

**Meridia®**  
(sibutramine hydrochloride monohydrate) Capsules  
R only  
Tear at Perforation to dispense Patient Information.

(Nos. 2457, 2458)

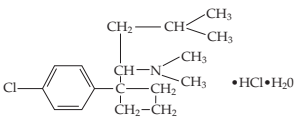
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## DESCRIPTION

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 cyclobutanethanamine, 1-(4-chlorophenyl)-N,N-dimethyl- $\alpha$ -(2-methylpropyl)-, hydrochloride, monohydrate, and has an empirical formula of C<sub>17</sub>H<sub>23</sub>Cl<sub>2</sub>NO. 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); and 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<sub>1</sub> and M<sub>2</sub>) do not act via release of monoamines.

### Pharmacodynamics

Sibutramine exerts its pharmacological actions predominantly via its secondary (M<sub>1</sub>) and primary (M<sub>2</sub>) amine metabolites. The parent compound, sibutramine, is a potent inhibitor of serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine reuptake *in vitro*, but not *in vivo*. However, metabolites M<sub>1</sub> and M<sub>2</sub> inhibit the reuptake of these neurotransmitters both *in vitro* and *in vivo*. In human brain tissue, M<sub>1</sub> and M<sub>2</sub> also inhibit dopamine reuptake *in vitro*, but with ~3-fold lower potency than for the reuptake inhibition of serotonin or norepinephrine.

	Serotonin	Norepinephrine	Dopamine
Sibutramine	298	5451	943
M <sub>1</sub>	15	20	49
M <sub>2</sub>	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<sub>1</sub> and M<sub>2</sub>) 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<sub>1</sub> and M<sub>2</sub> exhibit no evidence of anticholinergic or antihistaminergic actions. In addition, receptor binding profiles show that sibutramine, M<sub>1</sub> and M<sub>2</sub> have low affinity for serotonin (5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>), norepinephrine ( $\beta_1$ ,  $\beta_2$ ,  $\alpha_1$  and  $\alpha_2$ ), dopamine (D<sub>1</sub> and D<sub>2</sub>), 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<sub>max</sub> 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<sub>1</sub> and M<sub>2</sub>. Peak plasma concentrations of M<sub>1</sub> and M<sub>2</sub> 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; higher concentrations of radiolabeled material were found in the eliminating organs, liver and kidney. *In vitro*, sibutramine, M<sub>1</sub> and M<sub>2</sub> 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 (3A<sub>4</sub>) isoenzyme, to desmethyl metabolites, M<sub>1</sub> and M<sub>2</sub>. These active metabolites are further metabolized by hydroxylation and conjugation to pharmacologically inactive metabolites, M<sub>3</sub> and M<sub>6</sub>. Following oral administration of radiolabeled sibutramine, essentially all of the peak radiolabeled material in plasma was accounted for by unchanged sibutramine (3%), M<sub>1</sub> (6%), M<sub>2</sub> (12%), M<sub>3</sub> (52%), and M<sub>6</sub> (27%).

M<sub>1</sub> and M<sub>2</sub> 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<sub>1</sub> and M<sub>2</sub> 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<sub>3</sub> and M<sub>6</sub>; unchanged sibutramine, M<sub>1</sub>, and M<sub>2</sub> were not detected. The primary route of excretion for M<sub>1</sub> and M<sub>2</sub> is hepatic metabolism and for M<sub>3</sub> and M<sub>6</sub> is renal excretion.

### Summary of Pharmacokinetic Parameters

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

Study Population	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	AUC† (ng•h/mL)	T½ (h)
<b>Metabolite M<sub>1</sub></b>				
Target Population:				
Obese Subjects (n=18)	4.0 (42)	3.6 (28)	25.5 (63)	--
Special Population:				
Moderate Hepatic Impairment (n=12)	2.2 (36)	3.3 (33)	18.7 (65)	--
<b>Metabolite M<sub>2</sub></b>				
Target Population:				
Obese Subjects (n=18)	6.4 (28)	3.5 (17)	92.1 (26)	17.2 (58)
Special Population:				
Moderate Hepatic Impairment (n=12)	4.3 (37)	3.8 (34)	90.5 (27)	22.7 (30)
	3.4 - 5.2	3.1 - 4.5	76.9 - 104	18.9 - 26.5

† Calculated only up to 24 hr for M<sub>1</sub>.

