CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-210

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology OND IO
NDA: 22-210
Submission receipt date: December 17, 2007
Drug: Zenpep (pancrelipase) Delayed-Release Capsules
Sponsor: Eurand Pharmaceuticals, Ltd.
Indication: Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions

Reviewing Division: Division of Gastroenterology Products

Introductory Comments: The pharm/tox reviewer and supervisor have found the nonclinical information adequate to support approval of this NDA for the above indication. As noted by the reviewer, no new pharmacology studies and no toxicology studies are needed for new pancreatic enzyme products as outlined in the Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products - Submitting NDAs, which was published in 2006.

The sponsor submitted several studies of one of the excipients, hydroxypropyl methylcellulose phthalate. The reviewer found that the safety of the excipients was adequately supported for the indicated use.

The reviewer recommended that the product be labeled as pregnancy category C and that the labeling state that animal reproduction studies have not been conducted.

Conclusions:
I agree that the nonclinical information provided is adequate to support approval of this NDA from a pharm/tox perspective. No additional nonclinical studies are recommended. I agree with the labeling suggestions in the pharm/tox review.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22210	ORIG 1		ZENTASE

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

/s/

PAUL C BROWN
08/19/2009

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: 22,210

SERIAL NUMBER: 000 and 000BZ

DATE RECEIVED BY CENTER:

000: December 17, 2007
000BZ: March 21, 2008

DRUG NAME: Zentase, capsules

INTENDED CLINICAL POPULATION: Pancreatic enzyme preparation for treatment of exocrine pancreatic insufficiency.

SPONSOR: Eurand Pharmaceuticals Limited
Wicklow, Ireland

U.S. Agents: Bhanu Balasubramaniam, RAC
Vandalia, OH

DOCUMENTS REVIEWED: EDR – Module 4

REVIEW DIVISION: Division of Gastroenterology Products (HFD-180)

PHARM/TOX REVIEWER: Ke Zhang, Ph.D.

PHARM/TOX SUPERVISOR: Sushanta Charkder, Ph.D.

DIVISION DIRECTOR: Donna Griebel, M.D.

PROJECT MANAGER: Ms. Maureen Dewey

Date of review submission to Division File System (DFS):

May 1, 2008

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Executive Summary

1. Recommendations

1.1 Recommendation on approvability

From a preclinical standpoint, approval of Zentase is recommended for treatment of exocrine pancreatic insufficiency.

1.2 Recommendation for nonclinical studies: None

1.3 Recommendation on labeling: The labeling should be revised as follows: "Animal reproduction studies have not been conducted with Zentase. It is not known whether Zentase capsules can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Zentase capsules should be given to a pregnant woman only if clearly needed".

2. Summary of nonclinical findings:

Based on the Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs published in 2006, no new pharmacology studies and no toxicology studies are needed for pancreatic enzymes.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22,210
Review number: 01
Sequence number/date/type of submission:
000: December 17, 2007
000BZ: March 21, 2008

Information to sponsor: Yes () No (x)

Sponsor and/or agent: Eurand Pharmaceuticals Limited
Wicklow, Ireland

U.S. Agents: Bhanu Balasubramaniam, RAC
Vandalia, OH

Reviewer name: Ke Zhang
Division name: Division of Gastroenterology Products
HFD #: 180
Review completion date: May 1, 2008

Drug: Zentase / EUR-1008, capsules

Molecular Weight / Formula: Not applicable

Relevant INDs/NDAs/DMFs: IND 70,563

Drug class: Pancreatic enzyme preparation.

Indication: Zentase is indicated for treatment of exocrine pancreatic insufficiency. The recommended starting dose of Zentase is 1,000-2,000 lipase units/kg/meal with a total dose ≤10,000 lipase units/kg/day.

Clinical formulation:

The clinical formulation was presented in the following sponsor's table.

Table 2.6-1 Composition of EUR-1008 capsules and maximum accepted level for each excipient

Ingredient	Unit Composition per Capsule (mg)				Maximum Accepted Level for a Single Oral Dosage Form (mg)[1]
	5,000 USP Units	10,000 USP Units	15,000 USP Units	20,000 USP Units	
Croscarmellose Sodium	(b) (4)				
Hydrogenated Castor Oil					
Colloidal Silicon Dioxide					
Cellulose Microcrystalline					
Magnesium Stearate					
Hypromellose Phthalate					
Talc					
Triethyl Citrate					
Carrageenan					
Potassium Chloride					
Titanium Dioxide					
Hypromellose					
Carnauba Wax					
Yellow Ferric Oxide					
Red Ferric Oxide					
FDC Blue 2					
(b) (4)	(b) (4)		(b) (4)		

