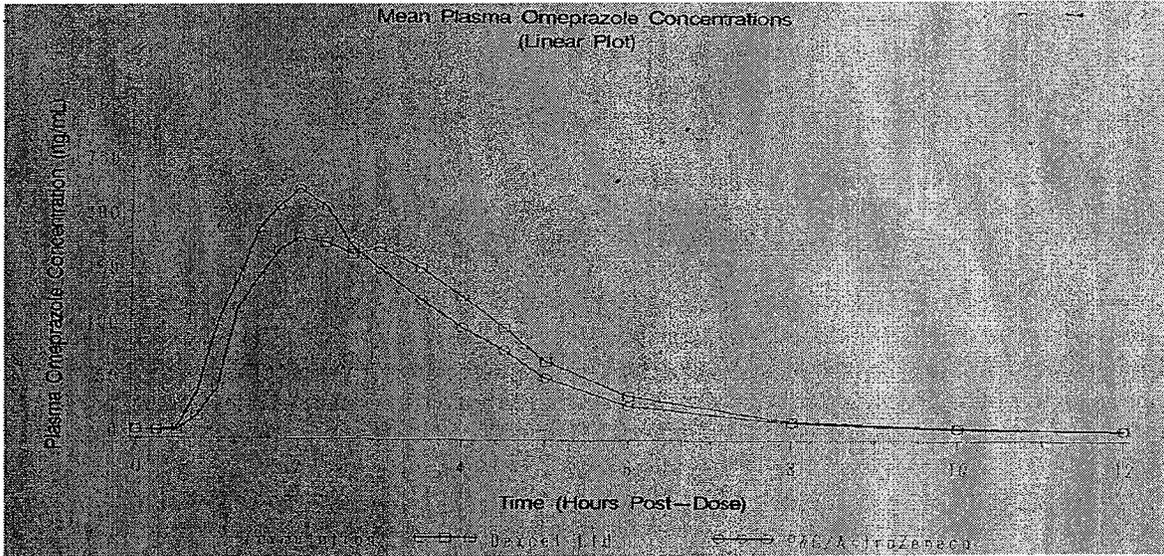
**Results:**

**Demographic Data:** A total of 76 subjects (42 males and 34 females) were dosed, and all 76 subjects completed the study. Subject 1 experienced emesis in both periods of the study and was replaced with alternate subject 37 prior to laboratory analyses. Subjects 38, 75 and 76 were alternate subjects and were not analyzed. The mean age of the subjects was 37 years (range of 18 - 54 years), the mean height of the subjects was 172 cm (range of 154 - 192 cm), and the mean weight of the subjects was 69.3 kg (range of 45.9 - 94.5 kg). There were 73 Caucasians and 3 Black subjects included in the study.

Plasma Concentration-Time Profiles:

b(4)

b(4)



**Pharmacokinetic Parameters:**

22-Aug-2005 12-22

Table 1  
Project No: AA24171  
Summary of Results - Omeprazole in Plasma  
Pharmacokinetic Parameters  
(N = 72)

	In AUC <sub>0-t*</sub> (ng·h/mL)	In AUC <sub>inf*</sub> (ng·h/mL)	In C <sub>max*</sub> (ng/mL)	Mean (h)	Half-life (h)	kel (1/h)
<b>Dexel Ltd (A)</b>						
Mean	440.34	449.97	311.4325	2.372	0.7269	1.1015
CV	95.6	94.5	70.1	45.3	48.9	32.9
n	72	70	72	72	70	70
<b>PMS/AstroZeneca (B)</b>						
Mean	427.97	438.42	312.0065	2.154	0.7352	1.0790
CV	95.8	100.5	74.1	44.2	44.9	32.4
n	72	70	72	72	70	70
<b>Least Squares Means</b>						
Dexel Ltd (A)	440.34	450.45	311.4325			
PMS/AstroZeneca (B)	427.97	432.13	312.0065			
<b>Ratio of Least Squares Means (A/B)</b>	102.9	104.2	99.8			
<b>90% Confidence Intervals (A/B)</b>						
Lower Limit:	93.0%	100.3%	93.0%			
Upper Limit:	107.6%	108.5%	107.1%			
<b>p-value (ANOVA)</b>						
A vs B	0.2241	0.0773	0.9658			
Period (Group)	0.9196	0.1171	0.5912			
Sequence	0.9483	0.5632	0.8256			
Group	0.6596	0.8920	0.3089			
<b>INTERSUBJECT CV</b>	14.0	13.5	25.9			

