

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-287

CHEMISTRY REVIEW(S)



CMC REVIEW



NDA 22-287

**Kapidex (dexlansoprazole)
Delayed Release Capsule**

TAP Pharmaceutical Products Inc.

Tarun Mehta

Review Chemist

**Office of New Drug Quality Assessment
Division of Pre-Marketing assessment II
Branch III**

**CMC REVIEW OF NDA 22-287
For the Division of Gastroenterology Products (HFD-180)**



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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 22-287
2. REVIEW #: 1
3. REVIEW DATE: 28-AUG-2008
4. REVIEWER: Tarun Mehta
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	28 - Dec - 2007
Correspondence (C)	
Amendment (0006)	28 - Apr - 2008
Amendment (0020)	10 - Sept - 2008
Amendment (0023)	21 - Oct - 2008
Amendment (0028)	17 - Dec - 2008
Amendment (0031)	13 - Jan - 2009

7. NAME & ADDRESS OF SPONSOR:

Name: TAP Pharmaceutical Products Inc.
Address: 675 North Field Drive, Lake Forest, IL 60045
Representative: Nancianne Knipfer, Ph.D., RAC
Telephone: 847-582-2193

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Kapidex
- b) Non-Proprietary Name: Dexlansoprazole
- c) Code Name/# (ONDQA only): TAK-390, TAK-390MR, T-168390
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Proton Pump Inhibitor (PPI)

11. DOSAGE FORM: Delayed Released Capsule

12. STRENGTH/POTENCY: 30 mg, 60 mg, (b) (4)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

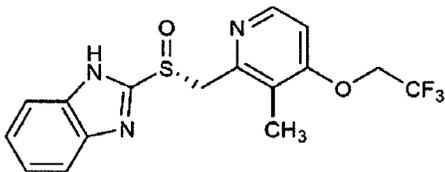
16. CHEMICAL NAMES:

(+)-2-[(R)-{[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1H-benzimidazole

2-[(R)-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole

R-(+)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-benzimidazole

STRUCTURAL FORMULA:



MOLECULAR FORMULA: C₁₆H₁₄F₃N₃O₂S

MOLECULAR WEIGHT: 369.36



CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b)	IV	(b) (4) (b) (4) (b) (4) (b)	(b) (4) (b) (4) (b) (4)	3	Adequate	Review by Amin Yusuf 10/12/05	No update since last review
(b)	III	(b) (4)	(b) (4) (b) (4)	4	Adequate		
(b)	III	(b) (4) (b) (4)	(b) (4)	4	Adequate		
(b)	III	(b) (4)	(b) (4) (b) (4)	4	Adequate		
(b)	III	(b) (4) (b) (4) (b) (4) (b)	(b) (4)	3	Adequate	Reviewed by Sarah Pope 10/29/03	No update for VPA 10400 since last review
(b)	III	(b) (4) (b) (4) (b) (4) (b)	(b) (4) (b) (4) (b)	3	Adequate	Reviewed by Yichun Sun 11/12/07	No update since last review
(b)	III	(b) (4) (b) (4) (b) (4) (b)	(b) (4)	3	Adequate	Reviewed by Kurtyka Bogdan 03/07/08	No update since last review
(b)	III	(b) (4) (b) (4) (b) (4) (b) (4)	(b) (4)	3	Adequate	Reviewed by Bertha Craig 06/06/07	No update since last review
(b)	III	(b) (4) (b) (4) (b)	(b) (4)	3	Adequate	Reviewed by Bertha Craig 09/24/07	No update since last review
(b)	III	(b) (4) (b) (4) (b) (4) (b)	(b) (4)	3	Adequate	Reviewed by Pope Sarah 07/27/04	No update since last review
(b)	IV	(b) (4) (b) (4) (b) (b) (4) (b)	(b) (4)	3	Adequate	Niu Chien Hau	No update since last review



CMC Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	69,927 and 30,159	TAK-390MR Capsule
NDA	20-406	Prevacid® Tablet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	16-Jan-09	Shawnte Adams (HFD-235)
Biopharm	Not acceptable*	30-Sept - 08	Patrick Marroum
DMETS	Acceptable	28-Dec-08	Deveonne Hamilton

