This information is intended for U.S. residents only.

MERIDIA®

(sibutramine hydrochloride monohydrate)

Capsules

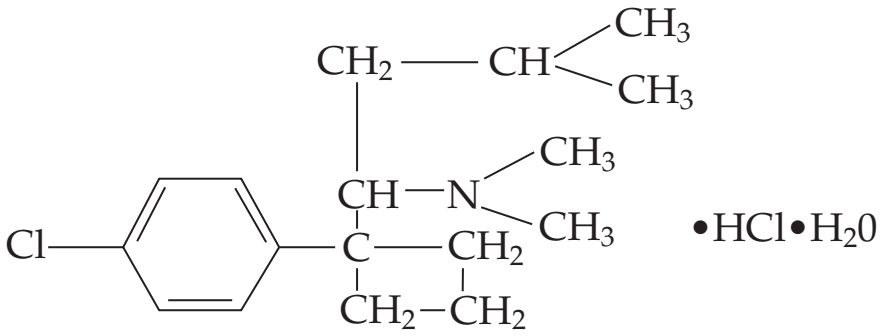
C-IV

℞ only

DESCRIPTION

MERIDIA® (sibutramine hydrochloride monohydrate) is an orally administered agent for the treatment of obesity. Chemically, the active ingredient is a racemic mixture of the (+) and (-) enantiomers of cyclobutanemethanamine, 1-(4-chlorophenyl)-*N,N*-dimethyl-α-(2-methylpropyl)-, hydrochloride, monohydrate, and has an empirical formula of $C_{17}H_{29}Cl_2NO$. 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)	T 1/2 (h)
Metabolite M_1				
Target Population:				
Obese Subjects	4.0 (42)	3.6 (28)	25.5 (63)	--
(n=18)	3.2 - 4.8	3.1 - 4.1	18.1 - 32.9	

Special Population:				
Moderate Hepatic	2.2 (36)	3.3 (33)	18.7 (65)	--
Impairment (n=12)	1.8 - 2.7	2.7 - 3.9	11.9 - 25.5	
Metabolite M_2				
Target Population:				
Obese Subjects	6.4 (28)	3.5 (17)	92.1 (26)	17.2 (58)
(n=18)	5.6 - 7.2	3.2 - 3.8	81.2 - 103	12.5 -21.8
Special Population:				
Moderate Hepatic	4.3 (37)	3.8 (34)	90.5 (27)	22.7 (30)
Impairment (n=12)	3.4 -5.2	3.1 - 4.5	76.9 - 104	18.9 - 26.5

† Calculated only up to 24 hr for M_1

Effect of Food

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

Special Populations

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

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

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

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

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

Hepatic Insufficiency: In 12 patients with moderate hepatic impairment receiving a single 15-mg oral dose of sibutramine, the combined AUCs of M_1 and M_2 were increased by 24% compared to healthy subjects while M_5 and M_6 plasma concentrations were unchanged. The observed differences in M_1 and M_2 concentrations do not warrant dosage adjustment in patients with mild to moderate hepatic impairment. MERIDIA should not be used in patients with severe hepatic dysfunction.

CLINICAL STUDIES

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

The long-term effects of MERIDIA on the morbidity and mortality associated with obesity have not been established. Weight loss was examined in 11 double-blind, placebo-controlled obesity trials (BMI range across all studies 27-43) with study durations of 12 to 52 weeks and doses ranging from 1 to 30 mg once daily. Weight was significantly reduced in a dose-related manner in sibutramine-treated patients compared to placebo over the dose range of 5 to 20 mg once daily. In two 12-month studies, maximal weight loss was achieved by 6 months and statistically significant weight loss was maintained over 12 months. The amount of placebo-subtracted weight loss achieved on MERIDIA was consistent across studies.

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

imately 80% did not go on to achieve a placebo-subtracted weight loss of ≥5% of their initial body weight on that dose by month 6.

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

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

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

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

		MERIDIA (mg)			
Study/Patient Group	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)	14.0 (152)	
Completers**	4.8 (76)		13.6 (80)	15.2 (93)	
Early responders***	10.7 (24)		18.2 (57)	18.8 (76)	
Study 3****					
All patients*	15.2 (78)		28.4 (81)		
Completers**	16.7 (48)		29.7 (60)		
Early responders***	21.5 (22)		33.0 (46)		

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

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

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

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

Maintenance of weight loss with 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.

