

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-632/S-017

Trade Name: Meridia Capsules

Generic Name: sibutramine hydrochloride monohydrate

Sponsor: Abbott Laboratories

Approval Date: September 23, 2003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-632/S-017

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-632/S-017

Rebecca McSwine, R.Ph., Ph.D.
Associate Director, PPD Regulatory Affairs
200 Abbott Park Road
D-491/AP30-1E
Abbott Park, IL 60064-6157

Dear Dr. McSwine:

Please refer to your supplemental new drug application dated December 16, 2002, received December 17, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Meridia (sibutramine hydrochloride monohydrate) Capsules.

This supplemental new drug application provides for revision to the PRECAUTIONS and ADVERSE REACTIONS sections of the package insert (PI), to reflect data analyzed and submitted to the European Committee for Proprietary Medicinal Products (CPMP). The patient package insert (PPI) has also been revised to be consistent with safety information included in the PI.

We completed our review of this application. This application is approved, effective on the date of this letter, for use as recommended in the labeling submitted on December 16, 2002.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert and patient package insert, submitted December 16, 2002).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 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-017." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We remind you that you must submit patent information on form FDA 3542, *Patent Information Submitted Upon and After Approval of an NDA or Supplement*, within 30 days of the date of this letter as required by 21 CFR 314.53(c)(2)(ii) and 314.53(d)(2) at the address provided by 21 CFR 314.53(d)(4). The form may be obtained at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>. To expedite review of this patent declaration form, we request you submit an additional copy of the form to the Center for Drug Evaluation and Research "Orange Book" staff at

Food and Drug Administration
Office of Generic Drugs, HFD-610
Orange Book Staff
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Project Manager, at (301) 827-6381.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

David Orloff
9/25/03 06:43:26 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-632/S-017

APPROVED LABELING

Nos. 2456, 2457, 2458
NEW

MERIDIA[®]
(sibutramine hydrochloride monohydrate) Capsules

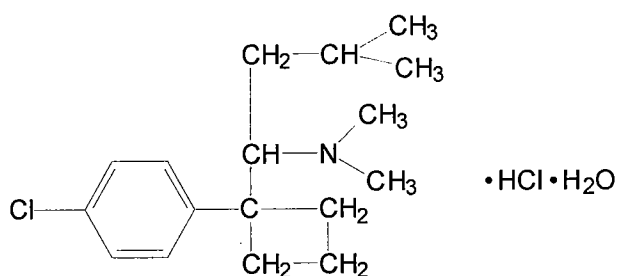


Rx only

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 C₁₇H₂₉Cl₂NO. 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, and 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 (M₁ and M₂) do not act via release of monoamines.

Pharmacodynamics

Sibutramine exerts its pharmacological actions predominantly via its secondary (M₁) and primary (M₂) 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 M₁ and M₂ inhibit the reuptake of these neurotransmitters both *in vitro* and *in vivo*.

In human brain tissue, M₁ and M₂ also inhibit dopamine reuptake *in vitro*, but with ~3-fold lower potency than for the reuptake inhibition of serotonin or norepinephrine.

Potencies of Sibutramine, M₁ and M₂ 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 (M₁ and M₂) are not serotonin, norepinephrine or dopamine releasing agents. Following chronic administration of sibutramine to rats, no depletion of brain monoamines has been observed.

Sibutramine, M₁ and M₂ exhibit no evidence of anticholinergic or antihistaminergic actions. In addition, receptor binding profiles show that sibutramine, M₁ and M₂ have low affinity for serotonin (5-HT₁, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}), norepinephrine (β , β_1 , β_3 , α_1 and α_2), dopamine (D₁ and D₂), 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 M₁ and M₂. Peak plasma concentrations of M₁ and M₂ 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.

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. *In vitro*, sibutramine, M₁ and M₂ 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, M₁ and M₂. These active metabolites are further metabolized by hydroxylation and conjugation to pharmacologically inactive metabolites, M₅ and M₆. Following oral administration of radiolabeled sibutramine, essentially all of the peak radiolabeled material

in plasma was accounted for by unchanged sibutramine (3%), M₁ (6%), M₂ (12%), M₅ (52%), and M₆ (27%).