### Effect of Food

Administration of a single 20 mg dose of sibutramine with a standard breakfast resulted in reduced peak M<sub>1</sub> and M<sub>2</sub> concentrations (by 27% and 32%, respectively) and delayed the time to peak by approximately three hours. However, the AUCs of M<sub>1</sub> and M<sub>2</sub> were not significantly altered.

### Special Populations

**Geriatric:** Plasma concentrations of M<sub>1</sub> and M<sub>2</sub> 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<sub>3</sub> and M<sub>6</sub> 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 sibutramine 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<sub>max</sub> and AUC of M<sub>1</sub> and M<sub>2</sub> to be slightly (<10% 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. Dose adjustment based upon the gender of a patient is not necessary (see **DOSE AND ADMINISTRATION**).

**Race:** The relationship between race and steady-state trough M<sub>1</sub> and M<sub>2</sub> 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<sub>1</sub> and M<sub>2</sub>. However, these differences are not considered to be of clinical significance.

**Renal Insufficiency:** The disposition of sibutramine metabolites (M<sub>1</sub>, M<sub>2</sub>, M<sub>3</sub> and M<sub>6</sub>) following a single oral dose of sibutramine was studied in patients with varying degrees of renal function. Sibutramine itself was not measurable.

In patients with moderate and severe renal impairment, the AUC values of the active metabolite M<sub>1</sub> were 24 to 46% higher and the AUC values of M<sub>2</sub> were similar as compared to healthy subjects. Cross-study comparison showed that the patients with end-stage renal disease on dialysis had similar AUC values of M<sub>1</sub> but approximately half of the AUC values of M<sub>2</sub> measured in healthy subjects (Cl<sub>CR</sub> ≥ 80 mL/min). The AUC values of inactive metabolites M<sub>3</sub> and M<sub>6</sub> increased 2-3 fold (range 1- to 7-fold) in patients with moderate impairment (30 mL/min < Cl<sub>CR</sub> < 60 mL/min) and 8-11 fold (range 5- to 15-fold) in patients with severe impairment (Cl<sub>CR</sub> ≤ 30 mL/min) as compared to healthy subjects. Cross-study comparison showed that the AUC values of M<sub>3</sub> and M<sub>6</sub> increased 22-33 fold in patients with end-stage renal disease on dialysis as compared to healthy subjects. Approximately 1% of the oral dose was recovered in the dialysate as a combination of M<sub>3</sub> and M<sub>6</sub> during the hemodialysis process, while M<sub>1</sub> and M<sub>2</sub> were not measurable in the dialysate.

Sibutramine should not be used in patients with severe renal impairment, including those with end-stage renal disease on dialysis.

**Hepatic Insufficiency:** In 12 patients with moderate hepatic impairment receiving a single 15-mg oral dose of sibutramine, the combined AUCs of M<sub>1</sub> and M<sub>2</sub> were increased by 24% compared to healthy subjects while M<sub>3</sub> and M<sub>6</sub> plasma concentrations were unchanged. The observed differences in M<sub>1</sub> and M<sub>2</sub> concentrations do not warrant dosage adjustment in patients with mild to moderate hepatic impairment. Sibutramine should not be used in patients with severe hepatic dysfunction.

### Drug-Drug Interactions

*In vitro* studies indicated that the cytochrome P450 (3A<sub>4</sub>)-mediated metabolism of sibutramine was inhibited by ketoconazole and to a lesser extent by erythromycin. Phase I clinical trials were conducted to assess the interactions of sibutramine with drugs that are substrates and/or inhibitors of various cytochrome P450 isozymes. The potential for studied 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<sub>max</sub> of 58% and 36% for M<sub>1</sub> and of 20% and 19% for M<sub>2</sub>, respectively.