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

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

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

Baseline mean values:

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

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

MERIDIA induced weight loss has been accompanied by reductions in serum uric acid.

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

The effect of sibutramine 15 mg once daily on measures of 24-hour blood pressure was evaluated in a 12-week placebo-controlled study. Twenty-six male and female, primarily Caucasian individuals with an average BMI of 34 kg/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., hypertension, diabetes, dyslipidemia).

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

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

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

CONTRAINDICATIONS

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

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

MERIDIA is contraindicated in patients who have anorexia nervosa.

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

WARNINGS

Blood Pressure and Pulse

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

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

Percent Outliers in Studies 1 and 2

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

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

Potential Interaction With Monoamine Oxidase Inhibitors

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

Concomitant Cardiovascular Disease

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

Glaucoma

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

Miscellaneous

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

PRECAUTIONS

Pulmonary Hypertension

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

Seizures

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

Gallstones

Weight loss can precipitate or exacerbate gallstone formation.

Renal/Hepatic Dysfunction

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

Interference With Cognitive and Motor Performance

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

Information For Patients

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

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

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

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

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

Drug Interactions

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

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

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

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

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

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

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

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

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Sibutramine was administered in the diet to mice (1.25, 5 or 20 mg/kg/day) and rats (1, 3, or 9 mg/kg/day) for two years generating combined maximum plasma AUC's of the two major active metabolites equivalent to 0.375 and 15.75 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 32.25 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 32.25 times those following the human dose of 15 mg. In rabbits dosed at 3, 15, or 75 mg/kg/day, plasma AUC's greater than approximately 5 times those following the human dose of 15 mg caused maternal toxicity. At markedly toxic doses, Dutch Belted rabbits had a slightly higher than control incidence of pups with a broad short snout, short rounded pinnae, short tail and, in some, shorter thickened long bones in the limbs; at comparably high doses in New Zealand White rabbits, one study showed a slightly higher than control incidence of pups with cardiovascular anomalies while a second study showed a lower incidence than in the control group.

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

ADVERSE REACTIONS

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

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

	Obese Patients in Placebo-Controlled Studies	
	MERIDIA® (n = 2068)	Placebo (n = 884)
BODY SYSTEM Adverse Event	% 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 MERIDIA in controlled and uncontrolled pre-marketing studies.

Body as a Whole: fever.
Digestive System: diarrhea, flatulence, gastroenteritis, tooth disorder.
Metabolic and Nutritional: peripheral edema.
Musculoskeletal System: arthritis.
Nervous System: agitation, leg cramps, hypertonia, thinking abnormal.
Respiratory System: bronchitis, dyspnea.
Skin and Appendages: pruritus.
Special Senses: amblyopia.
Urogenital System: menstrual disorder.

Postmarketing Reports

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

abnormal dreams, abnormal ejaculation, abnormal gait, abnormal vision, alopecia, amnesia, anaphylactic shock, anaphylactoid reaction, anemia, anger, angina pectoris, arthrosis, atrial fibrillation, blurred vision, bursitis, cerebrovascular accident, chest pressure, chest tightness, cholecystitis, cholelithiasis, concentration impaired, confusion, congestive heart failure, depression aggravated, dermatitis, dry eye, duodenal ulcer, epistaxis, eructation, eye pain, facial edema, gastrointestinal hemorrhage, Gilles de la Tourette's syndrome, goiter, heart arrest, heart rate decreased, hematuria, hyperglycemia, hyperthyroidism, hypesthesia, hypoglycemia, hypothyroidism, impotence, increased intraocular pressure, increased salivation, increased urinary frequency, intestinal obstruction, leukopenia, libido decreased, libido increased, limb pain, lymphadenopathy, manic reaction, micturition difficulty, mood changes, mouth ulcer, myocardial infarction, nasal congestion, nightmares, otitis externa, otitis media, petechiae, photosensitivity (eyes), photosensitivity (skin), respiratory disorder, serotonin syndrome, short term memory loss, speech disorder, stomach ulcer, sudden unexplained death, supraventricular tachycardia, syncope, thrombocytopenia, tinnitus, tongue edema, torsade de pointes, transient ischemic attack, tremor, twitch, urticaria, vascular headache, ventricular tachycardia, ventricular extrasystoles, ventricular fibrillation, vertigo, yawn.

