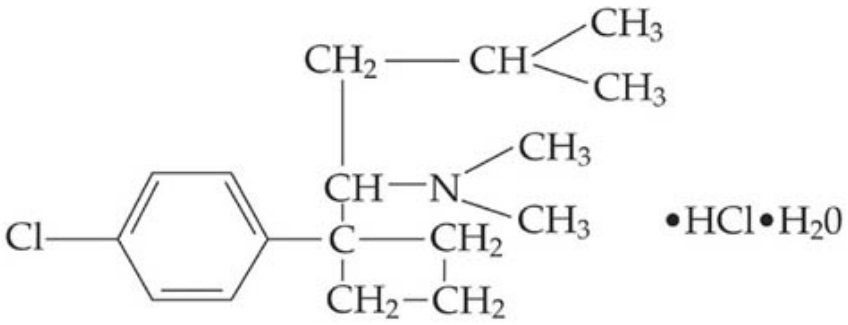
MERIDIA - sibutramine hydrochloride capsule

MERIDIA®
(sibutramine hydrochloride monohydrate) Capsule
CS-IV

DESCRIPTION

MERIDIA® (sibutramine hydrochloride monohydrate) is an orally administered agent for the treatment of obesity. Chemically, the active ingredient is a racemic mixture of the (+) and (-) enantiomers of cyclobutanemethanamine, 1-(4-chlorophenyl)-N,N-dimethyl-α-(2-methylpropyl)-, hydrochloride, monohydrate, and has an empirical formula of $C_{17}H_{29}Cl_2NO$. 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 (M_1 and M_2) do not act via release of monoamines.

Pharmacodynamics

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

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

Potencies of Sibutramine, M_1 and M_2 as In Vitro Inhibitors of Monoamine Reuptake in Human Brain Potency to Inhibit Monoamine Reuptake (K_i;nM)

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

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

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

Sibutramine, M_1 and M_2 exhibit no evidence of anticholinergic or antihistaminergic actions. In addition, receptor binding profiles show that sibutramine, M_1 and M_2 have low affinity for serotonin (5-HT_1, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}), norepinephrine (β, β_1, β_3, α_1 and α_2), dopamine (D_1 and D_2), benzodiazepine, and glutamate (NMDA) receptors. These compounds also lack monoamine oxidase inhibitory activity *in vitro* and *in vivo*.

Pharmacokinetics

Absorption

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

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, M_1 and M_2 are extensively bound (97%, 94% and 94%, respectively) to human plasma proteins at plasma concentrations seen following therapeutic doses.

Metabolism

Sibutramine is metabolized in the liver principally by the cytochrome P450 ($3A_4$) isoenzyme, to desmethyl metabolites, M_1 and M_2. These active metabolites are further metabolized by hydroxylation and conjugation to pharmacologically inactive metabolites, M_5 and M_6. Following oral administration of radiolabeled sibutramine, essentially all of the peak radiolabeled material in plasma was accounted for by unchanged sibutramine (3%), M_1 (6%), M_2 (12%), M_5 (52%), and M_6 (27%).

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

Excretion

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

Summary of Pharmacokinetic Parameters

Mean (% CV) and 95% Confidence Intervals of Pharmacokinetic Parameters (Dose = 15 mg)				
Study Population	C_{max} (ng/mL)	T_{max} (h)	AUC† (ng*h/mL)	T½ (h)
Metabolite M_1				
Target Population:				
Obese Subjects (n = 18)	4.0 (42)	3.6 (28)	25.5 (63)	– –
	3.2 - 4.8	3.1 - 4.1	18.1 - 32.9	
Special Population:				
Moderate Hepatic Impairment (n = 12)	2.2 (36)	3.3 (33)	18.7 (65)	– –
	1.8 - 2.7	2.7 - 3.9	11.9 - 25.5	
Metabolite M2				
Target Population:				
Obese Subjects	6.4 (28)	3.5 (17)	92.1 (26)	17.2 (58)
(n = 18)	5.6 - 7.2	3.2 - 3.8	81.2 - 103	12.5 - 21.8
Special Population:				
Moderate Hepatic	4.3 (37)	3.8 (34)	90.5 (27)	22.7 (30)
Impairment (n = 12)	3.4 - 5.2	3.1 - 4.5	76.9 - 104	18.9 - 26.5

† Calculated only up to 24 hr for M_1.