(b) (4)

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Executive Summary Section

The CMC Review for NDA 22-287

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The labels have adequate information as required. An "Acceptable" site recommendation from the Office of Compliance has been made. Therefore, from the CMC perspective, this NDA is now recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

Drug substance Dexlansoprazole is a R-enantiomer of the approved racemic (1:1 ratio) drug lansoprazole. Dexlansoprazole (API) is a new active ingredient in enantiomeric form. Proposed drug substance do not have a designated DMF. All the supporting CMC data is provided in the NDA submission.

Dexlansoprazole is pale yellowish white crystalline powder. It is freely soluble in polar organic solvent but practically insoluble in non-polar organic solvent. The solubility of the drug substance in aqueous solution increases with the pH value. It is slightly soluble in water (0.16mg/mL), but become soluble (58mg/mL) at the pH value of 10.9. Starting and intermediate materials for manufacturing dexlansoprazole and lansoprazole are the same. (b) (4)

The degradation products of the dexlansoprazole are similar to that of the lansoprazole. No new impurities were discovered during the synthesis as well as in the stability studies. The sponsor has submitted adequate information on manufacturing process and API characterization in this NDA. Adequate in-process controls are in place in manufacturing process to assure the consistent quality of the drug substance.



Executive Summary Section

Dexlansoprazole, the drug substance is further controlled per the release tests, i.e., appearance, identification, heavy metals, related substances, percentage of enantiomer, residual solvents, water, potency assay by (b) (4), and particle size distribution. Based on the stability data of clinical stability batches and, according to ICH Guidance Q1E, a retest date (b) (4) is granted.

(2) Drug Product

The drug product dexlansoprazole Modified Released Capsules (TAK-390MR Capsules) are available in 30, 60, (b) (4) strength. The drug product was modified from their approved product lansoprazole capsules to achieve the prolonged plasma concentration.

Modified capsules are filled with two types of enteric coated granules exhibiting dual delayed release mechanism. One type of granules will release the drug in the proximal region of the small intestine where the pH reaches approximately 5.5. The second type of granules will release the drug more distally in the intestine where the pH reaches approximately 6.75. The ratio of these granules is maintained at (b) (pH 5.5: pH 6.75) in order to optimize the drug concentration in plasma. The formulation components of both the granules are the same except for the enteric coating layer, as shown in the figure below.

(b) (4)



The enteric coating layer differed by the polymer composition. These different polymers give them the characteristic dual delayed release mechanism. The mixture (b) (4) of these granules filled in the color coded gelatin capsules printed with “TAP” logo and strengths.

The drug substance was manufactured at the manufacturing site in Osaka, Japan. All other excipients of this formulation are compendial (USP/NF) grade. The compendial monographs were used to test their quality.

The Takeda Pharmaceutical Company Limited Osaka Plant had conducted the drug product development and manufactured the clinical supplies. The compositions of the clinical formulation and the proposed commercial formulation are identical.



Executive Summary Section

(b) (4) commercial size batches were successfully manufactured at the proposed scale-up site, using the proposed commercial manufacturing process and equipments. The manufacturing process controls support the consistent quality of the drug product.

The drug product specification is deemed satisfactory. The identity, strength, and purity of the drug product are assured by the following analytical tests: appearance, identification, assay, related substances, content uniformity, dissolution, and loss on drying. (b) (4)

(b) (4) the final acceptance criteria were set based on the characteristic of the clinical batches.

The proposed container/closure system is deemed adequate. The container/closure system for the drug product is white (b) (4) bottle containing a silica gel desiccant with (b) (4) child-resistant caps and induction seal. The capsules are also packaged in thermoform blisters, which are then placed in cartons (100 capsules in each carton).

Stability results (updated in amendment 0006; April 28, 2008) derived from the (b) (4) stability batches packaged in the proposed container/closure met the specification. The drug products were stored up to 18 months for 30mg and 24 months for 60 (b) (4) strengths at 25°C/60% RH condition. The results met the specification and no significant trend was observed. Based on the available stability data, 24 months of expiration dating period for the drug product is granted.