M₁ and M₂ 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 M₁ and M₂, 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 M₅ and M₆; unchanged sibutramine, M₁, and M₂ were not detected. The primary route of excretion for M₁ and M₂ is hepatic metabolism and for M₅ and M₆ is renal excretion.

Summary of Pharmacokinetic Parameters

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

Study Population	C _{max} (ng/mL)	T _{max} (h)	AUC [†] (ng*h/mL)	T _{1/2} (h)
Metabolite M₁				
Target Population:				
Obese Subjects (n=18)	4.0 (42) 3.2 - 4.8	3.6 (28) 3.1 - 4.1	25.5 (63) 18.1 - 32.9	--
Special Population:				
Moderate Hepatic Impairment (n=12)	2.2 (36) 1.8 - 2.7	3.3 (33) 2.7 - 3.9	18.7 (65) 11.9 - 25.5	--
Metabolite M₂				
Target Population:				
Obese Subjects (n=18)	6.4 (28) 5.6 - 7.2	3.5 (17) 3.2 - 3.8	92.1 (26) 81.2 - 103	17.2 (58) 12.5 - 21.8
Special Population:				
Moderate Hepatic Impairment (n=12)	4.3 (37) 3.4 - 5.2	3.8 (34) 3.1 - 4.5	90.5 (27) 76.9 - 104	22.7 (30) 18.9 - 26.5

[†]Calculated only up to 24 hr for M₁

Effect of Food

Administration of a single 20 mg dose of sibutramine with a standard breakfast resulted in reduced peak M₁ and M₂ concentrations (by 27% and 32%, respectively) and delayed the time to peak by approximately three hours. However, the AUCs of M₁ and M₂ were not significantly altered.

Special Populations

Geriatric: Plasma concentrations of M₁ and M₂ 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 M₅ and M₆ 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 ($\leq 19\%$ and $\leq 36\%$, 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 patients 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_5 and M_6 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 Capsules on the morbidity and mortality associated with obesity have not been established. Weight loss was examined in 11 double-blind, placebo-controlled obesity trials (BMI range across all studies 27-43) 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 $\geq 5\%$ 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 $\geq 5\%$ 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_{1c} were not statistically significantly 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 ($\geq 5\%$ 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 the 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.

Maintenance of weight loss with MERIDIA[®] (sibutramine hydrochloride monohydrate) was examined in a 2-year, double-blind, placebo-controlled trial. After a 6-month run-in phase in which all patients received sibutramine 10 mg (mean weight loss, 26 lbs.), patients were randomized to sibutramine (10 to 20 mg, 352 patients) or placebo (115 patients). The mean weight loss from initial body weight to endpoint was 21 lbs. and 12 lbs. for sibutramine and placebo patients, respectively. A statistically significantly ($p < 0.001$) greater proportion of sibutramine treated patients, 75%, 62%, and 43%, maintained at least 80% of their initial weight loss at 12, 18, and 24 months, respectively, compared with the placebo group (38%, 23%, and 16%). Also 67%, 37%, 17%, and 9% of sibutramine treated patients compared with 49%, 19%, 5%, and 3% of placebo patients lost $\geq 5\%$, $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$, respectively, of their initial body weight at endpoint. From endpoint to the post-study follow-up visit (about 1 month),

weight regain was approximately 4 lbs for the sibutramine patients and approximately 2 lbs for the placebo patients.

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.

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.

The effect of sibutramine 15 mg once daily on measures of 24-hour blood pressure was evaluated in a 12-week placebo-controlled study. Twenty-six male and female, primarily Caucasian individuals with an average BMI of 34 kg/m² and an average age of 39 years underwent 24-hour ambulatory blood pressure monitoring (ABPM). The mean changes from baseline to Week 12 in various measures of ABPM are shown in the following table.