\*For Ln-transformed parameters, the antilog of the mean (i.e. geometric mean) is reported

Statistical Analysis:

**Table 11.4.3:1 Summary of Pharmacokinetic Results for Omeprazole**

Parameter	Dexcel Ltd. (A) vs. P&G AstraZeneca (B)
AUC 0-t	102.9% (99.0% – 107.0%)
AUCinf	104.2% (100.3% – 108.3%)
Cmax	99.8% (93.0% – 107.1%)

**Applicant's Conclusions**

The ratios of least-squares means and the 90% confidence intervals derived from the analyses of the In-transformed pharmacokinetic parameters AUC 0-t, AUCinf and Cmax for omeprazole in plasma were within 80-125%. Based on these results, the Dexcel Ltd. 20 mg omeprazole delayed-release tablet and Procter & Gamble/AstraZeneca LP (Prilosec OTC™) 20.6 mg omeprazole magnesium delayed-release tablet (equivalent to 20 mg omeprazole) have similar rate and extent of exposure under fasting conditions.

*Reviewer's Comments: See Analytical Method Validation section below for reasons why the acceptability of the applicant's conclusion is not acceptable at this time because of the pending applicant's response to a DSI audit.*

Gender Effect Analysis:

**Applicant's Conclusions:**

Although male and female subjects displayed statistically different In-transformed weight normalized AUC0-t, AUCinf and Cmax parameters, bioequivalence results of the test (Omeprazole DR tablets) and reference (Prilosec OTC) products in the male and female populations were consistent with those observed in the combined gender analysis since gender-specific ratios of LSM 90 % CIs were within the 80 % -125 % acceptance range. Based on the results of the current study (AA24171), the test product of omeprazole (Dexcel Ltd) was bioequivalent to the reference product (P&G/AstraZeneca) under fasting conditions regardless of the gender. This analysis supports the bioequivalence results of the other study performed in male subjects only (AA28531)

*Reviewer's Comments: The geometric mean values for both weight normalized AUCs in female subjects were approximately 1.7- and 1.6-fold higher than those observed in male subjects. Likewise, geometric mean values of weight normalized Cmax in female subjects were approximately 1.9- and 1.7- fold higher than those observed in male subjects. The half-life, Tmax and Kel for both genders were similar. Inter-subject variability of weight normalized PK parameters remained very high in the male and female populations for both formulations. However, the weight normalized parameters (AUC 0-t, AUC inf and Cmax) of omeprazole from Omeprazole DR tablets were found to be bioequivalent to the reference product in the male and female subjects, thus this difference may not be clinically relevant provided the bioequivalence data is found to be acceptable.*

**SYNOPSIS-Study # AA28531**

**Title:** Comparative, Randomized, Single-Dose, 2-Way Crossover Food Effect Bioavailability Study of Dexcel Ltd. 20 mg Omeprazole Delayed-Release Tablets in Healthy Adult Male Volunteers

**Objective:** The objective of this study was to assess the effect of food on the pharmacokinetics of omeprazole from Dexcel Ltd. 20 mg delayed-release tablet.

**Study Site:** \_\_\_\_\_

b(4)

**Study Dates:** September 24<sup>th</sup>, 2005 to October 3<sup>rd</sup>, 2005

**Study Design:** This was an open-label, randomized, single-dose, 2-way crossover, 2-sequence, food effect study performed on 18 healthy adult male volunteers.