B. Description of How the Drug Product is Intended to be Used

Dose of TAK390-MR 60mg (b) (4) capsules, once daily for up to 8 weeks for the healing of erosive esophagitis (EE) (b) (4)

(b) (4) TAK-390 MR capsules can be taken without food. Alternatively, TAK-390MR capsules can be opened, sprinkled on one tablespoon of applesauce and swallowed immediately.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing process and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All facilities have acceptable site recommendations.

All labels have the required information.



Executive Summary Section

III. Administrative

A. Reviewer's Signature:

Tarun Mehta

B. Endorsement Block:

Moo-Jhong Rhee, Ph.D. Branch Chief, Branch III, ONDQA

C. CC Block: entered electronically in DFS

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√ Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Tarun Mehta
1/26/2009 04:48:00 PM
CHEMIST

Moo-Jhong Rhee
1/26/2009 05:26:11 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

OND Division: Division of Gastroenterology Products
NDA: 22-287
Applicant: TAP Pharmaceutical Products
Stamp Date: 12/28/2007
Received by PAL: 1/8/2008
Review Date: 2/14/2008
PDUFA Date: 10/28/2008
Filing Meeting: 2/14/2008
Proposed Trademark: (b) (4)
Established Name: dexlansoprazole
Dosage Form: Delayed release capsules (30, 60 (b) mg)
Route of Administration: oral
Indication: erosive esophagitis
P.A.L.: Marie Kowblansky, PhD

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	
Comments for 74-Day Letter		<input checked="" type="checkbox"/>

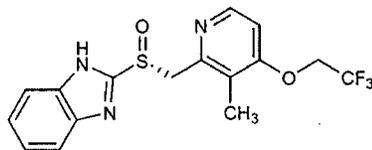
A. Summary

(b) (4) (dexlansoprazole) Delayed Release Capsules is intended for use in the treatment of erosive esophagitis. The proposed product is a capsule formulation containing 30, 60, (b) mg of dexlansoprazole, with a recommendation to administer one capsule daily for up to 8 weeks. This product, which was studied under IND 69,927, is being filed by TAP Pharmaceutical as a 505(b)(1) application. The same firm is the holder of NDA 20-406 for Prevacid® (lansoprazole) Delayed Release Capsules, which was approved in 1995. Dexlansoprazole is the R- enantiomer of lansoprazole. Since dexlansoprazole is a component of a currently approved racemic drug, this application is classified as Type 2 in the Chemical Classification Code.

(b) (4)

Drug Substance

Dexlansoprazole (or TAK-390), the R-enantiomer of lansoprazole, is a substituted benzimidazole with the following structure (where sulfur is the chiral center)



It is synthesized at Takeda Pharmaceutical Limited (b) (4) using the same starting materials that are used in the synthesis of lansoprazole, with exclusively the R-enantiomer being produced in the (b) (4) of the synthesis by (b) (4)

(b) (4) All information regarding the characterization, manufacture, and controls used in preparing this drug substance are submitted directly in the NDA (there is no DMF).

Dexlansoprazole is a crystalline powder that melts with decomposition at 140°C. According to the submission, there is no evidence of polymorphism in the drug substance; there is only one known crystalline form. Dexlansoprazole is soluble in a number of organic solvents, practically insoluble in nonpolar organic solvents, and only slightly soluble in water. Its aqueous solubility increases with pH, being very slightly soluble in the range pH 7 - 9, slightly soluble at pH 11, and very soluble at pH 13. Because of its low solubility and high permeability under physiological pH conditions, dexlansoprazole is classified as a Class II compound in the biopharmaceutical classification system (BCS).

Dexlansoprazole is stable when exposed to light. It is more stable in neutral and alkaline conditions than acidic conditions. It is unstable under a combination of high temperature and high humidity conditions.

The drug substance will conform to the following specification, which controls the properties that are critical to the manufacturability, performance, and safety of the drug product.

