CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-632/S006

Trade Name: Meridia Capsules

Generic Name: sibutramine hydrochloride monohydrate

Sponsor: Knoll Pharmaceutical Company

Approval Date: November 12, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-632/S006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-632/S006

APPROVAL LETTER

NDA 20-632/S-006

Knoll Pharmaceutical Company
Attention: Robert J. Mandetta
Associate Director, Regulatory Affairs
3000 Continental Drive, North
Mount Olive, NJ 07828-1234

NOV 12 1999

Dear Mr. Mandetta:

Please refer to your supplemental new drug application dated September 15, 1999, received September 16, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Meridia (sibutramine hydrochloride monohydrate) capsules, 5, 10, and 15 mg.

We acknowledge receipt of your submission dated September 16, 1999.

We note that this supplement was submitted as a "Special Supplement- Changes Being Effected" under 21 CFR 314.70(c).

This supplemental new drug application provides for revisions to the PRECAUTIONS section, specifically the Adverse Reactions subsection. Your submission did not specify the implementation date for the changes.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted September 15, 1999 with replacement page 008 submitted September 16, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-632/S-006." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Maureen Hess, MPH, RD, Regulatory Health Project Manager, at (301) 827-6411.

Sincerely,

11-12-99

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Cc:
NDA 20-632
HFD-510/Div. Files
HFD-510/MHess/EColman/GTroendle
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-21/ACS (with labeling)- for drug discussed at advisory committee meeting
HFd-095/DDMS-IMT (with labeling)
HFd-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: MHess/November 8, 1999
Initialed by: EColman/11.9.99/GTroendle/11.9.99/EGalliers/11.10.99
Final: 11.10.99

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-632/S006

LABELING

0995010-2 ← Change to: 0995010-3

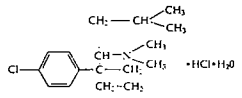
MERIDIA®

(sibutramine hydrochloride monohydrate) Capsules

DESCRIPTION

MERIDIA® (sibutramine hydrochloride monohydrate) is an orally administered agent for the treatment of obesity. Chemically, the active ingredient is a racemic mixture of the (+) and (-) enantiomers of cyclobutanemethanamine, 1-(4-chlorophenyl)-*N*,*N*-dimethyl-α-(2-methylpropyl)-, hydrochloride, monohydrate, and has an empirical formula of $C_{17}H_{26}ClNO \cdot HCl \cdot H_2O$. Its molecular weight is 334.33.

The structural formula is shown below:



Sibutramine hydrochloride monohydrate is a white to cream crystalline powder with a solubility of 2.9 mg/mL in pH 5.2 water. Its octanol:water partition coefficient is 30.9 at pH 5.0.

Each MERIDIA capsule contains 5 mg, 10 mg, 15 mg of sibutramine hydrochloride monohydrate. It also contains as inactive ingredients: lactose monohydrate, NF; microcrystalline cellulose, NF; colloidal silicon dioxide, NF; and magnesium stearate, NF in a hard-gelatin capsule [which contains titanium dioxide, USP; gelatin; FD&C Blue No. 2 (5- and 10-mg capsules only); D&C Yellow No. 10 (5- and 15-mg capsules only), and other inactive ingredients].

CLINICAL PHARMACOLOGY

Mode of Action

Sibutramine produces its therapeutic effects by norepinephrine, serotonin and dopamine reuptake inhibition. Sibutramine and its major pharmacologically active metabolites (M_1 and M_2) do not act via release of monoamines.

Pharmacodynamics

Sibutramine exerts its pharmacological actions predominantly via its secondary (M_1) and primary (M_2) amine metabolites. The parent compound, sibutramine, is a potent inhibitor of serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine reuptake *in vivo*, but not *in vitro*. However, metabolites M_1 and M_2 inhibit the reuptake of these neurotransmitters both *in vitro* and *in vivo*.

In human brain tissue, M_1 and M_2 also inhibit dopamine reuptake *in vitro*, but with ~3-fold lower potency than for the reuptake inhibition of serotonin or norepinephrine.

Potencies of Sibutramine, M_1 and M_2 as *In Vitro* Inhibitors of Monoamine Reuptake in Human Brain

Potency to Inhibit Monoamine Reuptake (K_i;nM)

	Serotonin	Norepinephrine	Dopamine
Sibutramine	298	5451	943
M_1	15	20	49
M_2	20	15	45

A study using plasma samples taken from sibutramine-treated volunteers showed monoamine reuptake inhibition of norepinephrine > serotonin > dopamine; maximum inhibitions were norepinephrine = 73%, serotonin = 54% and dopamine = 16%.

Sibutramine and its metabolites (M_1 and M_2) are not serotonin, norepinephrine or dopamine releasing agents. Following chronic administration of sibutramine to rats, no depletion of brain monoamines has been observed.

Sibutramine, M_1 and M_2 exhibit no evidence of anticholinergic or antihistaminergic actions. In addition, receptor binding profiles show that sibutramine, M_1 and M_2 have low affinity for serotonin (5-HT_1, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}), norepinephrine (β, β_1, β_2, α_1 and α_2), dopamine (D_1 and D_2), benzodiazepine, and glutamate (NMDA) receptors. These compounds also lack monoamine oxidase inhibitory activity *in vitro* and *in vivo*.

Pharmacokinetics

Absorption

Sibutramine is rapidly absorbed from the GI tract (T_{max} of 1.2 hours) following oral administration and undergoes extensive first-pass metabolism in the liver (oral clearance of 1750 L/h and half-life of 1.1 h) to form the pharmacologically active mono- and di- desmethyl metabolites M_1 and M_2. Peak plasma concentrations of M_1 and M_2 are reached within 3 to 4 hours. On the basis of mass balance studies, on average, at least 77% of a single oral dose of sibutramine is absorbed. The absolute bioavailability of sibutramine has not been determined.