In each period, subjects were housed from at least 10 hours before dosing until after the 24-hour post-dose blood draw. 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. Subjects randomized to Treatment A received a standard high-fat breakfast consisting of 2 slices of buttered toast, 2 fried eggs, 2 strips of bacon, 1 serving of hash brown potatoes, and 240 mL of whole milk, 30 minutes prior to dosing. Subjects randomized to Treatment B received a single oral dose of one omeprazole 20 mg delayed-release tablet taken with 240 mL of water under fasting conditions. There was a 7-day washout interval between the 2 dose administrations.

The applicant stated that the protocol design for this clinical study was approved by the FDA for IND 63,7991s-003. The FDA deemed that the protocol design and study endpoints were adequate to assess the effect of food on the pharmacokinetics of omeprazole from Dexcel Ltd. 20 mg delayed-release tablet.

*Reviewer's Comments:* In the FDA telecom minutes of October 10<sup>th</sup>, 2005, the Agency stated that "the proposed food-effect protocol is adequately designed to meet the study endpoints".

**Pharmacokinetic Sampling:** Blood samples (1 x 3 mL) were collected in blood collection tubes containing EDTA at Hour 0 (predose) and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5 and 24 hours postdose. A total of 100 blood samples (300 mL) were drawn during the study for drug analysis.

**Analytical Method:** Omeprazole in plasma was analyzed using a validated LC/MS/MS method developed at \_\_\_\_\_ The analytical range was 2.01 to 2010 ng/mL.

b(4)

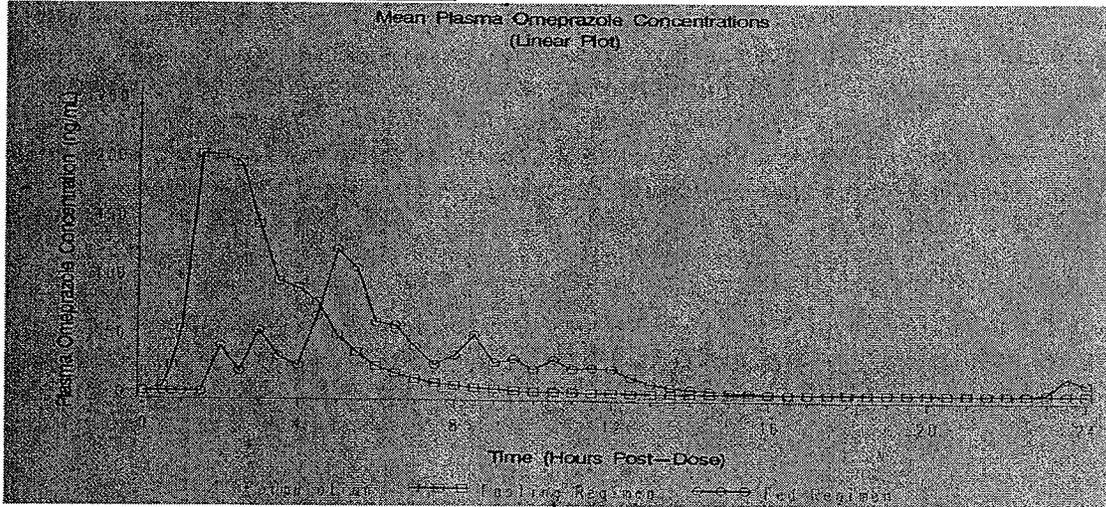
**Pharmacokinetic and Statistical Analysis:** The AUC 0-t, AUC<sub>inf</sub>, AUC/AUC<sub>inf</sub>, C<sub>max</sub>, t<sub>max</sub>, t<sub>lag</sub>, half-life and k<sub>el</sub> pharmacokinetic parameters were calculated for plasma omeprazole. Analyses of variance (ANOVA) were performed on the Ln-transformed AUC 0-t, AUC<sub>inf</sub>, and C<sub>max</sub>. The ANOVA model included sequence, regimen and period as fixed effects and subject nested within sequence as a random effect. The ratios of least-squares means (LSM) were calculated using the exponentiation of the LSM from the analyses on the Ln-transformed AUC 0-t, AUC<sub>inf</sub> and C<sub>max</sub>. These ratios were expressed as a percentage relative to the fasting regimen.