Test	Analytical Procedure	Document No.	Acceptance Criteria
Appearance	Visual inspection	TAK-390MR/00360	White to nearly white crystalline powder
Identification			
(b) (4)	(b) (4) (b) (4)	TAK-390MR/00361	Positive (Test sample exhibits similar (b) (4) to that of reference standard similarly prepared.)
(b) (4)	(b) (4)	TAK-390MR/00362	Positive (The retention time of the sample peak agrees within (b) (4) with that of the reference standard peak.)
Heavy metals	USP <231>Method II	-	Not more than 10 ppm
Related substances	(b) (4)	TAK-390MR/00364	(b) (4)
Total			Not more than 0.65%
Enantiomer	(b) (4)	TAK-390MR/00363	Not more than (b) (4)
Residual solvents	(b) (4)	TAK-390MR/00365	Not more than (b) (4) Not more than (b) (4)
Water	(b) (4) (KF), USP <921>	TAK-390MR/00366	Not more than 0.30%
Residue on ignition	USP <281>	-	Not more than 0.10%
Assay	(b) (4)	TAK-390MR/00363	(b) (4)
Particle size	(b) (4)	TAK-390MR/00367	(b) (4)
χ_{50}			Not larger than (b) (4)
χ_{90}			

It should be noted that the drug substance is assayed by (b) (4) which ensures its enantiomeric form. The impurity limits conform with ICH recommendations with regard to reporting, identification, and qualification thresholds. The exceptions are the (b) (4) impurity with

(b) (4) and the (b) (4) Since the sulfone is (b) (4) a metabolite, it is considered qualified. The (b) (4) is a component of an approved drug (constituting (b) (4) of lansoprazole) and consequently, is also considered safe. As a final point, regarding the particle size limits: the drug substance is (b) (4) but the applicant emphasizes that the proposed limits are required solely for manufacturability purposes (to enable easier deposition of drug onto (b) (4) for the granules). Data are presented to demonstrate that particle size does not affect dissolution profiles of the finished product within this particle size range.

Drug Product

(b) (4) (dexlansoprazole) Delayed Release Capsules (TAK-390MR Capsules) will be manufactured in (b) (4) strengths 30, 60, (b) (4) mg. Two types of granules are contained within a single capsule, each with a different pH-dependent enteric-coating and different release profile, creating an overall extended release profile for the product. Granules (b) (4) are designed to release the drug substance at pH 5.5 (after the granules reach the proximal small intestine) and granules (b) (4) are designed to release the drug substance at pH 6.75 (distally in the small intestine). The granules are schematically represented below (reproduced from submission)

(b) (4)



The (b) (4) granules have the same enteric coating (releasing at pH 5.5), but differ in the amount of drug substance; the (b) (4) granule is used in the 30 mg capsule and the (b) (4) is used in the 60 (b) (4) mg capsule. The (b) (4) granule is used in all (b) (4) capsule strengths. The (b) (4) o (b) (4) ratio is (b) (4) in the capsules. The drug loading for the different granules and capsule fill weights for the different capsule strengths are tabulated below.

(b) (4)



Except for the enteric coating, the components of the different granules are the same, containing the following ingredients: dexlansoprazole, sugar spheres, magnesium carbonate, sucrose, low-substituted hydroxypropyl cellulose, titanium dioxide, hydroxypropyl cellulose, hypromellose 2910, talc, methacrylic acid copolymer, polyethylene glycol 8000, triethyl citrate, polysorbate 80, and colloidal silicon dioxide.

Both pH-dependent enteric coatings are based on (b) (4) The coating releasing at pH 5.5 is a (b) (4) dispersion and the one releasing at pH 6.75 is a combination (b) (4) To demonstrate that the dual dissolution behavior is indeed a pH dependent phenomenon and not solely due to differences in the amount of the enteric coating, the applicant has used a pH (b) (4) dissolution medium for the (b) (4); capsules, b

showing that the (b) granules dissolve within 10 minutes, while the () granules do not dissolve, even after 180 minutes.

The granule composition of the commercial product is identical to that used in the phase 3 clinical studies but the commercial capsules differ from the Phase 3 product in capsule color and size.