001

Distribution

Radiolabeled studies in animals indicated rapid and extensive distribution into tissues: highest concentrations of radiolabeled material were found in the eliminating organs, liver and kidney. Tissue distribution was unaffected by pregnancy, with relatively low transfer to the fetus. *In vitro*, sibutramine, M_1 and M_2 are extensively bound (97%, 94% and 94%, respectively) to human plasma proteins at plasma concentrations seen following therapeutic doses.

Metabolism

Sibutramine is metabolized in the liver principally by the cytochrome P450(3A4) isoenzyme, to desmethyl metabolites, M_1 and M_2. These active metabolites are further metabolized by hydroxylation and conjugation to pharmacologically inactive metabolites, M_5 and M_6. Following oral administration of radiolabeled sibutramine, essentially all of the peak radiolabeled material in plasma was accounted for by unchanged sibutramine (3%), M_1 (6%), M_2 (12%), M_5 (52%), and M_6 (27%).

M_1 and M_2 plasma concentrations reached steady-state within four days of dosing and were approximately two-fold higher than following a single dose. The elimination half-lives of M_1 and M_2, 14 and 16 hours, respectively, were unchanged following repeated dosing.

Excretion

Approximately 85% (range 68-95%) of a single orally administered radiolabeled dose was excreted in urine and feces over a 15-day collection period with the majority of the dose (77%) excreted in the urine. Major metabolites in urine were M_1 and M_2; unchanged sibutramine, M_3, and M_4 were not detected. The primary route of excretion for M_1 and M_2 is hepatic metabolism and for M_5 and M_6 is renal excretion.

Summary of Pharmacokinetic Parameters

Mean (% CV) and 95% Confidence Intervals of Pharmacokinetic Parmeters (Dose = 15 mg)

Study Population	C_{max} (ng/mL)	T_{max} (h)	AUC† (ng*h/mL)	$T^1/_2$ (h)
Metabolite M_1				
Target Population:				
Obese Subjects	4.0 (42)	3.6 (28)	25.5 (63)	--
(n=18)	3.2 - 4.8	3.1 - 4.1	18.1 - 32.9	
Special Population:				
Moderate Hepatic	2.2 (36)	3.3 (33)	18.7 (65)	--
Impairment (n=12)	1.8 - 2.7	2.7 - 3.9	11.9 - 25.5	
Metabolite M_2				
Target Population:				
Obese Subjects	6.4 (28)	3.5 (17)	92.1 (26)	17.2 (58)
(n=18)	5.6 - 7.2	3.2 - 3.8	81.2 - 103	12.5 -21.8
Special Population:				
Moderate Hepatic	4.3 (37)	3.8 (34)	90.5 (27)	22.7 (30)
Impairment (n=12)	3.4 -5.2	3.1 - 4.5	76.9 - 104	18.9 - 26.5

† Calculated only up to 24 hr for M_1

Effect of Food

Administration of a single 20 mg dose of sibutramine with a standard breakfast resulted in reduced peak M_1 and M_2 concentrations (by 27% and 32%, respectively) and delayed the time to peak by approximately three hours. However, the AUCs of M_1 and M_2 were not significantly altered.

Special Populations

Geriatric: Plasma concentrations of M_1 and M_2 were similar between elderly (ages 61 to 77 yr) and young (ages 19 to 30 yr) subjects following a single 15-mg oral sibutramine dose. Plasma concentrations of the inactive metabolites M_5 and M_6 were higher in the elderly; these differences are not likely to be of clinical significance. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric: The safety and effectiveness of MERIDIA in pediatric patients under 16 years old have not been established.

Gender: Pooled pharmacokinetic parameters from 54 young, healthy volunteers (37 males and 17 females) receiving a 15-mg oral dose of sibutramine showed the mean C_{max} and AUC of M_1 and M_2 to be slightly (≤19% and ≤36%, respectively) higher in females than males. Somewhat higher steady-state trough plasma levels were observed in female obese patients from a large clinical efficacy trial. However, these differences are not likely to be of clinical significance. Dosage adjustment based upon the gender of a patient is not necessary (see **"DOSAGE AND ADMINISTRATION"**).

Race: The relationship between race and steady-state trough M_1 and M_2 plasma concentrations was examined in a clinical trial in obese patients. A trend towards higher concentrations in Black patients over Caucasian was noted for M_1 and M_2. However, these differences are not considered to be of clinical significance.

Renal Insufficiency: The effect of renal disease has not been studied. However, since sibutramine and its active metabolites M_1 and M_2 are eliminated by hepatic metabolism, renal disease is unlikely to have a significant effect on their disposition. Elimination of the inactive metabolites M_5 and M_6, which are renally excreted, may be affected in this population. MERIDIA, should not be used in patients with severe renal impairment.

Hepatic Insufficiency: In 12 patients with moderate hepatic impairment receiving a single 15-mg oral dose of sibutramine, the combined AUCs of M_1 and M_2 were increased by 24% compared to healthy subjects while M_1 and M_2 plasma concentrations were unchanged. The observed differences in M_1 and M_2 concentrations do not warrant dosage adjustment in patients with mild to moderate hepatic impairment. MERIDIA should not be used in patients with severe hepatic dysfunction.

CLINICAL STUDIES

Observational epidemiologic studies have established a relationship between obesity and the risks for cardiovascular disease, non-insulin dependent diabetes mellitus (NIDDM), certain forms of cancer, gallstones, certain respiratory disorders, and an increase in overall mortality. These studies suggest that weight loss, if maintained, may produce health benefits for some patients with chronic obesity who may also be at risk for other diseases.

The long-term effects of MERIDIA on the morbidity and mortality associated with obesity have not been established. Weight loss was examined in 11 double-blind, placebo-controlled obesity trials with study durations of 12 to 52 weeks and doses ranging from 1 to 30 mg once daily. Weight was significantly reduced in a dose-related manner in sibutramine-treated patients compared to placebo over the dose range of 5 to 20 mg once daily. In two 12-month studies, maximal weight loss was achieved by 6 months and statistically significant weight loss was maintained over 12 months. The amount of placebo-subtracted weight loss achieved on MERIDIA was consistent across studies.