Source: CTD Module 3, Section 3.2.P.2.1

[1] Reference: http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm (Inactive Ingredients for Approved Drug Products.), entry date 05/21/07
[2] Also relevant is FDA regulation (21 CFR, 73.1200), which specifies a maximum allowed elemental iron daily intake of 5 mg/day.
[3] See note 2

Zentase capsule contains: 5,000, 10,000, 15,000, and 20,000 USP lipase units. Based on the proposed labeling, the maximum daily dose is 10,000 units/kg/day or 500,000 units/day if 50 kg body weight assumed. Using the capsules containing 20,000 units lipase, one would consume up to 25 capsules/day to reach the maximum daily dose of 10,000 Units/kg/day or 500,000 units/day. Therefore, the estimated maximum daily consumptions for the following excipients are presented below.

- Hypromellose phthalate, (b) (4) mg/capsule

25 capsules/day = (b) (4) mg/day

- Triethyl citrate, (b) (4) mg/capsule

25 capsules/day = (b) (4) mg/day

- Hypromellose, (b) (4) mg/capsule

25 capsules/day = (b) (4) mg/day

Route of administration: Oral capsule.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: Following publications were reviewed:

1. 30-day and 6-month oral toxicity studies with hydroxypropyl methylcellulose phthalate (HPMCP) in rats.

2. 27-week oral toxicity study with HPMCP in dogs.

3. Reproductive toxicity study with HPMCP in mice and rats.

Studies not reviewed within this submission: None.

2.6.2 PHARMACOLOGY

Not applicable.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

Not applicable.

2.6.6 TOXICOLOGY

Triethyl citrate

Triethyl citrate (CAS Reg. No. 77-93-0) is considered as GRAS under 21 CFR part 184.1911 at levels not exceeding current

good manufacturing practice when used as a flavouring agent, a solvent or vehicle or a surface-active agent. An acceptable daily intake (ADI) for triethyl citrate up to 10 mg/kg was established by the Joint FAO/WHO Expert Committee on Food Additives.

The estimated maximum daily intake of triethyl Citrate from zentase is (b) (4) mg/day or (b) (4) mg/kg/day if 50 kg body weight is assumed.

Hypromellose

Hypromellose or hydroxypropyl methylcellulose (HPMC) (CAS Reg 009004-65-3) is considered as a food additive permitted for direct addition to food for human consumption in 21 CFR 172.874.

HPMC is one of the five modified celluloses (methyl cellulose, methyl ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, and sodium carboxymethyl cellulose). The modified celluloses were reviewed by the Joint FAO/WO Expert Committee on Food Additives (thirty-fifth report, 1990). The group ADI up to 25 mg/kg for these five modified celluloses was established by the Committee. The report also indicated that the modified celluloses have been used as laxatives as doses of 5-30 g/day and that "the amount of ingested in studies in human did not exceed 30 g per person per day, which has been recommended by the United State National Research Council as the upper safe level of dietary fibre in general". These modified celluloses were not carcinogenic in long-term carcinogenicity studies in mice and rats or embryotoxic in mice, rats, and rabbits based on the report.

The estimated maximum daily intake of HPMC from zentase is (b) (4) mg/day.

Hypromellose phthalate / Hydroxypropyl Methylcellulose Phthalate

Hydroxypropyl methylcellulose phthalate (HPMCP, CAS 9050-31-1), is a polymer consisting of approximately 24% phthalyl-, 8% hydroxypropoxy-, and 22% methoxy-substitution of the cellulose backbone. The approved oral formulations of HPMCP by the FDA are up to 302.4 mg/unit dose. The maximum daily acceptable oral level is not available. The estimated maximum daily intake of HPMCP from zentase is (b) (4) mg/day or (b) (4) mg/kg/day if 50 kg body weight is assumed. Reports of the following

toxicity studies were provided: 30-day and 6-month oral toxicity studies in rats and 27-week oral toxicity study in dogs.

30-day oral toxicity study in rats
(Pharmacometrics, 1970; 4(6):1017-1025; Kitagawa et. al.)