**Erythromycin:** The steady-state pharmacokinetics of sibutramine and metabolites M<sub>1</sub> and M<sub>2</sub> 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<sub>1</sub> and M<sub>2</sub>. A small reduction in C<sub>max</sub> for M<sub>1</sub> (11%) and a slight increase in C<sub>max</sub> for M<sub>2</sub> (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<sub>1</sub> and M<sub>2</sub>) plasma C<sub>max</sub> (3.4%) and AUC (7.3%).

**Simvastatin:** Steady-state pharmacokinetics of sibutramine and metabolites M<sub>1</sub> and M<sub>2</sub> were evaluated in 27 healthy volunteers after the administration of simvastatin 20 mg once daily in the evening and sibutramine 15 mg once daily in the morning for 7 days. Simvastatin had no significant effect on plasma C<sub>max</sub> and AUC of M<sub>2</sub> or M<sub>1</sub> and M<sub>2</sub> combined. The C<sub>max</sub> (16%) and AUC (12%) of M<sub>1</sub> were slightly decreased. Simvastatin slightly decreased sibutramine C<sub>max</sub> (14%) and AUC (21%). Sibutramine increased the AUC (7%) of the pharmacologically active moiety, simvastatin acid and reduced the C<sub>max</sub> (25%) and AUC (15%) of inactive simvastatin.

**Omeprazole:** Steady-state pharmacokinetics of sibutramine and metabolites M<sub>1</sub> and M<sub>2</sub> were evaluated in 26 healthy volunteers after the co-administration of omeprazole 20 mg once daily and sibutramine 15 mg once daily for 7 days. Omeprazole slightly increased plasma C<sub>max</sub> and AUC of M<sub>1</sub> and M<sub>2</sub> combined (approximately 15%). M<sub>3</sub> C<sub>max</sub> and AUC were not significantly affected whereas M<sub>6</sub> C<sub>max</sub> (30%) and AUC (40%) were modestly increased. Plasma C<sub>max</sub> (57%) and AUC (67%) of unchanged sibutramine were moderately increased. Sibutramine had no significant effect on omeprazole pharmacokinetics.

**Olanzapine:** Steady-state pharmacokinetics of sibutramine and metabolites M<sub>1</sub> and M<sub>2</sub> were evaluated in 24 healthy volunteers after the co-administration of sibutramine 15 mg once daily with olanzapine 5 mg twice daily for 3 days and 10 mg once daily thereafter for 7 days. Olanzapine had no significant effect on plasma C<sub>max</sub> and AUC of M<sub>2</sub> and M<sub>1</sub> and M<sub>2</sub> combined, or the AUC of M<sub>1</sub>. Olanzapine slightly increased M<sub>1</sub> C<sub>max</sub> (19%), and moderately increased sibutramine C<sub>max</sub> (47%) and AUC (63%). Sibutramine had no significant effect on olanzapine pharmacokinetics.

**Lorazepam:** Steady-state pharmacokinetics of sibutramine and metabolites M<sub>1</sub> and M<sub>2</sub> after sibutramine 15 mg once daily for 11 days were compared in 25 healthy volunteers in the presence or absence of lorazepam 2 mg twice daily for 3 days plus one morning dose. Lorazepam had no significant effect on the pharmacokinetics of sibutramine metabolites M<sub>1</sub> and M<sub>2</sub>. Sibutramine had no significant effect on lorazepam pharmacokinetics.

**Drugs Highly Bound to Plasma Proteins:** Although sibutramine and its active metabolites M<sub>1</sub> and M<sub>2</sub> 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.