**Results:**

**Demographic Data:** A total of 18 male Caucasian subjects were enrolled and 17 subjects completed the clinical phase of the study. The mean age of the subjects was 37 years (range of 19 - 54 years), the mean height of the subjects was 173 cm (range of 161 - 186 cm), and the mean weight of the subjects was 75.9 kg (range of 55.7 - 90.0 kg).

Subject No. 18 was withdrawn by the Study Physician following dosing in Period 1 (Treatment B-fasting) due to an adverse event (vomited) and therefore did not complete the clinical phase of the study.

**Plasma Concentration-Time Profiles:**



**Pharmacokinetic Parameters:**

15.03

Table 1  
Project No. AA20531  
Summary of Results - Omeprazole in Plasma  
Pharmacokinetic Parameters  
(n = 17)

	In ARE (B-14) (ng·h/mL)	In AUC(0-∞) (ng·h/mL)	C <sub>0</sub> (ng/mL)	t <sub>max</sub> (h)	tLag (h)	Half-life (h)	CV (%)
<b>Fed Regimen (A)</b>							
Mean	367.94	388.14	314.1111	7.654	7.418	0.7905	0.3612
CV	29.5	78.9	76.4	65.4	67.2	29.8	33.7
n	17	16	17	17	17	16	16
<b>Fasting Regimen (B)</b>							
Mean	514.03	493.29	319.0752	1.897	1.485	0.9980	0.3423
CV	69.5	71.3	60.2	46.8	47.0	44.5	45.9
n	17	15	17	17	17	15	15
<b>Least Squares Means</b>							
Fed Regimen (A)	366.08	344.18	312.6517				
Fasting Regimen (B)	511.77	504.20	317.2926				
<b>RATIO OF LEAST SQUARES MEANS (A/B)</b>	71.5	76.2	98.3				
<b>P-Value (ANOVA)</b>							
A vs B	0.0119	0.0535	0.9277				
Period	0.9627	0.5451	0.9568				
Sequence	0.5676	0.6089	0.5255				
<b>Intrasubject CV</b>	35.4	34.6	49.1				

† For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

PHAST - STAB 2.3-000

DEFAULT

Based on median tmax and flag values (Fed=5.50 hrs and Fasted = 1.50 hrs), when food was administered to healthy adult male volunteers, the time to reach peak plasma concentrations was found to be delayed by approximately 4.0 h, as compared to the fasting state.

*Reviewer's Comments: Inserted below are the tables showing the Cmax arithmetic means for fed and fasted states. Although the graph shows Cmax values that are somewhat less than those shown in the table, the mean arithmetic Cmax values are comparable to the geometric means (314.11 (fed) and 319.02 (fasted)). I think the graph looks different because it is a timed average and you have such a wide range in the Tmax, but the values in the graph are the same as that of the mean data for the plasma concentration-time data.*

20-Dec-2005

Table 4  
Project Number :AA28531  
Omeprazole in Plasma  
Pharmacokinetic Parameters by Formulation  
Formulation: Fed Regimen (A)