Methods: To evaluate oral toxicity study of HPMCP, Wistar rats (10/group) were given HPMCP at 0, 1.3, 2, 3, 4.5, and 10 g/kg by oral gavage for 30 days. Clinical signs of toxicity were monitored daily. Food consumption and body weights were recorded twice weekly. Some parameters of hematology, clinical chemistry, and urinalysis were monitored at termination. The animals were sacrificed and organ weights (liver, kidneys, spleen, heart, lungs, gonads, adrenals and thyroid) were determined. Gross and microscopic examinations were then conducted on the following organs: liver, heart, kidneys, spleen, adrenals, pancreas, thyroid, testis, ovary, stomach, small intestine, cerebrum and cerebellum.

Results: The animals in the 10 g/kg group had severe diarrhea and ataxia within 1 hour following dosing. The animals in this group received 12.5 ml/100 g solution. Diarrhea and ataxia were also noted in the vehicle control group that received 12.5 ml/100 g solution. All animals in the 10 g/kg dose group and in the vehicle control group that received 12.5 ml/100 g solution died within 10 and 16 days, suggesting that the excessive amount of solution may be the cause of the deaths. No treatment related changes were observed in animals receiving 4.5 g/kg or less. The no effect level was 4.5 g/kg.

6-month oral toxicity study in rats
(Pharmacometrics, 1973; 7(5):689-701; Kitagawa et. al.)

Methods: To investigate the long term toxicity of HPMCP, Wistar rats (10/sex/group) were given HPMCP at 0, 1.5, 3, and 6 g/kg/day by oral gavage for 6 months. Clinical signs and body weights were monitored daily. Some parameters of hemotology, clinical chemistry, and urinalysis were monitored at month 3 and at termination. Gross and microscopic pathological examinations were conducted at termination. Weights of liver, kidneys, heart, spleen, brain, lungs, adrenals, testes and ovaries were recorded.

Results: Some animals were found dead during the study and the investigator believed that the deaths were attributed to viral infection (cold or pneumonia). The number of animals that died in each group were not provided. There were no treatment related changes in body weight, hematology, urinalysis, organ weights, gross and histopathological examinations. The weights of liver, lungs, adrenals and ovaries of treated rats were slightly increased as compared to the controls. The no effect dose was 6.0 g/kg. The results were presented in the following tables.

TABLE I Body weight of rats orally administered with HPMCP for 6 months

	Dose mg/kg/day	0	1,500	3,000	6,000
weeks					
1	Male	96.6± 2.39*	98.6± 2.31*	97.0± 2.87*	105.7± 2.54
3		155.4± 4.54	159.8± 4.84	159.5± 6.93	163.7± 4.35
5		204.7± 5.73	209.4± 7.95	217.3±11.53	223.5± 4.48
7		257.8±10.83	266.9± 9.30	271.8±19.25	281.2± 6.16
9		296.3±15.54	313.7±11.61	324.7±19.91	319.1± 7.25
11		326.4±13.08	339.9±14.77	351.9±35.57	352.4± 7.45
13		361.3±17.00	373.8±16.86	372.9±12.98	384.5±10.31
15		368.2±19.31	377.3±18.71	378.3±15.27	390.0±11.97
17		379.6±17.14	391.3±17.71	410.8±17.38	418.1±14.61
19		404.2±14.87	425.7±20.55	440.2±17.04	436.7±20.44
21		422.3±16.72	440.6±21.07	449.6±20.62	435.4±29.63
23		443.4±21.50	442.2±26.59	446.8±23.19	440.8±16.76
25		462.1±21.85	472.6±33.50	461.3±32.74	467.6±19.00
26		470.7±23.45	475.3±33.80	475.3±29.86	498.5±16.62
1	Female	94.8± 2.96	93.6± 2.12	93.6± 2.58	101.4± 1.50
3		135.7± 5.08	137.0± 3.61	135.8± 5.51	142.9± 3.97
5		170.9± 6.56	169.6± 5.20	174.9± 5.89	173.6±10.44
7		207.8± 7.58	192.4± 6.96	206.0± 6.58	220.1± 5.63
9		220.4± 8.70	212.5± 9.09	220.6± 8.45	234.2± 6.94
11		231.2± 9.62	227.7± 6.62	232.3± 8.99	246.8± 7.39
13		239.6±12.44	234.5± 6.86	250.8± 8.77	261.9±12.81
15		250.0±12.94	238.5± 6.54	246.4±11.36	265.4±12.00
17		259,6±12.55	254.3± 6.69	258.1±15.29	287.5±17.63
19		266.0±13.24	257.5± 8.07	261.7±15.21	287.4±21.95
21		272.0±13.75	265.3± 8.16	272.0±22.62	293.4±16.43
23		279.4±16.85	269.6± 8.99	279.0±21.94	296.0±15.27
25		264.0± 4.57	274.7±10.00	284.8±25.14	313.4±21.86
26		262.4± 5.79	272.9±10.33	286.2±23.39	317.4±22.94

* : S.E.

