CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-327

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA 22-327
Clinical Pharmacology Review

REVIEW OF CLINICAL PHARMACOLOGY AND BIOPHARMCEUTICS

NDA	22-327 N000	*Submission Date(s)*	July 16, 2008, November 13, 2008, January 9, 2009, March 6, 2009, March 11, 2009
Brand Name		Prevacid 24HR (TBD)	
Generic Name		Lansoprazole delayed release capsule	
Reviewer		Insook Kim, Ph.D.	
Team Leader		Sue-Chih Lee, Ph.D.	
OCP Division		Division Of Clinical Pharmacology 3	
OND Division		Division of Non-prescription products	
Sponsor		Novartis	
Relevant IND(s)		IND 74,256 NDA 20-406, IND 30,159: Prevacid (Lansoprazole) delayed-release capsules	
Submission Type; Code		Original	505(b)(1)
Formulation; Strengths; Regimen		• Delayed release capsule 15 mg • 15 mg once daily for 14 days co-administered with water prior to breakfast	
Indication		• Over-the-counter (OTC) use • Short-term treatment of frequent heartburn (occurs 2 or more days a week), in adults aged 18 years and older.	

Executive Summary

NDA 22-327 was submitted in support of non-prescription lansoprazole delayed-release capsule for the short-term treatment of frequent heartburn (occurs 2 or more days a week), in adults aged 18 years and older. The sponsor refers to the clinical pharmacology information in the approved Rx Prevacid package insert as the proposed OTC lansoprazole granule formulation is the same as the Prevacid formulation currently on the market. As such there were no additional biopharmaceutics and clinical pharmacology studies conducted in support of non-prescription lansoprazole delayed-release capsule. The clinical pharmacology of the proposed non-prescription dosage regimen i.e. 15 mg once daily is adequately supported by the clinical pharmacology information in the current Prevacid label. Note that the approved Prevacid dosage regimen is 15 mg or 30 mg once daily. Therefore, this review will be focused on the proposed labeling.

Recommendation

The clinical pharmacology and biopharmaceutics information was reviewed by the division of clinical pharmacology III and found acceptable provided a mutual agreement regarding the label language can be reached between the sponsor and the Agency.

Background

The sponsor is seeking an approval of OTC use of lansoprazole 15 mg for the short-term treatment of frequent heartburn (occurs 2 or more days a week) in adults aged 18 years and older. The sponsor conducted three phase 3 trials to support the introduction of lansoprazole 15 mg capsules as OTC products. Lansoprazole, available in 15 and 30 mg dosage strengths, has been approved for prescription use in the United States since 1995. The marketed prescription product

of lansoprazole 15 and 30 mg (Prevacid® Delayed-Release Capsules 15 and 30 mg supplied by TAP Pharmaceuticals Inc.) were used for the active arms in the 3 Phase III clinical studies.
The clinical development program of lansoprazole 15 mg for OTC use consists of 3 large, placebo-controlled, Phase III trials (PRSW-GN-301, PRSW-GN-302 and PRSW-GN-305) in subjects with frequent heartburn. Overall, the objective of the program was to demonstrate that repeated daily morning doses of 15 mg of lansoprazole once a day are effective in increasing the proportion of days with no heartburn during 14 days (24-hour days) of treatment as compared to placebo in frequent heartburn sufferers. All 3 studies were conducted in the target population intended for OTC use of lansoprazole 15 mg in the management of frequent heartburn. The treatment period of 14 days is consistent with that currently approved for OTC omeprazole in the management of frequent heartburn. In addition to the 15 mg dose, the safety and efficacy of the 30 mg once daily dose was also investigated in Study PRSW-GN-305 on an exploratory basis for the management of heartburn symptoms.

Question Based Review

1. Is the to-be-marketed product same as the clinical formulation?

The proposed OTC product consists of enteric-coated granules in a gelatin capsule. The components of the drug product granules remained unchanged throughout the development program. The only differences in the finished drug product were minor changes in the composition of the two-piece gelatin capsules and the addition of a gelatin tamper evident band. Refer to Table 1 for the composition comparison in the finished drug product for the drug product clinical and stability batches.

The to-be-marketed OTC products are different from the products used in clinical trials in terms of capsule shell formulation and presence of banding. The clinical products were different in capsule shell formulation from the approved prescription products which were manufactured by Takeda Osaka Japan. Only the OTC products will have tamper-evident banding (Table 1).

Although the to-be-marketed OTC products are different from the clinical supplies, because the same enteric-coated lansoprazole granules as in the prescription products by Takeda were used in clinical trials and will be used for the OTC marketing, we consider the formulation change a minor change.