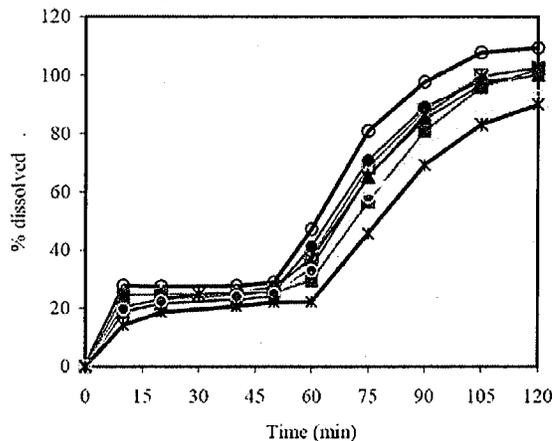
The drug product will be manufactured by Takeda Pharmaceuticals using a process that is similar to the commercial process used to manufacture Prevacid granules. The submission provides an extensive description of the manufacturing process and identifies critical process parameters and controls that are used in manufacturing the different types of granules and in the capsule filling operations.

As one of the in-process controls, each granule type has its own specifications which include testing for appearance, identification (b) (4) assay, related substances, moisture, and (b) (4) dissolution. The granules are tested for conformance to specifications prior to filling into the capsules.

The finished product specifications include visual examination for appearance, identification (b) (4) related substances (b) (4)

content uniformity (USP <905>), loss on drying (b) (4) assay by (b) (4), and (b) (4) dissolution testing (b) (4)

Because of the low solubility of the drug substance at pH (4) the dissolution test is conducted in PH 7 buffer with added surfactant. The buffer stage dissolution profile shows clear differentiation between the two types of granules that constitute the product, with the (b) or (b) granules dissolving first:



Acceptance criteria for the amount of drug dissolved (as % label claim) in the buffer stage are defined as

(b) (4)

(b) (4)

According to the submission, the dissolution specification is supported by the (b) (4)

Primary stability studies were conducted on all three strengths of the commercial product. Up to 18 months of RT stability data and 6 months of accelerated data were provided for product in all proposed packaging configurations, with no trends indicative of instability being observed. Up to 24 months of supporting stability data are also provided. An expiration period of 24 months is proposed.

TAP appropriately claims categorical exclusion from the requirement for submitting an environmental assessment on the basis that the estimated concentration of dexlansoprazole at the point of entry into the aquatic environment will be below 1 part per billion.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. (See appended list.)

B. Critical issues for review

Based on this initial assessment, the following issues will need particular attention during the full review of this NDA:

-- With the exception of information on the sugar spheres, (b) (4) and the hypromellose capsules used in the manufacture of the product, no quality control information regarding the numerous other excipients or certificates of analysis could be found in the submission. This, no doubt, is an oversight and the information should be requested as soon as possible.

--(b) (4)

However, since the applicant indicates that this (b) (4) is (b) (4) a metabolite, it is considered qualified per ICH. Confirmation should be obtained from the Clinical Toxicology reviewer that the sulfone analog is indeed a metabolite and therefore the proposed acceptance criteria are acceptable.

-- According to the applicant, the broad dissolution acceptance limits (e.g. 35 to 80% in 75 minutes) are justified on the basis of the (b) (4)

-- The dissolution test and acceptance criteria were modified during the course of the stability studies. The data will need to be closely scrutinized to determine if the reported dissolution data support the proposed expiration.

-- The clinical and stability batches used identical formulations, but different capsule sizes. Although data comparing the dissolution of the clinical capsules with the commercial capsules could not be found in the submission, this should not be an obstacle to filing or approval. In the (b) (4) dissolution test, the capsules would be degraded during the acid (b) (4), leaving the enteric coated granules to release drug substance in the buffer (b) (4)

