CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-032

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22,032**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**2/10/06**
PRODUCT:	**Omeprazole Delayed-Release Tablets, 20 mg**
INTENDED CLINICAL POPULATION:	**Patients with frequent heartburn, age 18 years and older**
SPONSOR:	**Dexcel Pharma Technologies Ltd.**
DOCUMENTS REVIEWED:	**Vol. 8, 9**
REVIEW DIVISIONS:	**Division of Gastroenterology Products (HFD-180)**
	Division of Nonprescription Clinical Evaluation (HFD-560)
PHARM/TOX REVIEWER:	**David B. Joseph, Ph.D. (HFD-180)**
PHARM/TOX SUPERVISOR:	**Jasti B. Choudary, B.V.Sc., Ph.D. (HFD-180)**
DIVISION DIRECTOR:	**Brain E. Harvey, M.D., Ph.D. (HFD-180)**
PROJECT MANAGER:	**Keith Olin (HFD-560)**

Date of review submission to Division File System (DFS): October 3, 2006

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From a preclinical viewpoint, the application should be approved.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

Not applicable.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Not applicable.

B. Pharmacologic activity

Not applicable.

C. Nonclinical safety issues relevant to clinical use

Not applicable.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22,032

Review number: 1

Sequence number/date/type of submission: 000/February 8, 2006/Original

Information to sponsor: Yes ( ) No (x)

Sponsor and/or agent: Dexcel Pharma Technologies Ltd.
Akiva, Israel

Manufacturer for drug substance: ——— b(4)

Reviewer name: David B. Joseph, Ph.D.

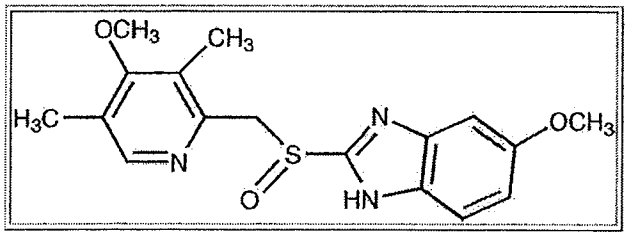
Division name: Division of Gastroenterology Products

HFD #: 180

Review completion date: October 3, 2006

Drug:

Trade name: Omeprazole Delayed-Release Tablets, 20 mg
Generic name: Omeprazole
Code name: not applicable
Chemical name: 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole
CAS registry number: 73590-58-6
Molecular formula/molecular weight: $C_{17}H_{19}N_3O_3S$/345.42
Structure:



Relevant INDs/NDAs/DMFs: NDA 21,229 (Prilosec OTC®, AstraZeneca)

Drug class: proton pump inhibitor

Intended clinical population: patients with frequent heartburn, age 18 years and older

Clinical formulation: Delayed-release tablets. The ingredients are shown in the table below.

Ingredients	mg/tablet
Active	
Omeprazole USP	20
Excipients	
Lactose monohydrate NF	
Sodium starch glycolate NF	
Sodium stearate NF	
Sodium stearyl fumarate NF	
Hypromellose acetate succinate JPE	
Triethyl citrate NF	
Sodium lauryl sulfate NF	
Talc USP	
Monoethanolamine NF	
[redacted]	
Carnauba wax NF	

b(4)

b(4)

Route of administration: oral

Disclaimer: Not applicable.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22,032 are owned by Dexcel Pharma Technologies Ltd. or are data for which Dexcel Pharma Technologies Ltd. has obtained a written right of reference. Any information or data necessary for approval of NDA 22,032 that Dexcel Pharma Technologies Ltd. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Dexcel Pharma Technologies Ltd. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22,032.

Studies reviewed within this submission: Toxicology information on two excipients, sodium stearate and monoethanolamine, is presented in the "OVERALL CONCLUSIONS AND RECOMMENDATIONS" section. This information was submitted in response to a request from the Agency in the meeting on May 20, 2005 for PIND 63,799.

Studies not reviewed within this submission: None.

LABELING:

This application is for a non-prescription drug product. Therefore, no pharmacology/toxicology review is needed.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

The present application is for Omeprazole Delayed-Release Tablets, 20 mg. In response to an inquiry from the Sponsor, the Agency requested toxicology information (i.e. 1-month repeat-dose studies in a rodent and non-rodent species) on sodium stearate and monoethanolamine. The Agency made this request in the meeting on May 20, 2005 for PIND 63,799. Both of these excipients are present at levels that exceed the maximum amounts listed in FDA's Inactive Ingredients Database. This application contains reviews of toxicology information about sodium stearate and monoethanolamine (commonly referred to as ethanolamine). These reviews were prepared by Phillip A. Johns, Ph.D., a toxicology and regulatory consultant. Information that is most relevant to the safety of the Sponsor's drug product is summarized below.

Sodium stearate is present at a level of ——— in the Sponsor's drug product. The proposed dosing regimen is 20 mg omeprazole/day (one tablet/day) for 14 days, resulting in a daily intake of —— sodium stearate. This compound is the sodium salt of stearic acid, a fatty acid categorized as GRAS (Generally Recognized as Safe) for use as a direct human food ingredient, with no limitation other than current good manufacturing practice (21 CFR 184.1090). Stearic acid occurs naturally as a glyceride in tallow and other animal or vegetable fats and oils and is a principal constituent of most hydrogenated fats. It is reasonable to expect that sodium stearate and stearic acid have similar physiological properties. Related compounds that are also considered as GRAS include oleic acid and sodium palmitate. The fatty acids as a group are permitted as direct food additives (21 CFR 172.210, 172.860, 173.340). The World Health Organization set an unlimited Acceptable Daily Intake for the salts of myristic, palmitic, and stearic acids (14-, 16-, and 18-carbon chain fatty acids, respectively). These fatty acids are normal products of fat metabolism and their metabolic fate is well established. Fatty acids are taken up by tissues and can be stored in the form of triglycerides (98% of which occurs in adipose tissue) or can be oxidized for energy production via the β-oxidation and tricarboxylic acid cycle pathways of catabolism.