In addition, the to-be-marketed products are proposed to be manufactured i.e. encapsulation and banding at sites in the US and ——— while the clinical supplies and the prescription products were manufactured by Takeda Osaka in Japan (Table 2). The change in manufacturing sites across continents is considered a major change and for this level of change in manufacturing site of modified release products in vivo bioequivalence study is normally required to bridge the to-be-marketed products and the clinical supplies. b(4)

During filing review, this issue was internally discussed with CMC reviewers and we concluded that a lack of in vivo BE study was not considered a major deficiency of this submission for filing. We made a conclusion based on the fact that the manufacturing site change only for encapsulation and banding, an in vivo BE study is not warranted because the Lansoprazole granules which controll release of the active drug will be procured from Takeda.

Nonetheless, an adequate bridging between the OTC products and the clinical supplies as well as the OTC products and the prescription products must be established by adequate in vitro dissolution studies unless the sponsor provides justification not to do so. Therefore, we

recommended that the sponsor submit in vitro comparative dissolution studies with the f2 test between OTC products and the prescription products as well as the OTC products and the clinical supplies.

In the 74-day letter, a request for comparative dissolution study was communicated by the CMC reviewer. For further information, please see CMC review by Dr. Yichun Sun.

Table 1. Drug product composition comparison

Components	TAP R_x commercial formula (mg)	Clinical drug product batch formula (mg) 1577-01	Stability batches formula (mg) no. 1577-03	Proposed commercial formula (mg) no. 1577-05
Prevacid granules (AG-1749) Takeda Japan				
Gelatin	*			
Titanium Dioxide	*			
D&C red no. 28	*	-		
FD&C blue no. 1	*	-		
FD&C red no. 40	*	-		
FD&C green no. 3	*	-		
Gelatin		-		
Polysorbate 80		-		
FD&C blue no. 1		-		
FD&C red no. 40		-		

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*Quantitative composition not disclosed in TAP NDA 20-406.

Table 2. Manufacturing sites with responsibilities

Name of facility	Encapsulation & banding	Packaging	Analytical release testing	Stability testing
Novartis Consumer Health Lincoln, Nebraska	x	x	x	x
		x		
	x		x	

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Labeling recommendations

Reviewer's detailed labeling comments for Warning section

Ask a doctor or pharmacist before use if you are taking	
Reviewer's revision	**Reviewer's comment**
• warfarin (blood-thinning medicine)	Acceptable.
• prescription antifungal or anti-yeast medicines	In the prescription Prevacid label, a potential drug interaction between Lansoprazole and drugs whose oral absorption could be affected by gastric pH is described. Ketoconazole is one of known drugs whose absorption is affected by gastric pH. However, the prescription label for Prevacid is not extended to the whole drug class of "prescription antifungal or anti-yeast medicines". Some prescription antifungal medicines e.g. ketoconazole and itraconazole require low gastric pH for absorption due to poor solubility. On the other hand, the absorption of Fluconazole was not altered by concomitant antacid (Maalox®) and the absorption of Voriconazole is not affected by changes in gastric pH (Vfend® package insert). As such there is inconsistent information to support the class labeling. It is possible that another prescription antifungal medicine, Voriconazole, an inhibitor of both CYP2C19 and CYP3A4 may increase systemic exposure of Lansoprazole. Although there was no information submitted to address this possibility between Lansoprazole and Voriconazole, 2 folds increase in AUC of Omeprazole by concomitant Voriconazole was observed (Prilosec Rx label).
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• digoxin (heart medicine)	Acceptable. Digoxin is a drug with a narrow therapeutic index and gastric pH is an important factor of its bioavailability.
• theophylline (asthma medicine)	In the current Prevacid Rx label, the clearance of theophylline was increased by 10% by lansoprazole. This magnitude of change may not be a clinical concern but individual patients may require additional titration of their theophylline dosage when Prevacid is started or stopped to ensure clinically effective blood levels (Prevacid label). The labeling includes "Titration of theophylline may be required when concomitant Prevacid use is started or stopped" in the highlight of PRL format. According to the study which supported the drug interaction between lansoprazole and theophylline in the original submission, oral theophylline exhibited a decrease in AUC by 6% and 13% when co-administered with single dose and multiple doses of 60 mg lansoprazole. (Biopharmaceutics review on study M90-444 for original submission). On the other hand, the sponsor also provided literature articles reporting