C. Comments for 74-Day Letter – None

D. Filing recommendation -- From the CMC perspective, this application should be filed.

Marie Kowblansky, PhD
Pharmaceutical Assessment Lead

2/12/08
Date

Moo-Jhong Rhee, PhD
Branch Chief

2/12/08
Date

Manufacturing Sites

Site Name	Site Address	Contact	Telephone No.	Registration No. (FEI)	DMF No.	Manufacturing Steps and/or Type of Testing
Takeda Pharmaceutical Company Limited (TPC) ¹ Pharmaceutical Production Division (Hikari Plant)	4720 Mitsui Hikari, Yamaguchi, 743-8502, Japan	Masakazu Matsui, General Manager, Quality Control Department Takayuki Kumamoto, Manager, Quality Control Department	+81.833.71.5580	3002808306	None	The following operations for the drug substance: <ul style="list-style-type: none"> • Manufacturing • Quality control • Testing • Packaging • Stability studies
Takeda Pharmaceutical Company Limited ¹ (Osaka Plant)	17-85 Jusonhonmachi 2-Chome, Yodogawa-ku, Osaka 532-8686, Japan	Futoshi Sanematsu, General Manager, Quality Control Department Tsunco Komatsubara, Manager, Quality Control Department	+81.6.6300.6641 +81.6.6300.6580	3002808311	None	The following operations for the drug product: <ul style="list-style-type: none"> • Manufacturing • Bulk packaging • Quality control • Testing • Stability studies
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	([REDACTED])
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	([REDACTED])
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	([REDACTED])
¹ The name change from Takeda Chemical Industries, Ltd. (TCI) to Takeda Pharmaceutical Company Limited (TPC) occurred during development of dexlansoprazole. Some documents written for the development were finalized prior to the name change; therefore, the names Takeda Chemical Industries, Ltd. and TCI were used in these documents.						

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Filing Checklists (NDA 22-287)

A. Administrative Checklists;

YES	NO		Comments
√		On its face, is the section organized adequately?	
√		Is the section indexed and paginated adequately?	
√		On its face, is the section legible?	
√		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
√		Has an environmental assessment report or categorical exclusion been provided?	

B. Technical Checklists;

1. Drug Substance

√		Does the section contain synthetic scheme with in-process parameters?	
√		Does the section contain structural elucidation data?	
√		Does the section contain specifications?	
√		Does the section contain information on impurities?	
√		Does the section contain validation data for analytical methods?	
√		Does the section contain container and closure information?	
√		Does the section contain stability data?	

2. Drug Product

√		Does the section contain manufacturing process with in-process controls?	
√		Does the section contain quality controls of excipients?	Not all excipients
√		Does the section contain information on composition?	
√		Does the section contain specifications?	
√		Does the section contain information on degradation products?	
√		Does the section contain validation data for analytical methods?	
√		Does the section contain information on container and closure systems?	
√		Does the section contain stability data with a proposed expiration date?	
√		Does the section contain information on labels of container and cartons?	
√		Does the section contain tradename and established name?	

C. Review Issues

	√	Has all information requested during the IND phases, and at the pre-NDA meetings been included?	(b) (4)
	√	Is a team review recommended?	
√		Are DMFs adequately referenced?	

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/s/

Marie Kowblansky
2/14/2008 12:23:51 PM
CHEMIST

Moo-Jhong Rhee
2/14/2008 01:31:47 PM
CHEMIST
Chief, Branch III



NDA 22-287

**Kapidex (dexlansoprazole)
Delayed Release Capsule**

TAP Pharmaceutical Products Inc.

Tarun Mehta

Review Chemist

**Office of New Drug Quality Assessment
Division of Pre-Marketing assessment II
Branch III**

**CMC REVIEW OF NDA 22-287
For the Division of Gastroenterology Products (HFD-180)**



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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 22-287
2. REVIEW #: 1
3. REVIEW DATE: 28-AUG-2008
4. REVIEWER: Tarun Mehta
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	28-DEC-2007
Correspondence (C)	
Amendment (0006)	28-April - 2008
Amendment (0020)	10-Sept-2008
Amendment (0023)	21-Oct-2208
Amendment (0028)	17-Dec - 2008

7. NAME & ADDRESS OF SPONSOR:

Name: TAP Pharmaceutical Products Inc.
Address: 675 North Field Drive, Lake Forest, IL 60045
Representative: Nancianne Knipfer, Ph.D., RAC
Telephone: 847-582-2193