15:02

Subject ID	Period	AUC 0-t (ng-h/mL)	AUCinf (ng-h/mL)	AUC/AUCinf (%)	Tlag (h)	Cmax (ng/mL)	tmax (h)	Half-life (h)
1	1	181	.	.	23.00	250.00	23.50	.
2	1	446	450	99.0	6.50	332.00	6.50	1.035
3	2	729	733	99.4	4.00	626.00	4.50	1.046
4	2	620	625	99.2	2.00	654.00	2.00	0.900
5	1	822	825	99.7	3.11	746.00	3.11	0.809
6	2	198	200	98.8	12.00	114.00	12.00	0.658
7	1	646	648	99.6	5.00	491.00	5.50	0.809
8	1	1659	1664	99.7	5.00	946.00	5.00	1.281
9	1	199	201	99.2	4.00	285.00	4.50	0.479
10	2	474	476	99.5	8.00	492.00	8.50	0.734
11	2	132	135	97.6	4.00	84.10	5.00	0.614
12	2	222	224	98.8	5.00	311.00	5.00	0.387
13	2	354	357	99.1	5.50	308.00	5.50	0.732
14	1	132	135	98.4	11.50	115.00	11.50	0.547
15	1	506	509	99.2	9.50	248.00	9.50	1.072
16	1	270	273	98.9	8.00	249.00	8.00	0.770
17	2	369	371	99.3	10.00	262.00	10.50	0.775
Arithmetic Mean		468.2	489.3	99.10	7.418	383.124	7.654	0.7905
± SD		374.61	379.72	0.530	4.9820	241.0684	5.0084	0.23559
CV%		80.0	77.6	0.5	67.2	62.9	65.4	29.8
Minimum		132	135	97.6	2.00	84.10	2.00	0.387
Maximum		1659	1664	99.7	23.00	946.00	23.50	1.281
Median		369	411	99.2	5.50	308.00	5.50	0.773
n		17	16	16	17	17	17	16

Kel could not be calculated for some subjects.

Table 5  
Project Number :AA28531  
Omeprazole in Plasma  
Pharmacokinetic Parameters by Formulation  
Formulation: Fasting Regimen (B)

Subject ID	Period	AUC 0-t (ng·h/mL)	AUCinf (ng·h/mL)	AUC/AUCinf (%)	tlag (h)	Cmax (ng/mL)	tmax (h)	Half-Life (h)
1	2	444	448	99.2	1.50	269.00	1.50	0.629
2	2	1034			2.00	662.00	2.50	
3	1	679	683	99.4	1.50	414.00	2.00	1.235
4	1	559	562	99.5	0.75	378.00	1.00	0.753
5	2	605	609	99.2	0.50	369.00	0.75	1.616
6	1	539	541	99.5	2.00	340.00	2.50	0.758
7	2	555	559	99.3	2.00	343.00	3.00	1.083
8	2	1335	1340	99.7	3.50	640.00	4.50	1.219
9	2	203	205	99.1	1.50	103.00	1.50	0.543
10	1	538			2.00	323.00	2.50	
11	1	139	141	99.0	1.50	94.10	1.50	0.400
12	1	226	228	99.2	1.50	161.00	1.50	0.581
13	1	656	660	99.4	1.00	341.00	1.50	1.302
14	2	256	258	99.2	1.00	267.00	1.50	0.622
15	2	1082	1088	99.5	1.00	460.00	1.50	1.834
16	2	491	494	99.5	1.00	409.00	1.50	0.836
17	1	974	980	99.4	1.00	554.00	1.50	1.558
Arithmetic Mean		606.8	586.3	99.33	1.485	360.418	1.897	0.9980
± SD		334.14	338.22	0.191	0.6986	161.7600	0.8886	0.44388
CV%		55.1	57.7	0.2	47.0	44.9	46.8	44.5
Minimum		139	141	99.0	0.50	94.10	0.75	0.400
Maximum		1335	1340	99.7	3.50	662.00	4.50	1.834
Median		535	559	99.4	1.50	343.00	1.50	0.836
n		17	15	15	17	17	17	15

Kel could not be calculated for some subjects.

### Statistical Analysis:

#### Median (Range)

Parameter	Dexcel Ltd.	
	Fed (A)	Fasting (B)
Tmax	5.50 h (2.00 – 23.50 h)	1.50 h (0.75 – 4.50 h)
tlag	5.50 (2.00 – 23.00 h)	1.50 h (0.50 – 3.50)

#### Ratios of LSM%

Parameter	Dexcel Ltd.
	Fed (A) vs. Fasting (B)
AUC 0-t	71.5%
AUCinf	76.2%
Cmax	98.5%

**Applicant's Conclusions:** When food was administered to healthy adult male volunteers, the time to reach peak plasma concentrations was found to be delayed by approximately 4.0 h, as compared to the fasting state. The total extent of drug exposure, AUC 0-t and AUCinf,

decreased by approximately 28.5% and 23.8%, respectively, when the Dexcel 20 mg omeprazole delayed-release tablet was administered with food, as compared to the fasted state. However, the rate of drug exposure (Cmax) was not affected since the ratio of LSM for the fed vs. fasting comparison was within 80-125%.