TABLE 2 Organ wet weight of male and female rats which were orally administered with HPMCP for 6 months

Sex	Dose mg/kg/day	Heart (g)	Spleen (g)	Hypophysis (mg)	Brain (g)	Liver (g)
Male	0	1.28±0.08*	0.67±0.05*	7.5±0.57*	1.56±0.44*	13.11±1.20*
	1,500	1.25±0.06	0.87±0.10	10.3±1.24	1.49±0.11	14.04±1.05
	3,000	1.41±0.16	0.91±0.07	7.9±2.10	1.63±0.04	16.38±2.60
	6,000	1.22±0.04	0.77±0.06	10.2±0.41	1.73±0.09	15.35±0.69
Female	0	0.81±0.04	0.68±0.09	10.3±1.84	1.41±0.03	8.76±0.22
	1,500	1.16±0.30	0.56±0.03	9.1±1.19	1.49±0.11	9.38±0.31
	3,000	0.80±0.82	0.57±0.06	17.2±1.90	1.42±0.04	9.30±0.67
	6,000	0.95±0.04	0.60±0.05	11.6±1.30	1.36±0.07	10.31±1.22

Sex	Dose mg/kg/day	Lung (g)	Kidney (g)	Adrenals (mg)	Testis (g)	Ovary (mg)
Male	0	1.61±0.13*	2.81±0.15*	37.2±2.49*	2.53±0.08*	
	1,500	1.99±0.27	2.82±0.13	50.8±4.93	2.65±0.06	
	3,000	2.23±0.57	3.32±0.36	57.5±5.36	2.66±0.10	
	6,000	2.08±0.21	3.00±0.06	62.3±3.61	2.71±0.28	
Female	0	1.72±0.30	1.67±0.06	51.6±5.40		48.7±5.87*
	1,500	1.74±0.21	1.69±0.14	47.3±3.81		51.5±3.25
	3,000	1.88±0.37	1.85±0.08	62.2±5.93		60.1±5.61
	6,000	1.58±0.31	2.08±0.19	62.2±5.42		63.6±6.33

* : S.E.

TABLE 3 Organ-body weight ratio of rats treated orally with HPMCP for 6 months

Sex	Dose mg/kg/day	Heart (%)	Spleen (%)	Hypophysis (×10⁻²%)	Brain (%)	Liver (%)
Male	0	0.28±0.01*	0.15±0.06*	0.16±0.02*	0.35±0.04*	2.89±0.15*
	1,500	0.27±0.03	0.19±0.02	0.22±0.03	0.32±0.01	3.01±0.15
	3,000	0.27±0.01	0.17±0.00	0.17±0.06	0.32±0.02	3.13±0.33
	6,000	0.26±0.02	0.16±0.09	0.21±0.02	0.36±0.03	3.17±0.16
Female	0	0.31±0.01	0.26±0.03	0.33±0.05	0.55±0.02	3.37±0.06
	1,500	0.34±0.01	0.21±0.01	0.34±0.04	0.57±0.06	3.53±0.10
	3,000	0.29±0.02	0.21±0.02	0.33±0.03	0.53±0.04	3.43±0.29
	6,000	0.31±0.03	0.19±0.05	0.36±0.02	0.45±0.05	3.80±0.19

Sex	Dose mg/kg/day	n	Lung (%)	Adrenals (×10⁻²%)	Testis (%)	Kidney (%)	Ovary (×10⁻²%)
Male	0	7	0.35±0.03*	0.87±0.05*	0.57±0.02*	0.64±0.02*	
	1,500	7	0.48±0.08	1.11±0.11	0.58±0.03	0.61±0.03	
	3,000	3	0.45±0.15	1.12±0.11	0.52±0.02	0.67±0.03	
	6,000	4	0.43±0.09	1.30±0.13	0.57±0.09	0.62±0.02	
Female	0	5	0.66±0.02	1.82±0.21		0.64±0.02	1.67±0.08*
	1,500	7	0.65±0.05	1.78±0.13		0.63±0.04	1.99±0.16
	3,000	5	0.68±0.13	2.30±0.25		0.68±0.04	2.23±0.25
	6,000	5	0.51±0.08	2.03±0.09		0.68±0.04	2.05±0.14

* ; S.E.