b(4)

b(4)

No repeat-dose toxicity studies of sodium stearate or stearic acid are available, aside from a 3-month dermal toxicity study in rabbits. One study has been performed using administration of caprenin, a triglyceride composed primarily of caprylic (C8), capric (C10), and behenic (C22) acids. Rats were treated for 91 days with dietary administration of 5.2%, 10.2%, or 15% caprenin. This study included a complete histopathologic evaluation, and all other standard

parameters routinely recorded in regulatory toxicology studies. The NOAEL was 15%, equivalent to 13.2 g/kg/day in males and 14.6 g/kg/day in females.

Safety margins for sodium stearate intake from the Sponsor's product cannot be estimated from the available preclinical toxicity information, due to the absence of appropriate studies. Given the known safety of sodium stearate and stearic acid as dietary components, there is no safety concern about the ingestion of sodium stearate in the Sponsor's product.

Ethanolamine is present at a level of ——— in the Sponsor's drug product. For the proposed dosing regimen of one tablet per day for 14 days, the total intake will be ——— b(4)
Although there are no approved drug products for oral administration that contain ethanolamine, there is one product for intravenous administration that contains ethanolamine oleate (———). Upon injection, ethanolamine oleate is rapidly converted to b(4)
ethanolamine and oleic acid. The maximum approved dose of Ethamolin® is 20 ml per treatment session. Therefore, the highest approved dose results in the release of 177.9 mg ethanolamine into systemic circulation, as compared to a total intake of ——— during the b(4)
recommended 14-day treatment with the Sponsor's product.

Most of the available repeat-dose toxicity studies of ethanolamine were performed using inhalation exposure. However, the use of inhalation toxicity studies for safety assessment of the Sponsor's product is inappropriate. The only reported experience of oral administration of ethanolamine in rats occurred in reproductive toxicology studies. In an embryofetal/postnatal developmental study, female rats were treated orally with 0, 40, 120, or 450 mg/kg/day ethanolamine, given on days 6-15 of pregnancy. Reductions in weight gain and food consumption occurred in the 450 mg/kg/day group. No adverse effects on fetal development were observed, nor were there any signs of treatment-related effects on postnatal growth and viability of the offspring (Hellwig and Liberacki, Fund Appl Toxicol, 40, pg. 158-162, 1997). A reproduction study of a commercial dye mixture containing ethanolamine was performed in rats using dietary administration of the test article. The ethanolamine dose levels were approximately 39 and 156 mg/kg/day. Females were treated from eight weeks prior to mating through weaning of litters. Males were treated from eight weeks prior to mating through the end of the mating period. No adverse effects on parents, fetuses, or offspring were observed (Wernick et al., Toxicol Appl Pharmacol, 32, pg. 452-460, 1975).

A 2-year oral toxicity study of a commercial dye mixture containing ethanolamine was performed in dogs using dietary administration. The dye mixture dose levels were 0, 19.5, and 97.5 mg/kg/day. The dose levels of ethanolamine were calculated to be 0, 4, and 22 mg/kg/day. No treatment-related effects were observed for the following parameters: clinical signs, bodyweight, hematology, clinical chemistry, urinalysis, organ weights, gross pathology, and histopathology (Wernick et al., Toxicol Appl Pharmacol, 32, pg. 452-460, 1975).

The 2-year dietary toxicity study in dogs provides information applicable for safety assessment of the Sponsor's drug product. It is noted that this study is not ideally suited for safety assessment of ethanolamine, given that the test article was a mixture of 13 types of commercial dyes, which could have affected the expression of ethanolamine-induced toxicity. The no observed adverse effect level in this study was 22 mg/kg/day, whereas the ethanolamine dose in

the Sponsor's product will be [redacted], based on a 50-kg bodyweight. Therefore, the safety margin derived from this study is [redacted] which is more than adequate to support the safety of the Sponsor's product. No repeat-dose oral toxicity studies in rodents are available, aside from the reproductive studies in rats described above. No signs of toxicity were observed in pregnant rats treated orally with up to 120 mg/kg/day ethanolamine. In a second study, dietary administration of ethanolamine as part of a commercial dye mixture produced no overt signs of toxicity at doses of up to approximately 156 mg/kg/day, given for about 14 weeks. The human experience with intravenous exposure to dose levels as high as 177.9 mg, as occurs at the highest approved dose of Ethamolin®, suggests that the daily oral intake of [redacted] ethanolamine in the Sponsor's product is a minimal safety risk with respect to systemic toxicity, even with long term administration. b(4) b(4)

Unresolved toxicology issues: None.

Recommendations:

From a preclinical viewpoint, the application should be approved.

Suggested labeling: Not applicable.

Reviewer Signature _____
David B. Joseph, Ph.D.
Pharmacologist, HFD-180

Supervisor Signature _____ Concurrence Yes ___ No ___
Jasti B. Choudary, B.V.Sc., Ph.D.
Supervisory Pharmacologist, HFD-180

cc:
Orig NDA 22,032
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Joseph

R/D Init.: J. Choudary 9/27/06

DJ/dbj: 10/3/06
C:\DATA\N22032610.0DJ

APPENDIX/ATTACHEMENTS

None

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/

David Joseph
10/3/2006 02:09:20 PM
PHARMACOLOGIST

Jasti Choudary
10/4/2006 10:39:44 AM
PHARMACOLOGIST