Parameter mm Hg	Systolic			Diastolic		
	Placebo n=12	Sibutramine		Placebo	Sibutramine	
		15 mg n=14	20 mg n=16		15 mg n=12	20 mg n=16
Daytime	0.2	3.9	4.4	0.5	5.0	5.7
Nighttime	-0.3	4.1	6.4	-1.0	4.3	5.4
Early am	-0.9	9.4	5.3	-3.0	6.7	5.8
24-hour mean	-0.1	4.0	4.7	0.1	5.0	5.6

Normal diurnal variation of blood pressure was maintained.

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., diabetes, dyslipidemia, controlled hypertension).

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 $\div$ 2.2 = kg; inches $\times$ 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	149	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
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
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
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
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
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
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 a major eating disorder (anorexia nervosa or bulimia nervosa).

MERIDIA is contraindicated in patients taking other centrally acting weight loss drugs.

WARNINGS

Blood Pressure and Pulse

MERIDIA SUBSTANTIALLY INCREASES BLOOD PRESSURE AND/OR PULSE RATE IN SOME PATIENTS . REGULAR MONITORING OF BLOOD PRESSURE AND PULSE RATE 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 $\geq$ 160 mm Hg or DBP $\geq$ 95 mm Hg), compared with 0.4% in the placebo group, and 0.4% of patients treated with MERIDIA were discontinued for tachycardia (pulse rate $\geq$ 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.

Dose (mg)	Percent Outliers in Studies 1 and 2		
	% 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 $\geq$ 15 mm Hg for three consecutive visits (SBP), $\geq$ 10 mm Hg for three consecutive visits (DBP), or pulse $\geq$ 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

MERIDIA substantially increases blood pressure and/or pulse rate in some patients. 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.

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) Capsules. 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.

Bleeding

There have been reports of bleeding in patients taking sibutramine. While a causal relationship is unclear, caution is advised in patients predisposed to bleeding events and those taking concomitant medications known to affect hemostasis or platelet function.

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 a 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 a 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 dextromethorphan, 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, in general, it should not be administered with other serotonergic agents such as those listed above. However, if such a combination is clinically indicated, appropriate observation of the patient is warranted.

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 ephedrine, or pseudoephedrine. Caution should be used when prescribing MERIDIA to patients who use these medications.

Drugs That Inhibit Cytochrome P450(3A₄) Metabolism:

In vitro studies indicated that the cytochrome P450(3A₄)-mediated metabolism of sibutramine was inhibited by ketoconazole and to a lesser extent by erythromycin. Clinical interaction trials were conducted on these substrates. The potential for such interactions is described below.

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 M₁ and of 20% and 19% for M₂, respectively.

Erythromycin: The steady-state pharmacokinetics of sibutramine and metabolites M₁ and M₂ 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 M₁ and M₂. A small reduction in C_{max} for M₁ (11%) and a slight increase in C_{max} for M₂ (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 (M₁ and M₂) 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 M₁ and M₂ 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 0.4 and 16 times, respectively, those following a daily human dose of 15 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 32 times those following a human dose of 15 mg. At 13 times the human combined AUC, there was maternal toxicity, and the dams' 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***

Radiolabeled studies in animals indicated that tissue distribution was unaffected by pregnancy, with relatively low transfer to the fetus. 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 32 times those following the human dose of 15 mg. In rabbits dosed at 3, 15, or 75 mg/kg/day, plasma AUC's greater than approximately 5 times those following the human dose of 15 mg 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 recommended. Women of childbearing 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 while taking MERIDIA.

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 studies, the most common events were dry mouth, anorexia, insomnia, constipation and headache. Adverse events in these studies occurring in $\geq 1\%$ of MERIDIA treated patients and more frequently than in the placebo group are shown in the following table.

BODY SYSTEM Adverse Event	Obese Patients in Placebo-Controlled Studies	
	MERIDIA [®] (n = 2068)	Placebo (n = 884)
	% Incidence	% 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 $\geq 1\%$ 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 disorders.

Other Adverse Events

Clinical Studies

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 phosphatase 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 ≥ 2 mg/dL; ALT, AST, GGT, LDH, or alkaline phosphatase ≥ 3 x 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.

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.