TABLE 4 Hematological findings in male and female rats orally treated with HPMCP for 3 months and 6 months

Test Period	Sex	Dose mg/kg/day	Red blood cell ($\times 10^4$/mm^3)	Hemoglobin (Sahli %)	W.B.C. ($\times 10^2$/mm^3)	Differentiation (%) of W.B.C. Neutro.	Lymph.
3 months	Male	0	757±77.9*	106±2.7*	50± 6.4*	23.7± 3.53*	73.7± 3.84*
		1,500	759±58.9	107±4.2	56±12.1	25.8± 6.30	68.6± 5.91
		3,000	708±37.6	106±2.8	38± 4.8	17.0± 1.87	78.0± 1.91
		6,000	785±35.5	102±1.0	43± 3.7	12.0± 1.92	83.6± 3.14
	Female	0	807±52.3	92±2.6	46± 2.6	25.3± 2.40	71.0± 2.38
		1,500	665±60.8	90±2.1	44± 3.6	18.8± 3.92	77.4± 2.94
		3,000	662±60.7	90±2.4	45± 2.7	21.6± 2.27	75.8± 2.31
		6,000	772±57.6	96±2.5	49± 6.6	19.0± 5.50	79.3± 6.06
6 months	Male	0	786±72.5	92±3.5	57± 5.5	16.9± 3.04	79.0± 3.16
		1,500	756±59.7	92±1.5	57± 1.0	21.0± 2.49	72.3± 2.81
		3,000	982±43.7	90±2.6	57± 4.0	21.3±11.83	73.3±13.20
		6,000	819±85.2	92±2.3	51± 8.2	16.3± 1.11	77.3± 3.20
	Female	0	786±10.3	92±1.8	59± 3.7	23.0± 5.82	70.5± 6.02
		1,500	705±22.2	85±2.3	44± 7.5	15.9± 1.18	78.7± 1.69
		3,000	845±56.6	91±2.1	57± 4.0	20.8± 4.85	75.0± 4.83
		6,000	828±30.9	90±2.1	46± 6.7	15.6± 2.68	80.2± 3.02

* : S.E.
W.B.C. : White Blood Cell

TABLE 5 Pathohistological findings in rats after oral administration of HPMCP for 6 months

	HPMCP		Control		1.5g/kg		3.0g/kg		6.0g/kg	
	sex		♂	♀	♂	♀	♂	♀	♂	♀
	n		3	3	3	3	3	5	4	5
			− +	− +	− +	− +	− +	− +	− +	− +
heart	epicardium fibrosis		3 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
heart	endocardium fibrosis		3 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
heart	mycardium fibrosis		2 1	3 0	3 0	3 0	3 0	5 0	4 0	5 0
liver	Glisson's sheath	cells infiltration	0 3	1 2	1 2	0 3	0 3	1 4	2 2	0 5
liver	Glisson's sheath	increa in bile duct	2 1	2 1	3 0	2 1	3 0	3 2	2 2	4 1
liver	liver cell	fatty degeneration	0 3	0 3	0 2	1 0	0 1	1 2	0 4	1 4
liver	liver cell	degeneration	3 0	2 1	3 0	3 0	3 0	5 0	4 0	5 0
liver	cell infiltration in the hepatic cell-cords		3 0	2 1	3 0	3 0	3 0	5 0	4 0	5 0
liver	kupffer cell	lipid	3 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
liver	kupffer cell	swelling	3 0	2 1	3 0	3 0	3 0	5 0	4 0	5 0
kidney	glomerlus		3 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
kidney	tubules	proxismal (lipid)	3 0 (1 2)	3 0 (1 2)	3 0 (2 0)	3 0 (0 1)	3 0 (1 0)	5 0 (0 3)	4 0 (3 1)	5 0 (4 1)
kidney	tubules	distal (lipid)	3 0 (3 0)	3 0 (3 0)	3 0 (2 0)	3 0 (1 0)	3 0 (1 0)	5 0 (3 0)	4 0 (4 0)	5 0 (5 0)
kidney	cells infiltration in the renal pelvis		1 2	0 3	0 3	0 3	1 2	2 3	2 2	0 5
kidney	artery		3 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
kidney	cell infiltration in interstitium		2 1	2 1	3 0	3 0	3 0	5 0	4 0	4 1
spleen	trabeculae		2 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
spleen	white pulp		2 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
spleen	red pulp		2 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
spleen	hemosiderosis		1 1	0 3	1 2	2 1	2 1	2 3	2 2	0 5

TABLE 6 Pathohistological findings in rats after oral administration of HPMCP for 6 months