Analysis of the data in three long-term (≥6 months) obesity trials indicates that patients who lose at least 4 pounds in the first 4 weeks of therapy with a given dose of MERIDIA are most likely to achieve significant long-term weight loss on that dose of MERIDIA. Approximately 60% of such patients went on to achieve a placebo-subtracted weight loss of ≥5% of their initial body weight by month 6. Conversely, of those patients on a given dose of MERIDIA who did not lose at least 4 pounds in the first 4 weeks of therapy, approximately 80% did not go on to achieve a placebo-subtracted weight loss of ≥5% of their initial body weight on that dose by month 6.

Significant dose-related reductions in waist circumference, an indicator of intra-abdominal fat, have also been observed over 6 and 12 months in placebo-controlled clinical trials. In a 12-week placebo-controlled study of non-insulin dependent diabetes mellitus patients randomized to placebo or 15 mg per day of MERIDIA, Dual Energy X-Ray Absorptiometry (DEXA) assessment of changes in body composition showed that total body fat mass decreased by 1.8 kg in the MERIDIA group versus 0.2 kg in the placebo group($p<0.001$). Similarly, truncal (android) fat mass decreased by 0.6 kg in the MERIDIA group versus 0.1 kg in the placebo group ($p<0.01$). The changes in lean mass, fasting blood sugar, and HbA_1 were not statistically different between the two groups.

Eleven double-blind, placebo-controlled obesity trials with study durations of 12 to 52 weeks have provided evidence that MERIDIA does not adversely affect glycemia, serum lipid profiles, or serum uric acid in obese patients. Treatment with MERIDIA (5 to 20 mg once daily) is associated with mean increases in blood pressure of 1 to 3 mm Hg and with mean increases in pulse rate of 4 to 5 beats per minute relative to placebo. These findings are similar in normotensives and in patients with hypertension controlled with medication. Those patients who lose significant (≥ 5% weight loss) amounts of weight on MERIDIA tend to have smaller increases in blood pressure and pulse rate (see "**WARNINGS**").

In Study 1, a 6-month, double-blind, placebo-controlled study in obese patients, Study 2, a 1-year, double-blind, placebo-controlled study in obese patients, and Study 3, a 1-year, double-blind, placebo-controlled study in obese patients who lost at least 6 kg on a 4-week very low calorie diet (VLCD), MERIDIA produced significant reductions in weight, as shown below. In two 1-year studies, maximal weight loss was achieved by 6 months and statistically significant weight loss was maintained over 12 months.

Mean Weight Loss (lbs) in the Six-Month and One-Year Trials

Study/Patient Group	Placebo (n)	MERIDIA (mg) 5 (n)	10 (n)	15 (n)	20 (n)
Study 1					
All patients*	2.0 (142)	6.6 (148)	9.7 (148)	12.1 (150)	13.6 (145)
Completers**	2.9 (84)	8.1 (103)	12.1 (95)	15.4 (94)	18.0 (89)
Early responders***	8.5 (17)	13.0 (60)	16.0 (64)	18.2 (73)	20.1 (76)
Study 2					
All patients*	3.5 (157)		9.8 (154)	14.0 (152)	
Completers**	4.8 (76)		13.6 (80)	15.2 (93)	
Early responders***	10.7 (24)		18.2 (57)	18.8 (76)	
Study 3****					
All patients*	15.2 (78)		28.4 (81)		
Completers**	16.7 (48)		29.7 (60)		
Early responders***	21.5 (22)		33.0 (46)		

* Data for all patients who received study drug and who had any post-baseline measurement (last observation carried forward analysis).

** Data for patients who completed the entire 6-month (Study 1) or one-year period of dosing and have data recorded for the month 6 (Study 1) or month 12 visit.

*** Data for patients who lost at least 4 lbs in the first 4 weeks of treatment and completed the study.

**** Weight loss data shown describe changes in weight from the pre-VLCD; mean weight loss during the 4-week VLCD was 16.9 lbs for sibutramine and 16.3 lbs for placebo.

MERIDIA induced weight loss has been accompanied by beneficial changes in serum lipids that are similar to those seen with nonpharmacologically-mediated weight loss. A combined, weighted analysis of the changes in serum lipids in 11 placebo-controlled obesity studies ranging in length from 12 to 52 weeks is shown below for the last observation carried forward (LOCF) analysis.

Combined Analysis (11 Studies) of Percentage Change in Serum Lipids (N) - LOCF

Category	TG	CHOL	LDL-C	HDL-C
All Placebo	0.53 (475)	-1.53 (475)	-0.09 (233)	-0.56 (248)
<5% Weight Loss	4.52 (382)	-0.42 (382)	-0.70 (205)	-0.71 (217)
≥5% Weight Loss	-15.30 (92)	-6.23 (92)	-6.19 (27)	0.94 (30)
All Sibutramine	-8.75 (1164)	-2.21 (1165)	-1.85 (642)	4.13 (664)
<5% Weight Loss	-0.54 (547)	0.17 (548)	-0.37 (320)	3.19 (331)
≥5% Weight Loss	-16.59 (612)	-4.87 (612)	-4.56 (317)	4.68 (328)

Baseline mean values:

Placebo: TG 187 mg/dL; CHOL 221 mg/dL; LDL-C 140 mg/dL; HDL-C 47 mg/dL

Sibutramine: TG 172 mg/dL; CHOL 215 mg/dL; LDL-C 140 mg/dL; HDL-C 47 mg/dL

MERIDIA induced weight loss has been accompanied by reductions in serum uric acid. In one study, serum uric acid has been identified as an independent risk factor for death from coronary artery disease.