Effect of Food

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

Special Populations

Geriatric

Plasma concentrations of M_1 and M_2 were similar between elderly (ages 61 to 77 yr) and young (ages 19 to 30 yr) subjects following a single 15-mg oral sibutramine dose. Plasma concentrations of the inactive metabolites M_5 and M_6 were higher in the elderly; these differences are not likely to be of clinical significance. Sibutramine is contraindicated in patients over 65 years of age (see **CONTRAINDICATIONS**).

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_{max} and AUC of M_1 and M_2 to be slightly (≤ 19% and ≤ 36%, respectively) higher in females than males. Somewhat higher steady-state trough plasma levels were observed in female obese patients from a large clinical efficacy trial. However, these differences are not likely to be of clinical significance. Dosage adjustment based upon the gender of a patient is not necessary (see **DOSAGE AND ADMINISTRATION**).

Race

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

Renal Insufficiency

The disposition of sibutramine metabolites (M_1, M_2, M_5 and M_6) 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_1 were 24 to 46% higher and the AUC values of M_2 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_1 but approximately half of the AUC values of M_2 measured in healthy

subjects (CLcr ≥ 80 mL/ min). The AUC values of inactive metabolites M5 and M6 increased 2 - 3 fold (range 1 - to 7 - fold) in patients with moderate impairment (30 mL/ min < CLcr = 60 mL/ min) and 8 - 11 fold (range 5 - to 15 - fold) in patients with severe impairment (CLcr ≤ 30 mL/ min) as compared to healthy subjects. Cross - study comparison showed that the AUC values of M_5 and M_6 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_5 and M_6 during the hemodialysis process, while M_1 and M_2 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_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. Sibutramine should not be used in patients with severe hepatic dysfunction.

Drug-Drug Interactions

In vitro studies indicated that the cytochrome P450 ($3A_4$)-mediated metabolism of sibutramine was inhibited by ketoconazole and to a lesser extent by erythromycin. Phase 1 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_{max} of 58% and 36% for M_1 and of 20% and 19% for M_2, respectively.

Erythromycin

The steady-state pharmacokinetics of sibutramine and metabolites M_1 and M_2 were evaluated in 12 uncomplicated obese subjects following concomitant administration of 500 mg of erythromycin three times daily and 20 mg of sibutramine once daily for 7 days. Concomitant erythromycin resulted in

small increases in the AUC (less than 14%) for M_1 and M_2. A small reduction in C_{max} for M_1 (11%) and a slight increase in C_{max} for M_2 (10%) were observed.

Cimetidine

Concomitant administration of cimetidine 400 mg twice daily and sibutramine 15 mg once daily for 7 days in 12 volunteers resulted in small increases in combined (M_1 and M_2) plasma C_{max} (3.4%) and AUC (7.3%).

Simvastatin

Steady-state pharmacokinetics of sibutramine and metabolites M_1 and M_2 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_{max} and AUC of M_2 or M_1 and M_2 combined. The C_{max} (16%) and AUC (12%) of M_1 were slightly decreased. Simvastatin slightly decreased sibutramine C_{max} (14%) and AUC (21%). Sibutramine increased the AUC (7%) of the pharmacologically active moiety, simvastatin acid and reduced the C_{max} (25%) and AUC (15%) of inactive simvastatin.

Omeprazole

Steady-state pharmacokinetics of sibutramine and metabolites M_1 and M_2 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_{max} and AUC of M_1 and M_2 combined (approximately 15%). M_2 C_{max} and AUC were not significantly affected whereas M_1 C_{max} (30%) and AUC (40%) were modestly increased. Plasma C_{max} (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_1 and M_2 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_{max} and AUC of M_2 and M_1 and M_2 combined, or the AUC of M_1. Olanzapine slightly increased M_1 C_{max} (19%), and moderately increased sibutramine C_{max} (47%) and AUC (63%). Sibutramine had no significant effect on olanzapine pharmacokinetics.

Lorazepam

Steady-state pharmacokinetics of sibutramine and metabolites M_1 and M_2 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_1 and M_2. Sibutramine had no significant effect on lorazepam pharmacokinetics.

Drugs Highly Bound to Plasma Proteins

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

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 a 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_1 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.