Other Notable Adverse Events

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

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

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

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance

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

Abuse and Physical and Psychological Dependence

Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for

signs of misuse or abuse (e.g., drug development of tolerance, incrementation of doses, drug seeking behavior).

OVERDOSAGE

Human Experience

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

Overdose Management

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

DOSAGE AND ADMINISTRATION

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

Doses above 15 mg daily are not recommended. In most 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 0074-2456-13, blue/yellow capsules imprinted with "MERIDIA" on the cap and "-5-" on the body, in bottles of 100 capsules.

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

15 mg, NDC 0074-2458-13, yellow/white capsules imprinted with "MERIDIA"on the cap and "-15-" on the body, in bottles of 100 capsules.

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

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A. by BASF Corporation, Mount Olive, NJ 07828, U.S.A.

IMITREX is a registered trademark of Glaxo Group Limited.

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

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MERIDIA®

(sibutramine hydrochloride monohydrate)

Capsules

PATIENT INFORMATION

IMPORTANT PATIENT INFORMATION. READ THIS PATIENT INFORMATION CAREFULLY AND COMPLETELY BEFORE YOU START TAKING MERIDIA AND REREAD IT EACH TIME THE PRESCRIPTION IS RENEWED. CONTACT YOUR DOCTOR IMMEDIATELY IF YOU HAVE ANY QUESTIONS OR CONCERNS. SAVE THIS PATIENT INFORMATION SHEET FOR FUTURE REFERENCE.

Patient information about MERIDIA® (sibutramine hydrochloride monohydrate) Capsules.

MERIDIA capsules come in three strengths: 5 mg, 10 mg, and 15 mg.

What is MERIDIA?

MERIDIA is an oral prescription medication used for the medical management of obesity, including weight loss and the maintenance of weight loss. MERIDIA can only be prescribed by a medical doctor.

MERIDIA comes in three different strength capsules (5 mg, 10 mg, and 15 mg). The recommended initial starting dose of MERIDIA is one 10 mg capsule per day. Your doctor will determine the starting dose that is best for you.

How does MERIDIA work?

MERIDIA works by affecting appetite control centers in the brain.

In medical studies in overweight people, MERIDIA, along with a reduced calorie diet, produced significant reductions in body weight.

MERIDIA should be used as part of a comprehensive weight-loss program, supervised by your doctor, that includes a reduced calorie diet and appropriate physical activity.

How long does it take for MERIDIA to work?

Every person will respond differently to MERIDIA when used as part of a comprehensive weight-loss program. You may be able to lose 4 or more pounds of body weight in the first month you take MERIDIA. If you find that you do not lose at least 4 pounds during the first month, you should notify your doctor so he or she can re-evaluate your situation. Your doctor may wish to change your dose of MERIDIA.

Most people who lose weight on MERIDIA lose it in the first 6 months of treatment. Scientific studies that lasted two years have shown that many people who lost weight and remained on MERIDIA therapy maintained their weight loss.

Who should take MERIDIA?

A weight-loss program that includes a reduced calorie diet and appropriate physical activity may be adequate in some patients. You should discuss with your doctor whether MERIDIA should be added to such a program.

MERIDIA is recommended for overweight people with an initial body mass index (BMI) of 30 or higher, or for overweight people with a BMI of 27 or higher if they have medical risk factors such as high blood pressure, diabetes, or high cholesterol. Your doctor can determine your BMI and will decide if you meet these criteria.

How and when should I take MERIDIA?

Follow your doctor's instructions on how and when to take MERIDIA.

Your doctor will recommend that you take one (1) MERIDIA capsule a day.

You can take MERIDIA on an empty stomach or after a meal.

What if I miss a dose?

If you forget to take a dose of MERIDIA, do not take an extra capsule to "make up" for the dose you forgot.

How long should I take MERIDIA?

Your doctor will determine how long you should take MERIDIA. Follow your doctor's advice.

The safety and effectiveness of MERIDIA have not been determined beyond two (2) years at this time.

Who should not take MERIDIA?