Certain centrally-acting weight loss agents that cause release of serotonin from nerve terminals have been associated with cardiac valve dysfunction. The possible occurrence of cardiac valve disease was specifically investigated in two studies. In one study 2-D and color Doppler echocardiography were performed on 210 patients (mean age, 54 years) receiving MERIDIA 15 mg or placebo daily for periods of 2 weeks to 16 months (mean duration of treatment, 7.6 months). In patients without a prior history of valvular heart disease, the incidence of valvular heart disease was 3/132 (2.3%) in the sibutramine treatment group (all three cases were mild aortic insufficiency) and 2/77 (2.6%) in the placebo treatment group (one case of mild aortic insufficiency and one case of severe aortic insufficiency). In another study, 25 patients underwent 2-D and color Doppler echocardiography before treatment with MERIDIA and again after treatment with MERIDIA 5 to 30 mg daily for three months; there were no cases of valvular heart disease.

INDICATIONS AND USAGE

MERIDIA is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet. MERIDIA is recommended for obese patients with an initial body mass index ≥ 30 kg/m², or ≥ 27 kg/m² in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).

Below is a chart of Body Mass Index (BMI) based on various heights and weights.

BMI is calculated by taking the patient's weight, in kg, and dividing by the patient's height, in meters, squared. Metric conversions are as follows: pounds ÷ 2.2 = kg; inches x 0.0254 = meters.

BMI		25	26	27	28	29	30	31	32	33	34	35	40
	WEIGHT (lbs)												
	4'10"	119	124	129	134	138	143	148	153	158	163	167	191
	4'11"	124	128	133	138	143	148	154	158	164	169	173	198
	5'	128	133	138	143	148	153	159	164	169	175	179	204
	5'1"	132	137	143	148	153	158	165	169	175	180	185	211
	5'2"	136	142	147	153	158	164	170	175	181	186	191	218
H	5'3"	141	146	152	158	163	169	175	181	187	192	197	225
	5'4"	145	151	157	163	169	174	181	187	193	199	204	232
E	5'5"	150	156	162	168	174	180	187	193	199	205	210	240
	5'6"	155	161	167	173	179	186	192	199	205	211	216	247
I	5'7"	159	166	172	178	185	191	198	205	211	218	223	255
	5'8"	164	171	177	184	190	197	204	211	218	224	230	262
G	5'9"	169	176	182	189	196	203	210	217	224	231	236	270
	5'10"	174	181	188	195	202	207	216	223	230	237	243	278
H	5'11"	179	186	193	200	208	215	222	230	237	244	250	286
	6'	184	191	199	206	213	221	228	236	244	251	258	294
T	6'1"	189	197	204	212	219	227	236	243	251	258	265	302
	6'2"	194	202	210	218	225	233	241	250	258	265	272	311
	6'3"	200	208	216	224	232	240	248	256	264	272	279	319

CONTRAINDICATIONS

MERIDIA is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs) (see "**WARNINGS**").

MERIDIA is contraindicated in patients with hypersensitivity to sibutramine or any of the inactive ingredients of MERIDIA.

MERIDIA is contraindicated in patients who have anorexia nervosa.

MERIDIA is contraindicated in patients taking other centrally acting appetite suppressant drugs.

WARNINGS

Blood Pressure and Pulse

MERIDIA SUBSTANTIALLY INCREASES BLOOD PRESSURE IN SOME PATIENTS. REGULAR MONITORING OF BLOOD PRESSURE IS REQUIRED WHEN PRESCRIBING MERIDIA.

In placebo-controlled obesity studies, MERIDIA 5 to 20 mg once daily was associated with mean increases in systolic and diastolic blood pressure of approximately 1 to 3 mm Hg relative to placebo, and with mean increases in pulse rate relative to placebo of approximately 4 to 5 beats per minute. Larger increases were seen in some patients, particularly when therapy with MERIDIA was initiated at the higher doses (see table below). In pre-marketing placebo-controlled obesity studies, 0.4% of patients treated with MERIDIA were discontinued for hypertension (SBP ≥ 160 mm Hg or DBP ≥ 95 mm Hg), compared with 0.4% in the placebo group, and 0.4% of patients with MERIDIA were discontinued for tachycardia (pulse rate ≥ 100 bpm), compared with 0.1% in the placebo group. Blood pressure and pulse should be measured prior to starting therapy with MERIDIA and should be monitored at regular intervals thereafter. For patients who experience a sustained increase in blood pressure or pulse rate while receiving MERIDIA, either dose reduction or discontinuation should be considered. MERIDIA should be given with caution to those patients with a history of hypertension (see "**DOSAGE AND ADMINISTRATION**"), and should not be given to patients with uncontrolled or poorly controlled hypertension.

Percent Outliers in Studies 1 and 2

Dose (mg)	% Outliers*		
	SBP	DBP	Pulse
Placebo	9	7	12
5	6	20	16
10	12	15	28
15	13	17	24
20	14	22	37

*Outlier defined as increase from baseline of ≥ 15 mm Hg for three consecutive visits (SBP), ≥10 mm Hg for three consecutive visits (DBP), or pulse ≥ 10 bpm for three consecutive visits.

Potential Interaction With Monoamine Oxidase Inhibitors

MERIDIA is a norepinephrine, serotonin and dopamine reuptake inhibitor and should not be used concomitantly with MAOIs (see "**PRECAUTIONS**", Drug Interactions subsection). There should be at least a 2-week interval after stopping MAOIs before commencing treatment with MERIDIA. Similarly, there should be at least a 2-week interval after stopping MERIDIA before starting treatment with MAOIs.

Concomitant Cardiovascular Disease

Treatment with MERIDIA has been associated with increases in heart rate and/or blood pressure. Therefore, MERIDIA should not be used in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke.

Glaucoma

Because MERIDIA can cause mydriasis, it should be used with caution in patients with narrow angle glaucoma.

Miscellaneous

Organic causes of obesity (e.g., untreated hypothyroidism) should be excluded before prescribing MERIDIA.

(Over)

PRECAUTIONS

Pulmonary Hypertension

Certain centrally-acting weight loss agents that cause release of serotonin from nerve terminals have been associated with pulmonary hypertension (PPH), a rare but lethal disease. In pre-marketing clinical studies, no cases of PPH have been reported with MERIDIA® (sibutramine hydrochloride monohydrate). Because of the low incidence of this disease in the underlying population, however, it is not known whether or not MERIDIA may cause this disease.