*Reviewer's Comments: This reviewer does not agree with the sponsor's comments with regards to the effect of food on Cmax. Although the ratio of LSM for the ln-transformed Cmax parameter was within 80-125 %, the 90 % CI (calculated by this reviewer) was not (see table below):*

Parameter	Dexcel Ltd. Fed (A) vs. Fasting (B) [Geometric Mean Ratio and 90 % CI]
AUC 0-t	71.5 % (58.2 % - 87.8 %)
AUC inf	76.2 % (60.8 % - 95.9 %)
Cmax	98.5 % (74.5 % - 130.4 %)

\* 90 % CI was calculated by this reviewer. Sponsor only provided GMR (geometric mean ratio)

**Analytical Method Validation Report:**

<b>OMEPRAZOLE VALIDATION SUMMARY</b>			
Analyte	Omeprazole		
Matrix (Anticoagulant)	Human Plasma (EDTA)		
Preservative	none		
BAM Number	BAM 170		
Assay Method	High performance liquid chromatographic mass spectrometric method		
Detector	PE Sciex API-3000 or API-4000		
Assay Volume Required	0.100 mL		
Standard Curve Range	2.00 – 2000 ng/mL		
Regression Type	Quadratic (1/concentration <sup>2</sup> )		
Quantitation Method	Area Ratio		
<b>Quality Control Samples Performance</b>			
Inter-batch	LLOQ	5.9	102.0
	Low	4.3	100.5
	Medium-Low	4.4	94.1
	Medium	4.1	91.4
	Medium-High	3.2	97.4
	High	2.8	103.5
Intra-batch 02DAK	LLOQ	4.5	101.0
	Low	3.6	103.3
	Medium-Low	2.9	95.7
	Medium	2.7	90.1
	Medium-High	2.7	95.4
	High	3.6	102.8
Intra-batch 05DAK	LLOQ	5.4	97.5
	Low	2.5	97.9
	Medium-Low	3.0	90.1
	Medium	3.2	89.5
	Medium-High	1.6	96.4
	High	2.6	103.5
Intra-batch 07DAK	LLOQ	3.9	106.9
	Low	5.1	101.0
	Medium-Low	3.6	96.4
	Medium	2.8	95.4
	Medium-High	2.6	100.7
	High	2.5	104.3

Quality Control Samples on API 1000		Accuracy (%)
Intra-batch DEF03	LLOQ	3.4
	Low	5.8
	Medium-Low	4.0
	Medium	2.8
	Medium-High	6.5
	High	2.3
Precision (%)		
17DDR	Low	2.9
	High	2.7
Accuracy (%)		
Analyte	Low	104.7
	Medium	98.2
	High	100.8
Internal Standard		74.9
Stability		
Long-term Stability	290 days at -20°C	
Short-term Stability	99.5 hours at ambient temperature	
Freeze and Thaw Stability	4 cycles at -20°C	
Post-preparative Stability	98.0 hours at ambient temperature under normal light conditions	
	74.5 hours at ambient temperature protected from light	
Primary Stock Solution Stability	837 days at 200 mcg/mL in methanol at -20°C	
Intermediate Stock Solution Stability	296 days at 0.200 mcg/mL in methanol at -20°C	
Internal Standard Primary Stock Stability	469 days at 100 mcg/mL in methanol at -20°C	
Internal Standard Intermediate Stock Stability	100 days at 2.00 mcg/mL in methanol at -20°C	
Dilution Integrity	up to 2820 ng/mL	
Processed Sample Integrity (Re-injection)	51.5 hours at ambient temperature under normal light	
	117.5 hours at ambient temperature protected from light	
Batch Size	200 injections	