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Kapidex
- b) Non-Proprietary Name: Dexlansoprazole
- c) Code Name/# (ONDQA only): TAK-390, TAK-390MR, T-168390
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Proton Pump Inhibitor (PPI)



CMC Review Data Sheet

11. DOSAGE FORM: Delayed Released Capsule
12. STRENGTH/POTENCY: 30 mg, 60 mg, (b) (4)
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product

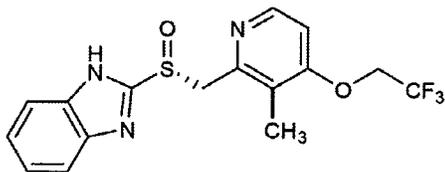
16. CHEMICAL NAMES:

(+)-2-[(R)-{[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1H-benzimidazole

2-[(R)-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole

R-(+)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-benzimidazole

STRUCTURAL FORMULA:



MOLECULAR FORMULA: C₁₆H₁₄F₃N₃O₂S

MOLECULAR WEIGHT: 369.36

**CMC REVIEW OF NDA 22-287****CMC Review Data Sheet****17. RELATED/SUPPORTING DOCUMENTS:****A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE¹	STATUS²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4) (b) (4) (b) (4) (b)	(b) (4)	3	Adequate	Review by Amin Yusuf 10/12/05	No update since last review
	III	(b) (4)	(b) (4) (b) (4)	4	Adequate		
	III	(b) (4)	(b) (4)	4	Adequate		
	III	(b) (4) (b) (4)	(b) (4) (b) (4)	4	Adequate		
	III	(b) (4) (b) (4) (b) (4) (b)	(b) (4) (b) (4) (b) (4)	3	Adequate	Reviewed by Sarah Pope 10/29/03	No update for (b) (4) since last review
	III	(b) (4) (b) (4) (b)	(b) (4) (b) (4) (b)	3	Adequate	Reviewed by Yichun Sun 11/12/07	No update since last review
	III	(b) (4) (b) (4) (b) (4) (b)	(b) (4) (b) (4)	3	Adequate	Reviewed by Kurtyka Bogdan 03/07/08	No update since last review
	III	(b) (4) (b) (4) (b) (4) (b) (4) (b)	(b) (4)	3	Adequate	Reviewed by Bertha Craig 06/06/07	No update since last review
	III	(b) (4) (b) (4) (b) (4) (b)	(b) (4)	3	Adequate	Reviewed by Bertha Craig 09/24/07	No update since last review
	III	(b) (4) (b) (4) (b) (4) (b)	(b) (4)	3	Adequate	Reviewed by Pope Sarah 07/27/04	No update since last review
IV	(b) (4) (b) (4) (b) (4) (b)	(b) (4)	3	Adequate	Niu Chien Hau	No update since last review	



CMC Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	69,927 and 30,159	TAK-390MR Capsule
NDA	20-406	Prevacid® Tablet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending (no 483 or issue)		
Biopharm	Not acceptable*	30-Sept - 08	Patrick Marroum
DMETS	Acceptable	28-Dec-08	Deveonne Hamilton

(b) (4)

The CMC Review for NDA 22-287

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, labeling issues are still pending and a site recommendation from Office of Compliance has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all issues are resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

Drug substance Dexlansoprazole is a R-enantiomer of the approved racemic (1:1 ratio) drug lansoprazole. Dexlansoprazole (API) is a new active ingredient in enantiomeric form. Proposed drug substance do not have a designated DMF. All the supporting CMC data is provided in the NDA submission.

Dexlansoprazole is pale yellowish white crystalline powder. It is freely soluble in polar organic solvent but practically insoluble in non-polar organic solvent. The solubility of the drug substance in aqueous solution increases with the pH value. It is slightly soluble in water (0.16mg/mL), but become soluble (58mg/mL) at the pH value of 10.9. Starting and intermediate materials for manufacturing dexlansoprazole and lansoprazole are the same. (b) (4)

The degradation products of the dexlansoprazole are similar to that of the lansoprazole. No new impurities were discovered during the synthesis as well as in the stability studies. The sponsor has submitted adequate information on manufacturing process and API characterization in this NDA. Adequate in-process controls are in place in manufacturing process to assure the consistent quality of the drug substance.