Seizures

During premarketing testing, seizures were reported in < 0.1% of MERIDIA treated patients. MERIDIA should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Gallstones

Weight loss can precipitate or exacerbate gallstone formation.

Renal/Hepatic Dysfunction

Patients with severe renal impairment or severe hepatic dysfunction have not been systematically studied; MERIDIA should therefore not be used in such patients.

Interference With Cognitive and Motor Performance

Although sibutramine did not affect psychomotor or cognitive performance in healthy volunteers, any CNS active drug has the potential to impair judgment, thinking or motor skills.

Information For Patients

Physicians should instruct their patients to read the patient package insert before starting therapy with MERIDIA and to reread it each time the prescription is renewed.

Physicians should also discuss with their patients any part of the package insert that is relevant to them. In particular, the importance of keeping appointments for follow-up visits should be emphasized.

Patients should be advised to notify their physician if they develop a rash, hives, or other allergic reactions.

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, especially weight-reducing agents, decongestants, antidepressants, cough suppressants, lithium, dihydroergotamine, sumatriptan (Imitrex®), or tryptophan, since there is a potential for interactions.

Patients should be reminded of the importance of having their blood pressure and pulse monitored at regular intervals.

Drug Interactions

CNS Active Drugs: The use of MERIDIA in combination with other CNS-active drugs, particularly serotonergic agents, has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of MERIDIA with other centrally-acting drugs is indicated (see "**CONTRAINDICATIONS**" and "**WARNINGS**").

In patients receiving monoamine oxidase inhibitors (MAOIs) (e.g. phenelzine, selegiline) in combination with serotonergic agents (e.g. fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine), there have been reports of serious, sometimes fatal, reactions ("serotonin syndrome," see below). Because MERIDIA inhibits serotonin reuptake, MERIDIA should not be used concomitantly with MAOI (see "**CONTRAINDICATIONS**"). At least 2 weeks should elapse between discontinuation of a MAOI and initiation of treatment with MERIDIA. Similarly, at least 2 weeks should elapse between discontinuation of MERIDIA and initiation of treatment with MAOI.

The rare, but serious, constellation of symptoms termed "serotonin syndrome" has also been reported with the concomitant use of selective serotonin reuptake inhibitors and agents for migraine therapy, such as Imitrex® (sumatriptan succinate) and dihydroergotamine, certain opioids, such as dextramethorphan, meperidine, pentazocine and fentanyl, lithium, or tryptophan. Serotonin syndrome has also been reported with the concomitant use of two serotonin reuptake inhibitors. The syndrome requires immediate medical attention and may include one or more of the following symptoms: excitement, hypomania, restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, motor weakness, myoclonus, tremor, hemiballismus, hyperreflexia, ataxia, dysarthria, incoordination, hyperthermia, shivering, pupillary dilation, diaphoresis, emesis, and tachycardia.

Because MERIDIA inhibits serotonin reuptake, it should not be administered with other serotonergic agents such as those listed above.

Drugs That May Raise Blood Pressure and/or Heart Rate: Concomitant use of MERIDIA and other agents that may raise blood pressure or heart rate have not been evaluated. These include certain decongestants, cough, cold, and allergy medications that contain agents such as phenylpropanolamine, ephedrine, or pseudoephedrine. Caution should be used when prescribing MERIDIA to patients who use these medications.

Drugs That Inhibit Cytochrome P450($3A_4$) Metabolism: *In vitro* studies indicated that the cytochrome P450($3A_4$)-mediated metabolism of sibutramine was inhibited by ketoconazole and to a lesser extent by erythromycin. Clinical interaction trials were conducted on these substrates. The data indicate that there is a potential for such interactions, but the magnitude appears to be small.

Ketoconazole: Concomitant administration of 200 mg doses of ketoconazole twice daily and 20 mg sibutramine once daily for 7 days in 12 uncomplicated obese subjects resulted in moderate increases in AUC and C_{max} of 58% and 36% for M_1 and of 20% and 19% for M_2, respectively.

Erythromycin: The steady-state pharmacokinetics of sibutramine and metabolites M_1 and M_2 were evaluated in 12 uncomplicated obese subjects following concomitant administration of 500 mg of erythromycin three times daily and 20 mg of sibutramine once daily for 7 days. Concomitant erythromycin resulted in small increases in the AUC (less than 14%) for M_1 and M_2. A small reduction in C_{max} for M_1 (11%) and a slight increase in C_{max} for M_2 (10%) were observed.

Cimetidine: Concomitant administration of cimetidine 400 mg twice daily and sibutramine 15 mg once daily for 7 days in 12 volunteers resulted in small increases in combined (M_1 and M_2) plasma C_{max} (3.4%) and AUC (7.3%); these differences are unlikely to be of clinical significance.

Alcohol: In a double-blind, placebo controlled, crossover study in 19 volunteers, administration of a single dose of ethanol (0.5 mL/kg) together with 20 mg of sibutramine resulted in no psychomotor interactions of clinical significance between alcohol and sibutramine. However, the concomitant use of MERIDIA and excess alcohol is not recommended.

Oral Contraceptives: The suppression of ovulation by oral contraceptives was not inhibited by MERIDIA. In a crossover study, 12 healthy female volunteers on oral steroid contraceptives received placebo in one period and 15 mg sibutramine in another period over the course of 8 weeks. No clinically significant systemic interaction was observed; therefore, no requirement for alternative contraceptive precautions are needed when patients taking oral contraceptives are concurrently prescribed sibutramine.

Drugs Highly Bound to Plasma Proteins: Although sibutramine and its active metabolites M_1 and M_2 are extensively bound to plasma proteins (≥94%), the low therapeutic concentrations and basic characteristics of these compounds make them unlikely to result in clinically significant protein binding interactions with other highly protein bound drugs such as warfarin and phenytoin. *In vitro* protein binding interaction studies have not been conducted.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Sibutramine was administered in the diet to mice (1.25, 5 or 20 mg/kg/day) and rats (1, 3, or 9 mg/kg/day) for two years generating combined maximum plasma AUC's of the two major active metabolites equivalent to 0.5 and 21 times, respectively, those following the maximum daily human dose (20 mg). There was no evidence of carcinogenicity in mice or in female rats. In male rats there was a higher incidence of benign tumors of the testicular interstitial cells; such tumors are commonly seen in rats and are hormonally mediated. The relevance of these tumors to humans is not known.