## 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 sibutramine 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 sibutramine 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 sibutramine are most likely to achieve significant long-term weight loss on that dose of sibutramine. Approximately 60% of such patients went on to achieve placebo-subtracted weight loss of ≥ 5% of their initial body weight by month 6. Conversely, of those patients on a given dose of sibutramine 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 sibutramine. 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 sibutramine group versus 0.2 kg in the placebo group (p < 0.001). Similarly, truncal (android) fat mass decreased by 0.6 kg in the sibutramine group versus 0.1 kg in the placebo group (p < 0.01). The changes in lean mass, fasting blood sugar, and HbA<sub>1c</sub> 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 sibutramine does not adversely affect glycemia, serum lipid profiles, or serum uric acid in obese patients. Treatment with sibutramine (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 sibutramine 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), sibutramine 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.

Study/Patient Group	Sibutramine (mg)				
	Placebo (n)	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)	9.8 (154)	14.0 (152)	
Completers**	4.8 (76)	16.7 (80)	15.6 (80)	15.2 (93)	
Early responders***	10.7 (24)	18.2 (57)	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 sibutramine 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 ≥ 5%, ≥ 10%, ≥ 15%, and ≥ 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.

Sibutramine 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.

Category	TG	CHOL	LDL-C	HDL-C
	% (n)	% (n)	% (n)	% (n)
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.
TG:	Triglycerides; CHOL: Cholesterol; LDL-C: Low Density Lipoprotein-Cholesterol
HDL-C:	High Density Lipoprotein-Cholesterol

Sibutramine 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 sibutramine 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 sibutramine and again after treatment with sibutramine 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/m<sup>2</sup> 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 15 mg n=14	Sibutramine 20 mg n=16	Placebo n=12	Sibutramine 15 mg n=12	Sibutramine 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® (sibutramine hydrochloride monohydrate) 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 of ≥ 30 kg/m<sup>2</sup>, or ≥ 27 kg/m<sup>2</sup> 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 = 2.2 = kg; inches x 0.0254 = meters.

BMI	25	26	27	28	29	30	31	32	33	34	35	40
<b>4'10"</b>	119	124	129	134	138	143	149	153	158	163	167	191
<b>4'11"</b>	124	128	133	138	143	148	154	158	164	169	173	198
<b>5'</b>	128	133	138	143	148	153	159	164	169	175	179	204
<b>5'1"</b>	132	137	143	148	153	158	165	169	175	180	185	211
<b>5'2"</b>	136	142	147	153	158	164	170	175	181	186	191	218
<b>H 5'3"</b>	141	146	152	158	163	169	175	181	187	192	197	225
<b>5'4"</b>	145	151	157	163	169	174	181	187	193	199	204	232
<b>E 5'5"</b>	150	156	162	168	174	180	187	193	199	205	210	240

# MERIDIA®

(mer-ID-dee-uh)

(sibutramine hydrochloride monohydrate) Capsules



## Patient Information

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:
  - o feel weak, restless, confused, or anxious
  - o lose consciousness
  - o have a fever, vomiting, sweating, shivering or shaking
  - o 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].

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Manufactured for:  
Abbott Laboratories, North Chicago, IL 60064, U.S.A.  
By: KNOLL BV, Barceloneta, PR 00617

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

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caution to those patients with a history of hypertension (see **DOSE AND ADMINISTRATION**), and should not be given to patients with uncontrolled or poorly controlled hypertension.

Dose (mg)	Percent Outliers in Studies 1 and 2		
	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 sibutramine 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 sibutramine 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 Impairment:** MERIDIA should be used with caution in patients with mild to moderate renal impairment. MERIDIA should not be used in patients with severe renal impairment, including those with end stage renal disease on dialysis (see **Pharmacokinetics- Special Populations- Renal Insufficiency**).

**Hepatic Dysfunction:** Patients with 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 triptophan, 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® (sibutramine hydrochloride monohydrate) 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 sibutramine 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 triptophan. 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, hyperreflexia, hyperreflexia, ataxia, dysarthria, incoordination, hyperthermia, shivering, pupillary dilation, diaphoresis, emesis, and tachycardia.

Because sibutramine 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.

**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 sibutramine. 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.