Psychiatric: Cases of depression, suicidal ideation and suicide have been reported rarely in patients on sibutramine treatment. However, a relationship has not been established between the occurrence of depression and/or suicidal ideation and the use of sibutramine. If depression occurs during treatment with sibutramine, further evaluation may be necessary.

Hypersensitivity: Allergic hypersensitivity reactions ranging from mild skin eruptions and urticaria to angioedema and anaphylaxis have been reported (see “**CONTRAINDICATIONS**” and “**PRECAUTIONS-Information For Patients**”, and other reports of allergic reactions listed below).

Other Postmarketing Reported Events:

Body as a Whole: anaphylactic shock, anaphylactoid reaction, chest pressure, chest tightness, facial edema, limb pain, sudden unexplained death.

Cardiovascular System: angina pectoris, atrial fibrillation, congestive heart failure, heart arrest, heart rate decreased, myocardial infarction, supraventricular tachycardia, syncope, torsade de pointes, vascular headache, ventricular tachycardia, ventricular extrasystoles, ventricular fibrillation.

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

Endocrine System: goiter, hyperthyroidism, hypothyroidism.

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

Metabolic and Nutritional: hyperglycemia, hypoglycemia.

Musculoskeletal System: arthrosis, bursitis.

Nervous System: abnormal dreams, abnormal gait, amnesia, anger, cerebrovascular accident, 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, transient ischemic attack, tremor, twitch, vertigo.

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

Skin and Appendages: alopecia, dermatitis, photosensitivity (skin), urticaria.

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

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance

MERIDIA is controlled 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

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 overdose: 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 "**WARNINGS**" and "**PRECAUTIONS**").

Doses above 15 mg daily are not recommended. In most of the 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 2 years at this time.

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 0074-2456-12, blue/yellow capsules imprinted with "MERIDIA" on the cap and "-5-" on the body, in bottles of 30 capsules.

10 mg, NDC 0074-2457-12, blue/white capsules imprinted with "MERIDIA" on the cap and "-10-" on the body, in bottles of 30 capsules.

15 mg, NDC 0074-2458-12, yellow/white capsules imprinted with "MERIDIA" on the cap and "-15-" on the body, in bottles of 30 capsules.

5 mg, NDC 0074-2456-13, blue/yellow capsules imprinted with "MERIDIA" on the cap and "-5-" on the body, in bottles of 100 capsules.

10 mg, NDC 0074-2457-13, blue/white capsules imprinted with "MERIDIA" on the cap and "-10-" on the body, in bottles of 100 capsules.

15 mg, NDC 0074-2458-13, 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 capsules from heat and moisture. Dispense in a tight, light-resistant container as defined in USP.

Manufactured by Abbott Laboratories
North Chicago, IL 60064, U.S.A.

IMITREX is a registered trademark of Glaxo Group Limited.

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

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Patient Information
MERIDIA®
(mer-ID-dee-uh)

(sibutramine hydrochloride monohydrate) Capsules 

Read the Patient Information that comes with MERIDIA before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about MERIDIA?

Some people taking MERIDIA can have a large increase in blood pressure or heart rate (pulse). Do not take MERIDIA if your blood pressure is not well controlled. Contact your doctor if you experience an increase in blood pressure while taking MERIDIA.

Your doctor should check your blood pressure and heart rate before you start MERIDIA and continue checking it regularly while you are using MERIDIA. It is important to have regular check-ups while taking MERIDIA.

What is MERIDIA?

MERIDIA is a medicine that may help obese people, as determined by their doctor, lose weight and keep weight off. MERIDIA may help with weight loss because it affects areas of the brain that control hunger. You should use MERIDIA with a low calorie diet.

The use of MERIDIA for more than 2 years has not been studied.

MERIDIA has not been studied in children under 16 years of age.

Who should not take MERIDIA?

Do not take MERIDIA if you:

- have uncontrolled or poorly controlled high blood pressure.
- **are taking or have taken a medicine called a monoamine oxidase inhibitor (MAOI).** Ask your doctor or pharmacist if you are not sure if any of your medicines are MAOIs. Do not take MAOIs for at least 2 weeks before using MERIDIA. Do not take MAOIs for at least 2 weeks after stopping MERIDIA.