Mutagenicity

Sibutramine was not mutagenic in the Ames test, in vitro Chinese hamster V79 cell mutation assay, *in vitro* clastogenicity assay in human lymphocytes or micronucleus assay in mice. Its two major active metabolites were found to have equivocal bacterial mutagenic activity in the Ames test. However, both metabolites gave consistently negative results in the *in vitro* Chinese hamster V79 cell mutation assay, *in vitro* clastogenicity assay in human lymphocytes, *in vitro* DNA-repair assay in HeLa cells, micronucleus assay in mice and *in vivo* unscheduled DNA-synthesis assay in rat hepatocytes.

Impairment of Fertility

In rats, there were no effects on fertility at doses generating combined plasma AUC's of the two major active metabolites up to 43 times those following the maximum human dose (20 mg). At 13 times the human combined AUC, there was maternal toxicity, and the dam's nest-building behavior was impaired, leading to a higher incidence of perinatal mortality; there was no effect at approximately 4 times the human combined AUC.

Pregnancy

Teratogenic Effects-Pregnancy Category C

In rats, there was no evidence of teratogenicity at doses of 1, 3, or 10 mg/kg/day generating combined plasma AUC's of the two major active metabolites up to approximately 43 times those following the maximum human dose (20 mg). In rabbits dosed at 3, 15, or 75 mg/kg/day, plasma AUC's greater than approximately 5 times those following the maximum human dose caused maternal toxicity. At markedly toxic doses, Dutch Belted rabbits had a slightly higher than control incidence of pups with a broad short snout, short rounded pinnae, short tail and, in some, shorter thickened long bones in the limbs; at comparably high doses in New Zealand White rabbits, one study showed a slightly higher than control incidence of pups with cardiovascular anomalies while a second study showed a lower incidence than in the control group.

No adequate and well controlled studies with MERIDIA have been conducted in pregnant women. The use of MERIDIA during pregnancy is not recommend. Women of child-bearing potential should employ adequate contraception while taking MERIDIA. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing Mothers
It is not known whether sibutramine or its metabolites are excreted in human milk. MERIDIA is not recommended for use in nursing mothers. Patients should be advised to notify their physician if they are breast-feeding.

Pediatric Use
The safety and effectiveness of MERIDIA in pediatric patients under 16 years of age have not been established.

Geriatric Use
Clinical studies of MERIDIA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Pharmacokinetics in elderly patients are discussed in "**CLINICAL PHARMACOLOGY.**"

ADVERSE REACTIONS
In placebo-controlled studies, 9% of patients treated with MERIDIA (n=2068) and 7% of patients treated with placebo (n=884) withdrew for adverse events.

In placebo-controlled obesity studies, the most common events were dry mouth, anorexia, insomnia, and constipation. Adverse events in these studies occurring in ≥ 1% of MERIDIA treated patients and more frequently than in the placebo group are shown in the following table.

	Obese Patients in Placebo-Controlled Studies	
BODY SYSTEM Adverse Event	MERIDIA® (n = 2068) % incidence	Placebo (n = 884) % incidence
BODY AS A WHOLE:		
Headache	30.3	18.6
Back pain	8.2	5.5
Flu syndrome	8.2	5.8
Injury accident	5.9	4.1
Asthenia	5.9	5.3
Abdominal pain	4.5	3.6
Chest pain	1.8	1.2
Neck pain	1.6	1.1
Allergic reaction	1.5	0.8
CARDIOVASCULAR SYSTEM		
Tachycardia	2.6	0.6
Vasodilation	2.4	0.9
Migraine	2.4	2.0
Hypertension/increased blood pressure	2.1	0.9
Palpitation	2.0	0.8
DIGESTIVE SYSTEM		
Anorexia	13.0	3.5
Constipation	11.5	6.0
Increased appetite	8.7	2.7
Nausea	5.9	2.8
Dyspepsia	5.0	2.6
Gastritis	1.7	1.2
Vomiting	1.5	1.4
Rectal disorder	1.2	0.5
METABOLIC & NUTRITIONAL		
Thirst	1.7	0.9
Generalized edema	1.2	0.8
MUSCULOSKELETAL SYSTEM		
Arthralgia	5.9	5.0
Myalgia	1.9	1.1
Tenosynovitis	1.2	0.5
Joint disorder	1.1	0.6
NERVOUS SYSTEM		
Dry mouth	17.2	4.2
Insomnia	10.7	4.5
Dizziness	7.0	3.4
Nervousness	5.2	2.9
Anxiety	4.5	3.4
Depression	4.3	2.5
Paresthesia	2.0	0.5
Somnolence	1.7	0.9
CNS stimulation	1.5	0.5
Emotional lability	1.3	0.6
RESPIRATORY SYSTEM		
Rhinitis	10.2	7.1
Pharyngitis	10.0	8.4
Sinusitis	5.0	2.6
Cough increase	3.8	3.3
Laryngitis	1.3	0.9
SKIN & APPENDAGES		
Rash	3.8	2.5
Sweating	2.5	0.9
Herpes simplex	1.3	1.0
Acne	1.0	0.8
SPECIAL SENSES		
Taste perversion	2.2	0.8
Ear disorder	1.7	0.9
Ear pain	1.1	0.7
UROGENITAL SYSTEM		
Dysmenorrhea	3.5	1.4
Urinary tract infection	2.3	2.0
Vaginal monilia	1.2	0.5
Metrorrhagia	1.0	0.8

The following additional adverse events were reported in ≥ 1% of all patients who received MERIDIA in controlled and uncontrolled pre-marketing studies.
Body as a Whole: fever.
Digestive System: diarrhea, flatulence, gastroenteritis, tooth disorder.
Metabolic and Nutritional: peripheral edema.
Musculoskeletal System: arthritis.
Nervous System: agitation, leg cramps, hypertonia, thinking abnormal.
Respiratory System: bronchitis, dyspnea.
Skin and Appendages: pruritus.
Special Senses: amblyopia.
Urogenital System: menstrual disorder.