	HPMCP	Control		1.5g/kg		3.0g/kg		6.0g/kg	
	sex	♂	♀	♂	♀	♂	♀	♂	♀
	n	3	3	3	3	3	3	3	3
		− +	− +	− +	− +	− +	− +	− +	− +
lung	bronchitis	1 2	1 2	1 2	2 1	2 1	4 1	3 1	3 2
	pneumonia	2 1	1 2	2 1	2 1	2 1	5 0	3 1	4 1
	hemorrhage	3 0	1 2	3 0	3 0	3 0	3 2	3 1	3 2
adrenal	cortex	3 0	3 0	3 0	3 0	1 0	5 0	4 0	5 0
	medulla	3 0	3 0	3 0	3 0	2 0	5 0	4 0	5 0
pancreas	pancreatic ducts	2 0	1 0	1 0	2 0	1 0	2 0	3 0	2 0
	lobules	2 0	1 0	1 0	2 0	1 0	2 0	3 0	2 0
	islets of Langerhans		1 0	1 0	1 0	1 0	2 0	3 0	2 0
thyroid gland	hypertrophy of the follicular epishelium	1 0	3 0	3 0		1 0	3 0	4 0	4 0
	decrease in colloid	1 0	3 0	3 0		1 0	3 0	2 2	4 0
	interfollicular connective tissue	1 0	3 0	3 0		1 0	3 0	4 0	4 0
testis	hyposper matogenesis	3 0		3 0		3 0		4 0	
	decrease in interstitial cells	3 0		3 0		3 0		4 0	
ovary	decrease in follicles		3 0		2 0		5 0		5 0
	abnormal graafian follicles		3 0		2 0		5 0		5 0
stomach	mucosa	3 0	3 0	2 1	3 0	3 0	5 0	4 0	5 0
	submucosa	3 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
	muscle layer	3 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
	serosa	3 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
	mucosa	3 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
small intestine	submucosa	3 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
	muscle layer	3 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
	serosa	3 0	3 0	3 0	3 0	3 0	5 0	4 0	5 0
hypophysis	antenior lobe		2 0			2 0		2 0	2 0
	postenor lobe		2 0			2 0		1 0	2 0

27-week oral toxicity study in dogs

(b) (4) (1973)

Methods: To investigate the long term toxicity study in dogs, HPMCP was given to dogs (4/sex/group) by oral capsules at 0, 0.75, 1.5 and 3.0 g/kg/day for 27 weeks. Compositions of HPMCP were summarized in the following table (Table 6).

Table 6: Tabulation of Properties of Test Materials used in chronic toxicity study in dogs on HPMCP

HPMCP type	Molecular Weight	Hydroxypropyl Content	Methoxy Content	Phthalyl Content
HP-50	84,000	8%	22%	24%
HP-55	78,000	7%	31%	20%

Clinical evaluations were recorded daily. Body weights were recorded weekly. Hematology, clinical chemistry, and urinalysis were conducted at weeks 13 and 26. Blood pressures were monitored during weeks 0, 4, 8, 13, and 26. Ophthalmological examinations were conducted at weeks 0, 13, and 26. The gross or histopathological examinations were not reported.

Results: There were no deaths. Soft feces and diarrhea were noted in the mid and high dose groups. There were no treatment related changes in body weights, hematology, clinical chemistry, urinalysis, and ophthalmological examinations. The high dose of 3.0 g/kg was well tolerated.

2.6.6.4 Genetic toxicology

Not applicable.

2.6.6.5 Carcinogenicity

Not applicable.

2.6.6.6 Reproductive and developmental toxicology

Studies on the Teratogenicity of HPMCP in mice and rats

(J. Med. Soc. Tokyo, Japan, 1972; 19(5):453-461)

Methods: To investigate the teratogenic potential of HPMCP in mice and rats, HPMCP was administered by oral gavage to mice at

0, 20, 200, and 4000 mg/kg or to rats at 0, 20, 200, and 2400 mg/kg during pregnancy. Dams were observed for clinical signs, body weights and food consumption and sacrificed on day 18 of gestation (mice) and on day 20 of gestation (rats). Following observations were monitored in each fetus: numbers of implantation sites, dead and live embryos, body weight, sex, gross observations, ossification and skeletal abnormalities.

Results: The results indicated that treatment with HPMCP delayed ossification at the high dose in rats. No treatment related malformations were observed in both mice and rats. Some of the results were presented in the following tables.

Tab. 1 Findings of rat fetuses receiving HPMCP.