**Sponsor's Narrative of exclusion of some samples from BE determination:**

- Analytical Site: "Event Identification BLN-EIR-2005-32: Upon initial analysis in batch 12DAU, samples (32, 1 hr, P2) and (32, 1.25hr, P2) had concentrations of 35.6 ng/mL and BLQ, respectively. It was suspected that the study samples had been inverted. During the investigation, as part of hypothesis testing, both samples were re-analyzed as "test sample" in batch 17DAU. The concentrations obtained did not confirm the original values. Since an inversion was not confirmed and the original values were not confirmed either, all unknown samples from batch 12DAU became doubtful. Since this batch met the acceptance criteria, it cannot be rejected. However, all study samples from batch 12DAU were coded "Not used" since a manipulation error was suspected. Study samples were re-assayed in a subsequent batch (27DAU). Comparison of original results (12DAU) and re-assay results (27DAU) confirmed that a manipulation error had occurred in batch 12DAU."

**DSL's Comments (12/05/06 following inspection on 12/01/06):**

The results from the original run (batch 12DAU) for subjects 30-32 in Study AA24171 were not reported although the run met the acceptance criteria. The firm's investigation fails to justify the exclusion of the entire results from the original run. There was no SOP in place to address this issue.

*Reviewer's Comments: Therefore the applicant needs to re-analyze the data to evaluate the impact of using the re-assayed repeat results (run #27) instead of the original concentrations (run # 12) on the bioequivalence determination. The DSI is currently awaiting these results as a response to their audit report. On 12/6/06, the applicant was only able to provide a preliminary report, and would not be able to provide the final complete response (including the raw data) to the 483 audit until next week. Although, the preliminary report suggests that*

*the use of including the original concentrations instead of the repeat results may not change the BE conclusions, a conclusive determination cannot be made until after the raw data supporting the preliminary results is reviewed.*

4.4 OCPB Filing Form:

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information about the Submission				
	Information		Information	
<b>NDA Number</b>	22-032		<b>Brand Name</b>	Omeprazole Delayed-Release (Not yet determined)
<b>OCPB Division (I, II, III)</b>	DCP3		<b>Generic Name</b>	Omeprazole
<b>Medical Division</b>	ONP-DNCE		<b>Drug Class</b>	Proton Pump Inhibitor
<b>OCP Reviewer</b>	Abi Adebowale		<b>Indication(s)</b>	Treatment of frequent heartburn (occurs 2 or more days a week)
<b>OCP Team Leader</b>	Dennis Bashaw		<b>Dosage Form</b>	Delayed-release 20 mg tablets
			<b>Dosing Regimen</b>	One tablet per day for a 14-day course of treatment
<b>Stamp Date</b>	February 10 <sup>th</sup> , 2006		<b>Route of Administration</b>	Oral (OTC)
<b>Estimated Due Date of OCPB Review</b>	September 8 <sup>th</sup> , 2006		<b>Sponsor</b>	Dexcel Pharma Technologies Ltd.
<b>PDUFA Due Date</b>	December 10 <sup>th</sup> , 2006		<b>Priority Classification</b>	5S
<b>Division Due Date</b>	November 10 <sup>th</sup> , 2006		<b>IND Number</b>	63,799
Clin. Pharm. and Biopharm. Information				
<b>Background and Introduction:</b> The applicant has submitted an 505(b)(2) NDA for a new formulation of omeprazole delayed release tablets which utilizes omeprazole base rather than omeprazole magnesium, which is the active ingredient of their proposed RLD, Prilosec OTC (NDA 21-229), approved for OTC marketing on June 20, 2003, for the treatment of frequent heartburn. Protocols for relative BA and food effect studies included in this NDA were found acceptable by OCPB during meetings with the sponsor on May 20 <sup>th</sup> , 2005 and October 10 <sup>th</sup> , 2005.				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference (IR):	X			Study # AA24171
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>	X			Study # AA28531 (used FDA high fat diet)
<b>Dissolution:</b>	X			
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Other (in vitro percutaneous absorption study)</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		2		
<b>Filability and QBR comments</b>				



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/s/

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Abi Adebawale  
12/7/2006 05:21:05 PM  
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Sue Chih Lee  
12/7/2006 05:30:38 PM  
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