Change first sentence to: In placebo-controlled obesity studies the most common events were dry mouth, anorexia, insomnia, constipation, and headache.

Reason: Placebo corrected % incidence is 11.7% and is second to dry mouth.

Change to:
Urogenital System: menstrual disorders.

Reason: There was more than one menstrual disorder observed.

Other Notable Adverse Events

Seizures: Convulsions were reported as an adverse event in three of 2068 (0.1%) MERIDIA treated patients and in none of 884 placebo-treated patients in placebo-controlled premarketing obesity studies. Two of the three patients with seizures had potentially predisposing factors (one had a prior history of epilepsy; one had a subsequent diagnosis of brain tumor). The incidence in all subjects who received MERIDIA (three of 4,588 subjects) was less than 0.1%.

Ecchymosis/Bleeding Disorders: Ecchymosis (bruising) was observed in 0.7% of MERIDIA treated patients and in 0.2% of placebo-treated patients in pre-marketing placebo-controlled obesity studies. One patient had prolonged bleeding of a small amount which occurred during minor facial surgery. MERIDIA may have an effect on platelet function due to its effect on serotonin uptake.

Interstitial Nephritis: Acute interstitial nephritis (confirmed by biopsy) was reported in one obese patient receiving MERIDIA during pre-marketing studies. After discontinuation of the medication, dialysis and oral corticosteroids were administered; renal function normalized. The patient made a full recovery.

Altered Laboratory Findings: Abnormal liver function tests, including increases in AST, ALT, GGT, LDH, alkaline phosphate and bilirubin, were reported as adverse events in 1.6% of MERIDIA-treated obese patients in placebo-controlled trials compared with 0.8% of placebo patients. In these studies, potentially clinically significant values (total bilirubin ≥ 2mg/dL; ALT, AST, GGT, LDH, or alkaline phosphatase ≥ 3x upper limit of normal) occurred in 0% (alkaline phosphatase) to 0.6% (ALT) of the MERIDIA treated patients and in none of the placebo-treated patients. Abnormal values tended to be sporadic, often diminished with continued treatment, and did not show a clear dose-response relationship.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

MERIDIA is a controlled substance in Schedule IV of the Controlled Substances Act (CSA).

Abuse and Physical and Psychological Dependence

Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., drug development of tolerance, incrementation of doses, drug seeking behavior).

OVERDOSAGE

Human Experience

There is very limited experience of overdose with MERIDIA . Three cases of overdose have been reported with MERIDIA. The first was in a 2-year-old child of one patient who ingested up to eight 10 mg capsules. No complications were observed during the overnight hospitalization, and the child was discharged the following day with no sequela. The second report was in a 30-year-old male in a depression study who ingested approximately 100 mg of sibutramine in an attempt to commit suicide. The patient suffered no adverse effects or ECG abnormalities post-ingestion. The third report was in the 45-year-old husband of a patient in an obese dyslipidemic study. He ingested 400 mg of his wife's drug supply and was hospitalized for observation; a heart rate of 120 bpm was noted. He was discharged the next day with no apparent sequelae.

Overdose Management

There is no specific antidote to MERIDIA. Treatment should consist of general measures employed in the management of overdosage: an airway should be established; cardiac and vital sign monitoring is recommended; general symptomatic and supportive measures should be instituted. Cautious use of β-blockers may be indicated to control elevated blood pressure or tachycardia. The benefits of forced diuresis and hemodialysis are unknown.

DOSAGE AND ADMINISTRATION

The recommended starting dose of MERIDIA is 10 mg administered once daily with or without food. If there is inadequate weight loss, the dose may be titrated after four weeks to a total of 15 mg once daily. The 5 mg dose should be reserved for patients who do not tolerate the 10 mg dose. Blood pressure and heart rate changes should be taken into account when making decisions regarding dose titration (see "**PRECAUTIONS**").

Doses above 15 mg daily are not recommended. In most clinical trials, MERIDIA was given in the morning.

Analysis of numerous variables has indicated that approximately 60% of patients who lose at least 4 pounds in the first 4 weeks of treatment with a given dose of MERIDIA in combination with a reduced-calorie diet lose at least 5% (placebo-subtracted) of their initial body weight by the end of 6 months to 1 year of treatment on that dose of MERIDIA. Conversely, approximately, 80% of patients who do not lose at least 4 pounds in the first 4 weeks of treatment with a given dose of MERIDIA do not lose at least 5% (placebo-subtracted) of their initial body weight by the end of 6 months to 1 year of treatment on that dose. If a patient has not lost at least 4 pounds in the first 4 weeks of treatment, the physician should consider reevaluation of therapy which may include increasing the dose or discontinuation of MERIDIA.

The safety and effectiveness of MERIDIA, as demonstrated in double-blind, placebo-controlled trials, have not been determined beyond 1 year at this time.

Postmarketing Reports

Voluntary reports of adverse events temporally associated with the use of MERIDIA are listed below. It is important to emphasize that although these events occurred during treatment with MERIDIA, they may have no causal relationship with the drug. Obesity itself, concurrent disease states/risk factors, or weight reduction may be associated with an increased risk for some of these events.

Body as a whole: anaphylactic shock, anaphylactoid reaction, facial edema, fluid retention, lack of drug effect.

Cardiovascular: angina pectoris, abnormal ECG, arrhythmia, atrial fibrillation, cerebrovascular accident, chest pressure, chest tightness, congestive heart failure, heart arrest, heart rate decreased, hemorrhage, myocardial infarction, sudden unexplained death, supraventricular tachycardia, syncope, torsade de pointes, transient ischemic attack, ventricular extrasystoles, ventricular fibrillation, ventricular tachycardia.