	no significant effect of co-administered multiple doses of 30 mg lansoprazole on theophylline PK[123]. It should be noted that the effect of lansoprazole on theophylline PK was evaluated at a higher dose level e.g. 30 or 60 mg than the proposed 15 mg dose for lansoprazole OTC product. Notably, Ko et al. (1999) reported that in CYP2C19 poor metabolizers there was no change in theophylline clearance when 30 mg lansoprazole was co administered twice daily for 7 days. Taken together a potential of clinically relevant effect of 15 mg lansoprazole on theophylline pharmacokinetics appears low from a clinical pharmacology standpoint.
• tacrolimus (immune system medicine)	Acceptable. Lansoprazole (CYP2C19, CYP3A4 substrate) may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby substantially increase tacrolimus whole blood concentrations, especially in transplant patients who are intermediate or poor CYP2C19 metabolizers, as compared to those patients who are efficient CYP2C19 metabolizers. (Package insert for PROGRAF capsule). Plasma concentration of tacrolimus was significantly increased in healthy subjects when 30 mg lansoprazole was concomitantly administered. The percent increase for tacrolimus AUC^{0-8} in subjects with and without CYP2C19 mutant alleles was 81% and 29%, respectively[4] However, the Rx label for lansoprazole does not describe drug interaction between tacrolimus and lansoprazole. The drug interaction between lansoprazole and tacrolimus is expected to be more significant for prescription lansoprazole with higher dose level. [ ]

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[1] Ko et al. (1999) Theophylline pharmacokinetics are not altered by lansoprazole in CYP2C19 poor metabolizers, Clin. Pharmacol. Ther. 65(6): 606-614

[1] Dilger et al. (1999) Lack of drug interaction between Omeprazole, lansoprazole, pantoprazole and theophylline, Br.J. Clin. Pharmacol. 48,438-444

[1] Pan et al. (2000) Lack of a pharmacokinetic interaction between lansoprazole or pantoprazole and theophylline, Aliment PHarmacol Ther, 14: 345-352

[1] Fumio et al. 2004, Effect of lansoprazole and rabeprazole on tacrolimus pharmacokinetics in healthy volunteers with CYP2C19 mutations. J. pharm. Pharmacol.,56 (8) 1055-1059).

• atazanavir (medicine for HIV infection)	Acceptable. This reviewer recommend that "do not use with atazanavir" to be consistent with the Rx label, "atazanavir should not be co-administered with lansoprazole". Lansoprazole substantially decreases the systemic concentrations of atazanavir, which is dependent on the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance (Prevacid label). The AUC of atazanavir was decreased by 94% when a single-dose of 60 mg lansoprazole was co-administered. [1]
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Reviewer's labeling comments

How to Take PREVACID® 24 HR

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[1] Tomilo et al. (2006) Inhibition of Atazanavir oral absorption by lansoprazole gastric acid suppression in healthy volunteers, Pharmacotherapy, 26(3): 341-346

6 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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OFFICE OF CLINICAL PHARMACOLOGY FILING MEMO

NDA	22-327	*Submission Date(s)* *74 day- letter date*	July 16, 2008 September 28, 2008
Brand Name		Prevacid 24HR	
Generic Name		Lansoprazole delayed release capsule	
Reviewer		Insook Kim, Ph.D.	
Team Leader		Sue-Chih Lee, Ph.D.	
OCP Division		Division Of Clinical Pharmacology 3	
OND Division		Division of Gastroenterology Products and In-born Errors of Metabolism	
Sponsor		Novartis	
Relevant IND(s)		IND 74,256 NDA 20-406, IND 30,159: Prevacid (lansoprazole) delayed-release capsules	
Submission Type; Code		Original	505(b)(1)
Formulation; Strengths; Regimen		• Delayed release capsule 15 mg • 15 mg once daily for 14 days co-administered with water prior to breakfast	
Indication		• Over-the-counter (OTC) use • Short-term treatment of frequent heartburn (occurs 2 or more days a week), in adults aged 18 years and older.	

Filing recommendation

This application is fileable from a clinical pharmacology standpoint. However, we request that the sponsor submit comparative in vitro dissolution study reports with the f2 test for the OTC products vs. the prescription products as well as the OTC products vs. the clinical supplies.

Background

The sponsor is seeking an approval of lansoprazole 15 mg for the short-term treatment of frequent heartburn (occurs 2 or more days a week) in adults aged 18 years and older. The sponsor conducted three phase 3 trials to support the introduction of lansoprazole 15 mg capsules as OTC products. Lansoprazole, available in 15 and 30 mg dosage strengths, has been approved for prescription use in the United States since 1995. The similar products with the same lansoprazole granules same as in Prevacid® Delayed-Release Capsules 15 and 30 mg by TAP Pharmaceuticals Inc. were used for the active arms in the 3 Phase III clinical studies.

The clinical development program of lansoprazole 15 mg for OTC use consists of 3 large, placebo-controlled, Phase III trials (PRSW-GN-301, PRSW-GN-302 and PRSW-GN-305) and in subjects with frequent heartburn. Overall, the objective of the program was to demonstrate that repeated daily morning doses of 15 mg of lansoprazole once a day are effective in increasing the proportion of days with no heartburn during 14 days (24-hour days) of treatment as compared to placebo in frequent heartburn sufferers. All 3 studies were conducted in the target population intended for OTC use of lansoprazole 15 mg in the management of frequent heartburn. The treatment period of 14 days is consistent with that currently approved for OTC omeprazole in the management of frequent heartburn. In addition to the 15 mg dose, the safety and efficacy of the

30 mg once daily dose was also investigated in Study PRSW-GN-305 on an exploratory basis for the management of heartburn symptoms.