- **have an eating disorder called anorexia nervosa or bulimia nervosa.**
- **are taking weight loss medicines to control your appetite.**
- **are allergic to MERIDIA.** The active ingredient is sibutramine hydrochloride monohydrate. See the end of this leaflet for a complete list of ingredients in MERIDIA.

How should I take MERIDIA?

- Take MERIDIA exactly as prescribed. Your doctor may adjust your dose. Do not change your dose unless your doctor tells you to do so.
- You can take MERIDIA with or without food.
- If you miss a dose of MERIDIA, just skip it. Do not take an extra dose to make up for missed doses.
- If you take too much MERIDIA, call your doctor or Poison Control Center right away, or go to the emergency room.
- Tell your doctor if you do not lose at least 4 pounds in the first 4 weeks of taking MERIDIA and eating a low calorie diet. Your doctor may change your dose or stop MERIDIA. MERIDIA does not work for everyone.

What should I avoid while taking MERIDIA?

MERIDIA may not be the right medicine for you if you have certain medical conditions. Tell your doctor about all of your medical conditions, especially if you:

- **have high blood pressure.**
- **have or had heart problems** such as a heart attack, heart failure, chest pain or an irregular heartbeat.
- **had a stroke or stroke symptoms.**
- **have liver or kidney problems.**
- **have an eye problem called glaucoma.**
- **have a thyroid problem (hypothyroidism).**
- **have or had seizures (convulsions, fits).**
- **have bleeding problems.**
- **have or had gallstones.**
- **have depression.**
- **are over age 65.**
- **are under age 16.**

- **are pregnant or planning to become pregnant.** The effects of MERIDIA on your unborn baby are not known. If you can become pregnant, you should use birth control while taking MERIDIA. Tell your doctor right away if you get pregnant while taking MERIDIA.
- **are breastfeeding.** It is not known if MERIDIA passes into your milk. The effects of MERIDIA on your baby are not known. You should not breastfeed while taking MERIDIA.

Do not drive, operate heavy machinery or do other dangerous activities until you know how MERIDIA affects you.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Taking MERIDIA and certain other medicines may affect each other and may cause serious and in some cases life-threatening side effects. Make sure you tell your doctor if you take:

- medicines called MAOIs, see "Who should not take MERIDIA?"
- other weight loss medicines
- cough and cold medicines
- migraine medicines
- depression medicines
- narcotic pain-killers
- lithium
- tryptophan
- medicines that increase bleeding
- antibiotic medicines

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get new medicine. They can tell you if it is okay to take MERIDIA with other medicines.

What are the possible side effects of MERIDIA?

Common side effects of MERIDIA include: dry mouth, headache, loss of appetite, trouble sleeping, and constipation.

The following serious side effects have been reported with MERIDIA:

- **a large increase in blood pressure or heart rate in some people.** See "What is the most important information I should know about MERIDIA?"
- **seizures**
- **bleeding**
- **a rare, but life-threatening problem called "serotonin syndrome."** It may occur when people take drugs that affect a brain chemical called serotonin along with MERIDIA. Do not take other medicines with MERIDIA unless your doctor has told you it is okay to do so. Get medical help right away if you have any of the following symptoms especially when taking other medicines with MERIDIA:
 - feel weak, restless, confused, or anxious
 - lose consciousness
 - have a fever, vomiting, sweating, shivering or shaking
 - have a fast heartbeat

Certain weight loss medicines have been associated with a rare, but life-threatening condition that affects the blood pressure in lungs (pulmonary hypertension). Because the condition is so rare it is not known if MERIDIA may cause this disease. If you experience new or worsening shortness of breath notify your doctor immediately.

Tell your doctor if you get a rash or hives while taking MERIDIA. You may be having an allergic reaction.

Tell your doctor if you get effects that bother you or that do not go away.

These are not all the side effects of MERIDIA. For more information, ask your doctor or pharmacist.