Digestive: abnormal stools, cholecystitis, cholelithiasis, duodenal ulcer, eructation, gastrointestinal hemorrhage, increased salivation, intestinal obstruction, mouth ulcer, stomach ulcer, tongue edema.

Endocrine: goiter, hyperthyroidism, hypothyroidism.

Hemic and Lymphatic: anemia, leukopenia, lymphadenopathy, petechiae, thrombocytopenia.

Metabolic and Nutritional: hyperglycemia, hypoglycemia

Musculoskeletal: arthrosis, bursitis.

Nervous: abnormal dreams, abnormal gait, amnesia, anger, concentration impaired, confusion, depression aggravated, Gilles de la Tourette's syndrome, hypesthesia, libido decreased, libido increased, manic reaction, mood changes, nightmares, serotonin syndrome, short term memory loss, speech disorder, tremor, twitch, vascular headache, vertigo.

Respiratory: epistaxis, nasal congestion, respiratory disorder, yawn .

Skin and Appendages: alopecia, dermatitis, limb pain, photosensitivity, urticaria.

Special Senses: abnormal vision, blurred vision, dry eye, eye pain, increased intraocular pressure, otitis externa, otitis media, photosensitivity, tinnitus.

Urogenital: abnormal ejaculation, hematuria, impotence, increased urinary frequency, micturition difficulty.

Reason: Addition of postmarketing adverse events

HOW SUPPLIED

MERIDIA (sibutramine hydrochloride monohydrate) Capsules contain 5 mg, 10 mg, or 15 mg sibutramine hydrochloride monohydrate and are supplied as follows:

5 mg, NDC 0048-0605-01, blue/yellow capsules imprinted with "MERIDIA" on the cap and "-5-" on the body, in bottles of 100 capsules.

10 mg, NDC 0048-0610-01, blue/white capsules imprinted with "MERIDIA" on the cap and "-10-" on the body, in bottles of 100 capsules.

15 mg, NDC 0048-0615-01, yellow/white capsules imprinted with "MERIDIA" on the cap and "-15-" on the body, in bottles of 100 capsules.

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature]. Protect from heat and moisture. Dispense in a tight, light-resistant container as defined in USP.

Caution: Federal law prohibits dispensing without prescription.

Change to: Rx Only

MERIDIA is a registered trademark of Knoll Pharmaceutical Company.

IMITREX® is a registered trademark of Glaxo Group Limited.

Change to: IMITREX

Sibutramine is covered by US Patent Nos. 4,746,680; 4,929,629; and 5,436,272.

Change to: 1999

Printed in USA

Revised: January 1998
0995010-2

Change to: Revised: September 1999
0995010-3

Knoll Pharmaceutical Company
3000 Continental Drive - North
Mount Olive, New Jersey 07828-1234

BASF Pharma

knoll®

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-632/S006

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-632/S-006

OCT - 4 1999

Knoll Pharmaceutical Company
3000 Continental Drive - North
Mount Oliver, New Jersey 07828-1234

Attention: Robert J. Mandetta
Associate Director, Regulatory Affairs

Dear Mr. Mandetta:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Meridia (sibutramine hydrochloride monohydrate) Capsules
NDA Number:	20-632
Supplement Number:	S-006
Date of Supplement:	September 15, 1999
Date of Receipt:	September 16, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on November 15, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-632/S-006
HFD-510/Div. Files
HFD-510/CSO/Hess

filename: C:\WPFILES\20632ACK.WPD

SUPPLEMENT ACKNOWLEDGEMENT

Knoll Pharmaceutical Company

ORIGINAL

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BASF Pharma

SUPPL NEW CORRESP
SLR-006
BL

FEDERAL EXPRESS

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 20 1999
HFD-510

September 16, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine Drug Products
HFD-510, Document Control Room 14B-04
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1506

RE: MERIDIA® (sibutramine hydrochloride monohydrate) Capsules
NDA 20-632/S-006
Revised Labeling - Replacement Page

Noted 10/13/99

Dear Dr. Sobel:

The purpose of this communication is to provide a replacement page for the revised labeling that was submitted to the Agency on September 15, 1999. We inadvertently submitted an earlier version of the postmarketing section. The enclosed replacement page will replace page 008 of the revised labeling submission.

We apologize for this error. If you have any questions or need additional information, please contact me at (973) 426-6022.

Sincerely,

5/10/99

Kimberly A. Davis for
Robert J. Mandetta
Associate Director, Regulatory Affairs

Enc.

REVIEWS COMPLETED
CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
MDN 11/10/99
CSO INITIALS DATE

Noted DK 13 Oct 99

3000 Continental Drive-North, New Jersey 07828-1234 (973) 426-0000 Fax (973) 426-1000

Knoll Pharmaceutical Company

NDA NO 20.632 REF. NO 006
NDA SUPPL FOR S<R

knoll®

ORIGINAL

September 15, 1999

BASF Pharma

Solomon Sobel, MD
Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

10/5/99

SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED

SUBJECT: **Meridia (sibutramine hydrochloride monohydrate) Capsules**
NDA 20-632/S-006
Revised Labeling

Dear Dr. Sobel:

In accordance with 21CFR §314.65 Knoll Pharmaceutical Company submits a supplemental application to provide revisions in the package insert for MERIDIA Capsules.

These revisions incorporate safety information from our postmarketing reports. In addition, the package insert has also been amended to include minor editorial changes.

Attached for your convenience, please find an annotated draft copy of the revised package insert. Final printed labeling will be submitted as soon as it is available.

If you have any questions or require additional information, please contact me at (973) 426-6022.

Sincerely,

Robert J. Mandetta
Associate Director, Regulatory Affairs

cc: Maureen Hess, CSO

REVIEWS COMPLETED
CSO ☑ MEMO
MPH 11/10/99
CSO INITIALS DATE

3000 Continental Drive-North, Mount Olive, New Jersey 07828-1234 (973) 426-2600