**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 AUCs 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 equivalent 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 vitro* unscheduled DNA-synthesis assay in rat hepatocytes.

**Impairment of Fertility:** In rats, there were no effects on fertility at doses generating combined plasma AUCs 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 AUCs 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 AUCs 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 sibutramine 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 efficacy of sibutramine in adolescents who are obese has not been adequately studied.

Sibutramine’s mechanism of action inhibiting the reuptake of serotonin and norepinephrine is similar to the mechanism of action of some antidepressants. Pooled analyses of short-term placebo-controlled trials of antidepressants in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), and other psychiatric disorders have revealed a greater risk of adverse events representing suicidal behavior or thinking during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%.

No placebo-controlled trials of sibutramine have been conducted in children or adolescents with MDD, OCD, or other psychiatric disorders. In a study of adolescents with obesity in which 368 patients were treated with sibutramine and 130 patients with placebo, one patient in the sibutramine group and one patient in the placebo group attempted suicide. Suicidal ideation was reported by 2 sibutramine-treated patients and none of the placebo patients. It is unknown if sibutramine increases the risk of suicidal behavior or thinking in pediatric patients.

The data are inadequate to recommend the use of sibutramine for the treatment of obesity in pediatric patients.

**Geriatric Use**  
Clinical studies of sibutramine 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 sibutramine (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 sibutramine treated patients and more frequently than in the placebo group are shown in the following table.

	Obese Patients in Placebo-Controlled Studies	
	Sibutramine (n = 2068)	Placebo (n = 884)
<b>BODY SYSTEM</b>		
<b>Adverse Event</b>	% Incidence	% Incidence
<b>BODY AS A WHOLE:</b>		
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
<b>CARDIOVASCULAR SYSTEM</b>		
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

	Obese Patients in Placebo-Controlled Studies (con’t)	
	Sibutramine (n = 2068)	Placebo (n = 884)
<b>BODY SYSTEM</b>		
<b>Adverse Event</b>	% Incidence	% Incidence
<b>DIGESTIVE SYSTEM</b>		
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
<b>METABOLIC &amp; NUTRITIONAL</b>		
Thirst	1.7	0.9
Generalized edema	1.2	0.8
<b>MUSCULOSKELETAL SYSTEM</b>		
Arthralgia	5.9	5.0
Myalgia	1.9	1.1
Tenosynovitis	1.2	0.5
Joint disorder	1.1	0.6
<b>NERVOUS SYSTEM</b>		
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
<b>RESPIRATORY SYSTEM</b>		
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
<b>SKIN &amp; APPENDAGES</b>		
Rash	3.8	2.5
Sweating	2.5	0.9
Herpes simplex	1.3	1.0
Acne	1.0	0.8
<b>SPECIAL SENSES</b>		
Taste perversion	2.2	0.8
Ear disorder	1.7	0.9
Ear pain	1.1	0.7
<b>UROGENITAL SYSTEM</b>		
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 sibutramine 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**  
**Special Senses:** blurred vision.

**Cardiovascular System:** chest pain, chest tightness, chest pressure, chest heaviness, 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:** cholelithiasis, cholelithiasis, duodenal ulcer, enucation, 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**  
**Overdose Management**  
There is limited experience of overdose with sibutramine. The most frequently noted adverse events associated with overdose are tachycardia, hypertension, headache and dizziness. Treatment should consist of general measures employed in the management of overdose; an airway should be established as needed; cardiac and vital sign monitoring is recommended; general symptomatic and supportive measures should be instituted. Cautionous use of  $\beta$ -blockers may be indicated to control elevated blood pressure or tachycardia. The results from a study in patients with end-stage renal disease on dialysis showed that sibutramine metabolites were not eliminated to a significant degree with hemodialysis. (see **Pharmacokinetics-Special Populations- Renal Insufficiency**).

**DOSE 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 at 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.

Mfd. for Abbott Laboratories, North Chicago, IL 60064, U.S.A. By KNOLL BV, Barceloneta, PR 00617

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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