Groups	Mothers	Number of implantations	Number of dead fetuses	Number of living fetuses	Sex ratio (♂/♀)	Average weight of living fetuses	Average weight of placenta	External abnormality
Control	15	164 (10.9±0.64)	13 (7.9%)	151 (10.1±0.60)	72/79 (0.911)	3.60±0.030	360.2±4.70	0
20mg/kg	15	162 (10.8±0.45)	10 (6.2%)	152 (10.1±0.46)	81/71 (1.141)	3.62±0.031	348.4±4.55	0
200mg/kg	15	158 (10.5±0.44)	15 (9.5%)	143 (9.5±0.41)	72/71 (1.014)	3.67±0.032	374.0±4.85	0
2400mg/kg	15	180 (12.0±0.53)	21 (11.7%)	159 (10.6±0.54)	85/74 (1.149)	3.64±0.054	374.7±4.59 (mean±S.E.)	0

Tab. 2 Finding of mouse fetuses receiving HPMCP.

Groups	Mothers	Number of implantations	Number of dead fetuses	Number of living fetuses	Sex ratio (♂/♀)	Average weight of living fetuses	Average weight of placenta	External abnormality
Control	16	134 (8.4±0.24)	14 (10.4)	120 (2.5±6.40)	52/68 0.765	1.03±0.006	89.5±0.89	0
20mg/kg	15	127 (8.5±0.35)	13 (10.2)	114 (7.6±0.39)	57/57 1.000	1.04±0.016	91.5±1.62	0
200mg/kg	15	136 (9.1±0.45)	8 (5.9)	128 (8.5±0.48)	59/69 0.855	1.14±0.004**	87.3±1.11	0
4000mg/kg	16	137 (8.6±0.52)	6 (4.4)	131 (8.2±0.50)	66/65 1.015	1.08±0.011**	90.4±1.44	0

Tab. 3 Skeletal observation of rat fetuses receiving HPMCP.

Groups	Number of fetuses	Sternabra		Decreased ossification of midphalanges of forlegs	Number of ossified caudal vertebrae	14th ribs	Other sites
		decreased ossification	delayed formation				
Control	151	5(3.3)	13(8.6)	36(23.8)	3.41±0.058	10(6.6)	d.s. 1(0.7)
20mg/kg	152	4(2.6)	17(11.2)	27(17.8)	3.36±0.059	22(14.5)*	
200mg/kg	143	5(3.5)	16(11.2)	33(23.1)	3.51±0.067	25(17.5)*	d.s. 3(2.1)
2400mg/kg	159	6(3.8)	23(14.5)	36(22.6)	3.25±0.059	21(13.2)	d.s. 2(1.3)
							d.s.+fused ribs

( ) shows standard error. * p 0.05 significant
d.s.: deforimity of sternabae

Tab. 4 Skeletal observation of mouse fetuses.

Group	Number of fetuses	Non-fused supra-occipital	Sternabrae		Non-ossified midphalanges forelegs	
			decrease	delay	r	l
Control	120	19 (15.8)	10 (8.3)	34 (28.3)	22 (18.3)	21 (17.5)
20mg/kg	114	16 (14.0)	10 (8.8)	34 (29.8)	32 (28.1)	32 (28.1)
200mg/kg	128	1** (0.8)	0* (0.0)	28 (21.9)	12 (9.4)	13 (10.2)
4000mg/ks	131	0** (0.0)	2* (1.5)	37 (28.2)	18 (13.7)	19 (14.5)

*: p 0.05,
a. s. : asymmetry of sternabrae
f.c.a. : fused cervical arch

2.6.6.7 Local tolerance

Not applicable.

2.6.6.8 Special toxicology studies

Not applicable.

Labeling: The sponsor's proposed labeling is in accordance with the current Structured Product Labeling Format.

1. Pregnancy

Sponsor's version:

(b) (4)

Evaluation: Some editorial changes are recommended.

Recommended version:

Animal reproduction studies have not been conducted with Zentase. It is not known whether Zentase capsules can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Zentase capsules should be given to a pregnant woman only if clearly needed.

2. Nonclinical Toxicology

Sponsor's version:

(b) (4)

(b) (4)

Recommended version:

Carcinogenesis, Mutagenesis and Impairment of Fertility
Carcinogenecity, genetic toxicology, and animal fertility studies have not been performed with Zentase.