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

		Sibutramine (mg)			
Study/Patient Group	**Placebo**	**5**	**10**	**15**	**20**
	(n)	**(n)**	**(n)**	**(n)**	**(n)**

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

Combined Analysis (11 Studies) of Changes in Serum Lipids - LOCF

Category	TG % (n)	CHOL % (n)	LDL-C % (n)	HDL-C % (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^2 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	Systolic			Diastolic		
mm Hg	Placebo	Sibutramine		Placebo	Sibutramine	
	n=12	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/m^2, or ≥ 27 kg/m^2 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 × 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
H	5'4"	145	151	157	163	169	174	181	187	193	199	204	232
E	5'5"	150	156	162	168	174	180	187	193	199	205	210	240
I	5'6"	155	161	167	173	179	186	192	199	205	211	216	247
G	5'7"	159	166	172	178	185	191	198	205	211	218	223	255
H	5'8"	164	171	177	184	190	197	204	211	218	224	230	262
T	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	266	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:

- with a history of coronary artery disease (e.g., angina, history of myocardial infarction), congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or cerebrovascular disease (stroke or transient ischemic attack (TIA)) (see **WARNINGS**).
- with inadequately controlled hypertension > 145/90 mm Hg (see **WARNINGS**).
- over 65 years of age.
- receiving monoamine oxidase inhibitors (MAOIs) (see **WARNINGS**).
- with hypersensitivity to sibutramine or any of the inactive ingredients of MERIDIA.
- who have a major eating disorder (anorexia nervosa or bulimia nervosa).
- taking other centrally acting weight loss drugs.

WARNINGS

Concomitant Cardiovascular Disease

Due to an increased risk of heart attack and stroke in patients with cardiovascular disease, MERIDIA should not be used in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke.

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, sibutramine 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 sibutramine was initiated at the higher doses (see table below). In premarketing placebo-controlled obesity studies, 0.4% of patients treated with sibutramine were discontinued for hypertension (SBP ≥160 mm Hg or DBP ≥ 95 mm Hg), compared with 0.4% in the placebo group, and 0.4% of patients treated with sibutramine were discontinued for tachycardia (pulse rate ≥ 100 bpm), compared with 0.1% in the placebo group. **Blood pressure and pulse should be measured prior to starting therapy with MERIDIA and should be monitored at regular intervals thereafter.** For patients who experience a sustained increase in blood pressure or pulse rate while receiving MERIDIA, either dose reduction or discontinuation should be considered. MERIDIA should be given with caution to those patients with a history of hypertension (see **DOSAGE AND ADMINISTRATION**), and should not be given to patients with uncontrolled or poorly controlled hypertension.

Percent Outliers in Studies 1 and 2

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

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

Potential Interaction With Monoamine Oxidase Inhibitors

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

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions

The development of a potentially life-threatening serotonin syndrome, or Neuroleptic Malignant Syndrome (NMS)-like reactions, has been reported with SNRIs and SSRIs alone, including MERIDIA treatment, but particularly with concomitant use of serotonergic drugs (including triptans), with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms [e.g., nausea, vomiting, diarrhea] (see **PRECAUTIONS, Drug Interactions**). Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

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 premarketing 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 Medication Guide 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 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 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 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 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 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 over 65 years of age. Sibutramine is contraindicated in this group of patients (see CONTRAINDICATIONS). 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 ≥ 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

BODY SYSTEM Adverse Event	Sibutramine (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 ≥ 1% of all patients who received sibutramine in controlled and uncontrolled premarketing 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%) sibutramine 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 sibutramine (three of 4,588 subjects) was less than 0.1%.

Ecchymosis/Bleeding Disorders

Ecchymosis (bruising) was observed in 0.7% of sibutramine treated patients and in 0.2% of placebo-treated patients in premarketing placebo-controlled obesity studies. One patient had prolonged bleeding of a small amount which occurred during minor facial surgery. Sibutramine 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 sibutramine during premarketing 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 sibutramine-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 × upper limit of normal) occurred in 0% (alkaline phosphatase) to 0.6% (ALT) of the sibutramine 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 sibutramine are listed below. It is important to emphasize that although these events occurred during treatment with sibutramine, 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, psychosis, mania, suicidal ideation and suicide have been reported rarely in patients on sibutramine treatment. However, a relationship has not been established between these events and the use of sibutramine. If any of these events should occur during treatment with sibutramine, discontinuation should be considered.

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, mood changes, nightmares, 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 overdosage: an airway should be established as needed; 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 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**).

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.

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 for Abbott Laboratories, North Chicago, IL 60064 USA by KNOLL LLC B.V. Jayuya, PR, 00664.

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