There is no biopharmaceutics and clinical pharmacology studies conducted for the current NDA as the pharmacology of lansoprazole is well documented in the literature and the same lansoprazole granule formulation were used in clinical trials.

Reviewer's comments

The to-be-marketed OTC products are different from the products used in clinical trials in terms of capsule formulation and presence of banding. The clinical supplies were slightly different in capsule formulation from the approved prescription products manufactured by Takeda Osaka Japan. Only the OTC products have tamper-evident banding.

Although the to-be-marketed OTC products are different from the clinical supplies, because the same enteric-coated lansoprazole granules as in the prescription products by Takeda were used in clinical trials and will be used for the OTC marketing, we consider the formulation change a minor change.

In addition, the to-be-marketed products are proposed to be manufactured i.e. encapsulation and banding at sites in the US and in — while the clinical supplies and the prescription products were manufactured by Takeda Osaka in Japan. The change in manufacturing sites across continents is considered a major change and for this level of change in manufacturing site of modified release products normally an in vivo bioequivalence study is required to bridge the to-be-marketed products and the clinical supplies. b(4)

However, we believe that the manufacturing site change only for encapsulation and banding for the product do not warrant an in vivo BE study because the lansoprazole granules will be procured from Takeda. Therefore, lack of the in vivo BE study is not considered a major deficiency of the current application. As such, this application is fileable from a clinical pharmacology standpoint.

Nevertheless, we believe that adequate bridging between the OTC products and the clinical supplies as well as the OTC products and the prescription products must be established by in vitro dissolution studies unless the sponsor provides justification not to do so. Therefore, we recommend the sponsor submit in vitro comparative dissolution studies with the f2 test between OTC products and the prescription products as well as the OTC products and the clinical supplies.

Appendix-Excerpts from the NDA

2.3 Biopharmaceutics conclusions

The currently marketed prescription formulation was used in the Phase III development program for the OTC switch of lansoprazole 15 mg. The same formulation is proposed to be used for OTC marketing once approval is granted by the Agency. The capsules to be marketed OTC will also have a tamper-evident band.

Table 1-2 Lansoprazole AG-1749 Granule Composition

Component	Reference to quality standard	Function	mg/capsule
Lansoprazole	USP	Active substance	15.0
Magnesium carbonate	USP		
Sugar spheres	NF		
Sucrose,	NF		
starch	NF		
Low-substituted hydroxypropyl cellulose, LH-T	NF		
Hydroxypropyl cellulose, L	NF		
	USP		
Methacrylic acid copolymer	NF		
Polyethylene glycol	NF		
Titanium dioxide	USP		
Polysorbate 80	NF		
Talc	USP		
	USP		
Talc	USP		
Colloidal silicon dioxide	NF		

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2.4.3 Clinical, stability and commercial formulation comparison

The components of the drug product granules remained unchanged throughout the development program. The only differences in the finished drug product were minor changes in the composition of the two-piece gelatin capsules and the addition of a gelatin tamper evident band. Refer to Table 2-3 for the composition comparison in the finished drug product for the drug product clinical and stability batches. The minor differences do not affect the quality, stability or efficacy of the drug product.

Table 2-3 Drug product composition comparison

Components	TAP R_x commercial formula (mg)	Clinical drug product batch formula (mg) 1577-01	Stability batches formula (mg) no. 1577-03	Proposed commercial formula (mg) no. 1577-05
Prevacid granules (AG-1749) Takeda Japan	[redacted]			[redacted]
Gelatin	[redacted]	[redacted]	[redacted]	
Titanium Dioxide	[redacted]	[redacted]		
D&C red no. 28	[redacted]	-		
FD&C blue no. 1	[redacted]	-		
FD&C red no. 40	[redacted]	-		
FD&C green no. 3	[redacted]	-		
Gelatin		-		
Polysorbate 80		-		
FD&C blue no. 1		-		
FD&C red no. 40		-		

*Quantitative composition not disclosed in TAP NDA 20-406.

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All active granules were supplied from commercial production by Takeda under TAP NDA 20-406 with only minor changes made in the quantity of polysorbate 80, gelatin and dye content, as shown in Table 2-3.

Table 3-1 Manufacturing sites with responsibilities

Name of facility	Encapsulation & banding	Packaging	Analytical release testing	Stability testing
Novartis Consumer Health Lincoln, Nebraska	X	X	X	X
[redacted]		X		
	X		X	

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/s/

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