Overall conclusions and recommendations:

Pancreatic enzyme preparations (PEPs) have been available in the U. S. for the treatment of exocrine pancreatic insufficiency (EPI) in children and adults with cystic fibrosis and chronic pancreatitis prior to the enactment of the Federal Food, Drug, and Cosmetic Act of 1938. On April 28, 2004 (69 FR 23410), the FDA announced that all orally administered PEPs are new drugs that will be approved for prescription use only. In the present NDA 505 (b)2 application, the sponsor is seeking approval to market Zentase for treatment of EPI.

In support of this NDA, the sponsor did not conduct any preclinical studies with zentase but provided published information for the excipients in the clinical formulation of Zentase. This is consistent with the pharmacology and toxicology requirements in the Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs published in 2006. In accordance with this guidance, no new pharmacology studies for such products are necessary and no toxicology studies are needed if excipients are classified as GRAS for oral administration or are USP/NF compendial excipients and are present at levels previously found acceptable.

The sponsor also submitted an IND (IND 70,563) with zentase on November 11, 2005. Based on the pharmacology review of this IND, all excipients in the clinical formulation of zentase are present in FDA approved oral drug products. The estimated daily intakes of these excipients were less than the amounts present in the FDA approved drug products except for the following three: hypromellose phthalate, triethyl citrate, and hypromellose. The estimated maximum daily consumptions for the hypromellose phthalate, triethyl citrate, and hypromellose are (b) (4) mg/capsule), (b) (4) mg/capsule), and (b) (4) mg/capsule), respectively if 25 capsules of zentase are consumed daily. These are higher than the allowable levels in the FDA approved products for a single dose

(hypromellose phthalate = 302 mg, triethyl citrate = 20 mg, hypromellose = 480 mg). The sponsor did not provide the maximum daily allowable levels for these excipients. Therefore, the sponsor was asked in the 74 day letter dated February 28, 2008 to provide the maximum daily allowable levels in the FDA approved products of the following excipients: hypromellose phthalate, triethyl citrate and hypromellose and to justify the safety of these excipients by published literature or by supporting toxicology studies if the estimated DAILY intakes of these excipients are higher than the maximum daily allowable levels present in the FDA approved products. In response to these requests, the sponsor provided their response in amendment #00BZ on March 21, 2008.

Hypromellose or hydroxypropyl methylcellulose (HPMC) is considered as a food additive permitted for direct addition to food for human consumption in 21 CFR 172.874. HPMC is a modified cellulose. The dose of 30 g per person per day has been recommended by the United State National Research Council as the upper safe level of dietary fiber in general for the modified celluloses. The maximum daily intake of HPMC from zentase is (b) (4) mg/day which is much less than the recommended level.

Triethyl citrate is considered as GRAS under 21 CFR part 184.1911. An acceptable daily intake (ADI) for triethyl citrate up to 10 mg/kg was established by the Joint FAO/WHO Expert Committee on Food Additives. This is much higher than the estimated maximum daily intake of triethyl Citrate from zentase (b) (4) mg/day or (b) (4) mg/kg/day if 50 kg body weight is assumed).

The approved oral formulations of Hydroxypropyl methylcellulose phthalate (HPMCP) by the FDA are up to 302.4 mg/unit dose. The maximum daily acceptable oral level is not available. The estimated maximum daily intake of HPMCP from zentase is (b) (4) mg/day or (b) (4) mg/kg/day if 50 kg body weight is assumed. The sponsor provided published toxicology studies to justify the safety of HPMCP including 30-day and 6-month oral toxicity studies in rats and 27-week oral toxicity study in dogs.

No effect level of 4.5 g/kg/day was identified in the 30-day oral toxicity study in rats. The no effect dose of 6.0 g/kg/day was identified in the 6-month oral toxicity study in rats. In the 27-month oral toxicity study in dogs, the dose of 3.0 g/kg/day was well tolerated. These would provide sufficient safety margin for the estimated maximum daily intake of HPMCP

from zentase of (b)(4) mg/kg/day. Therefore, from a preclinical standpoint, this NDA is approvable.

Recommendations:

1. From a preclinical standpoint, approval of zentase is recommended for treatment of exocrine pancreatic insufficiency.

2. The labeling should be revised as recommended.

_____ _____
Ke Zhang, Ph.D. Date
Pharmacologist, HFD-180

Comments:

_____ _____
Sushanta Chakder, Ph.D. Date
Acting Supervisory Pharmacologist
HFD-180

CC:
IND
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakder
HFD-180/Dr. Zhang

R/D Init.: SChakder 4/29/08

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/s/

Ke Zhang
5/1/2008 10:24:46 AM
PHARMACOLOGIST

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