Executive Summary Section

Dexlansoprazole, the drug substance is further controlled per the release tests, i.e., appearance, identification, (b) (4) related substances, percentage of enantiomer, (b) (4) potency assay by (b) (4), and particle size distribution. Based on the stability data of clinical stability batches and, according to ICH Guidance Q1E, a retest date of (b) (4) is granted.

(2) Drug Product

The drug product dexlansoprazole Modified Released Capsules (TAK-390MR Capsules) are available in 30, 60, (b) (4) mg strength. The drug product was modified from their approved product lansoprazole capsules to achieve the prolonged plasma concentration.

Modified capsules are filled with two types of enteric coated granules exhibiting dual delayed release mechanism. One type of granules will release the drug in the proximal region of the small intestine where the pH reaches approximately 5.5. The second type of granules will release the drug more distally in the intestine where the pH reaches approximately 6.75. The ratio of these granules is maintained at (b) (pH 5.5: pH 6.75) in order to optimize the drug concentration in plasma. The formulation components of both the granules are the same except for the enteric coating layer, as shown in the figure below.

(b) (4)



The enteric coating layer differed by the polymer composition. These different polymers give them the characteristic dual delayed release mechanism. The mixture (b) of these granules filled in the color coded gelatin capsules printed with "TAP" logo and strengths.

The drug substance was manufactured at the manufacturing site in Osaka, Japan. All other excipients of this formulation are compendial (USP/NF) grade. The compendial monographs were used to test their quality.

The Takeda Pharmaceutical Company Limited Osaka Plant had conducted the drug product development and manufactured the clinical supplies. The compositions of the clinical formulation and the proposed commercial formulation are identical.



Executive Summary Section

(b) (4) commercial size batches were successfully manufactured at the proposed scale-up site, using the proposed commercial manufacturing process and equipments. The manufacturing process controls support the consistent quality of the drug product.

The drug product specification is deemed satisfactory. The identity, strength, and purity of the drug product are assured by the following analytical tests: appearance, identification, assay, related substances, content uniformity, dissolution, and loss on drying. (b) (4)

(b) (4) the final acceptance criteria were set based on the characteristic of the clinical batches.

The proposed container/closure system is deemed adequate. The container/closure system for the drug product is white (b) (4) bottle containing a silica gel desiccant with (b) (4) child-resistant caps and induction seal. The capsules are also packaged in thermoform blisters, which are then placed in cartons (100 capsules in each carton).

Stability results (updated in amendment 0006; April 28, 2008) derived from the (b) (4) stability batches packaged in the proposed container/closure met the specification. The drug products were stored up to 18 months for 30mg and 24 months for 60 (b) (4) 1g strengths at 25°C/60% RH condition. The results met the specification and no significant trend was observed. Based on the available stability data, 24 months of expiration dating period for the drug product is granted.

B. Description of How the Drug Product is Intended to be Used

Dose of TAK390-MR 60mg (b) (4) capsules, once daily for up to 8 weeks for the healing of erosive esophagitis (EE) (b) (4)

(b) (4) TAK-390 MR capsules can be taken without food. Alternatively, TAK-390MR capsules can be opened, sprinkled on one tablespoon of applesauce and swallowed immediately.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing process and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA has also provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

No acceptable site recommendation has been made by the Office of Compliance. Issues on Labels are still pending.



Executive Summary Section

III. Administrative

A. Reviewer's Signature:

Tarun Mehta

B. Endorsement Block:

Moo-Jhong Rhee, Ph.D. Branch Chief, Branch III, ONDQA

C. CC Block: entered electronically in DFS

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 √ Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Tarun Mehta
12/22/2008 02:10:11 PM
CHEMIST

Moo-Jhong Rhee
12/22/2008 04:11:38 PM
CHEMIST
Chief, Branch III