MERIDIA is a controlled substance (CIV). This means that MERIDIA can be a target for people who abuse prescription medicines. Keep your MERIDIA in a safe place. Selling or giving away MERIDIA is against the law.

How should I store MERIDIA?

- Store MERIDIA at room temperature between 59° to 86° F (15° to 30° C). Never leave it in a hot or moist place.
- Safely throw away MERIDIA that is out of date or no longer needed.
- Keep MERIDIA and all medicines out of reach of children. If your child accidentally takes MERIDIA, call their doctor or Poison Control Center right away, or take your child to the emergency room.

General information about MERIDIA.

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use MERIDIA for a condition for which it was not prescribed. Do not give MERIDIA to other people, even if they have the same symptoms you have. It may harm them and it is against the law.

This leaflet summarizes the most important information about MERIDIA. If you would like more information, talk to your doctor. You can also ask your doctor or pharmacist for information that is written for health professionals.

For more information call Abbott Laboratories at 1-800-633-9110 or visit www.Meridia.net.

What are the ingredients in MERIDIA?

Active Ingredient: sibutramine hydrochloride monohydrate
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].

Manufactured by: Knoll BV, Barceloneta, PR 00617

For:

ABBOTT  LABORATORIES
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-632/S-017

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE

Division of Metabolic & Endocrine Drug Products
REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-632/S-017

Name of Drug: Meridia (sibutramine hydrochloride monohydrate) Capsules

Applicant: Abbott

Material Reviewed:

Submission Date(s): December 16, 2002, draft labeling

Receipt Date(s): December 17, 2002

Background and Summary

MERIDIA is indicated for the management of obesity, including weight loss and maintenance of weight loss, when used in conjunction with a reduced calorie diet.

S-017 was submitted to revise the PRECAUTIONS and ADVERSE REACTIONS sections of the package insert (PI), to reflect data analyzed and submitted to the European Committee for Proprietary Medicinal Products (CPMP). The patient package insert (PPI) has been revised to be consistent with safety information included in the PI.

Review

Package Insert

The proposed labeling was compared to the currently approved package insert (Identifier 03-5116-R1, Revised: July, 2001, Supplements -08 and -011, Acknowledged and Retained 2/8/02). No other changes have been made other than those identified in the supplement cover letter, and the firm has made the revisions requested in the Acknowledge and Retain letter for supplements -08 and -011.

Patient Package Insert

The proposed labeling was compared to the currently approved patient package insert (same identifier and revision date as package insert). No other changes have been made other than those identified in the supplement cover letter.

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Conclusions

The proposed labeling revisions were found acceptable by the medical team leader, Dr. Eric Colman. An approval letter will issue.

Kati Johnson

Chief, PM Staff, HFD-510

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this page is the manifestation of the electronic signature.**

/s/

Kati Johnson
9/25/03 06:18:28 AM
CSO



NDA 20-632/S-017

PRIOR APPROVAL SUPPLEMENT

Abbott Laboratories
Attn: Rebecca McSwine, R.Ph., Ph.D.
Associate Director, PPD Regulatory Affairs
200 Abbott Park Road, D-491/Building AP30-1E
Abbott Park, IL 60064-6157

Dear Ms. McSwine:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Meridia® (sibutramine hydrochloride monohydrate) Capsules
NDA Number: 20-632
Supplement number: S-017
Date of supplement: December 16, 2002
Date of receipt: December 17, 2002

This supplemental application proposes the following:

- 1) Revise the PRECAUTIONS and ADVERSE REACTIONS sections of the package insert (PI) to reflect data analyzed and submitted to European committee for proprietary medicinal products (CPMC).
- 2) Revise the patient package insert to be consistent with the revised PI.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 15, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 15, 2003.

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All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Metabolic & Endocrine Drug Products, HFD-510

Attention: Fishers Document Room, 8B45

5600 Fishers Lane

Rockville, Maryland 20857

If you have any question, call me at (301) 827-6380.

Sincerely,

{See appended electronic signature page}

Kati Johnson

Chief, Regulatory Project Management Staff

Division of Metabolic & Endocrine Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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/s/

Kati Johnson
12/31/02 03:47:36 PM