MERIDIA should not be taken by people who:

1. **HAVE UNCONTROLLED OR POORLY CONTROLLED HIGH BLOOD PRESSURE BECAUSE MERIDIA SUBSTANTIALLY INCREASES BLOOD PRESSURE IN SOME PATIENTS.**
2. Are taking prescription medicines called monoamine oxidase inhibitors (MAOIs) for depression, Parkinson's Disease, or any other disorder (for example: Eldepryl®, Parnate®, Nardil®).
3. Are taking other weight loss medications that act on the brain (for example: phentermine). This includes prescription and over-the-counter medications and herbal products.

4. Have had prior allergic reactions to MERIDIA or sibutramine.
5. Have a diagnosis of coronary artery disease and/or who have angina pectoris (heart-related chest pain).
6. Have arrhythmias (irregular heart beats).
7. Have had a prior heart attack.
8. Have a diagnosis of congestive heart failure.
9. Have severe liver or kidney disease.
10. Have had a stroke or symptoms of a stroke (transient ischemic attacks [TIAs]).
11. Are pregnant or planning to become pregnant.
12. Are breast-feeding their infants.
13. Are suffering from anorexia nervosa.
14. Are taking prescription medications for depression.
15. Have had seizures (epilepsy or convulsions).
16. Have an eye disorder called narrow angle glaucoma.
17. Are under 16 years of age.
18. Are taking other medications that regulate the neurotransmitter serotonin in the brain (for example: Prozac®, Zoloft®, Effexor®, Luvox®, Paxil® or Zyban®).

If you have any concerns or questions about whether or not you should take MERIDIA, talk to your doctor.

IMPORTANT: It is very important that you make sure that your primary care doctor and all your other health care providers know what medications you take and what medical conditions and allergies you have.

What medical conditions or information should I tell my doctor?

It is important that you tell your doctor all about your medical history, whether you are taking or have taken weight loss drugs in the past, current medical problems, current symptoms, what other medications you take or have taken (prescription and over-the-counter medicines and herbal products) and any prior allergies to medicines.

It is important to make sure your doctor knows if you have heart disease of any kind, high blood pressure, migraine headaches, glaucoma, seizures, depression, Parkinson's Disease, prior strokes, prior transient ischemic attacks (TIAs), thyroid disorders, osteoporosis, gallstones, liver disease, kidney disease, history of a major eating disorder (anorexia nervosa or bulimia nervosa) or any other medical problem.

What about physician follow-up visits?

You should make sure you see your doctor as directed for regular follow-up visits, during which your doctor can follow your body weight, and carefully monitor your overall health as you try to lose weight and maintain weight loss.

What medications can cause problems if taken at the same time I take MERIDIA?

You cannot take MERIDIA if you are taking prescription medicines called monoamine oxidase inhibitors (MAOIs). It is especially important to make sure you tell your doctor if you are taking MAOIs which are sometimes used to treat depression or Parkinson's Disease (for example: Eldepryl®, Nardil®, Parnate®). This is very important because serious, sometimes even fatal, reactions can occur if MERIDIA is taken at the same time MAOIs are taken.

If you are currently taking an MAOI, your doctor will want you to stop taking it for at least two (2) full weeks before starting you on MERIDIA.

If you are currently taking MERIDIA, your doctor will want you to stop taking it for at least two (2) full weeks before starting you on an MAOI.

MERIDIA should not be taken if you are taking other weight-loss medications that act on the brain (for example: phentermine). This includes both prescription and over-the-counter medications and herbal products.

In addition to the above, a rare, but serious, medical syndrome called the "serotonin syndrome" has been reported in patients when medications like MERIDIA are taken along with other drugs that may alter serotonin activity such as: drugs for depression (for example: Desyrel®, Effexor®, Eldepryl®, Remeron®, Serzone®, Wellbutrin®, Nardil®, Parnate®, Paxil®, Prozac®, Zoloft®, Ludiomil®, Adapin®, Asendin®, Elavil®, Etrafon®, Limbitrol®, Norpramin®, Pamelor®, Sinequan®, Surmontil®, Tofranil®, Triavil®, Vivactil®, Luvox®, Anafranil®), drugs for migraine headache therapy (Imitrex® [sumatriptan succinate]) and dihydroergotamine, certain pain medications such as Demerol® (meperidine), Duragesic® (fentanyl), and Talwin® (pentazocine); the cough suppressant dextromethorphan found in many cough medicines; lithium; and the amino acid tryptophan. The syndrome requires immediate medical attention and may include one or more of the following symptoms: restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, weakness, tremor, incoordination, fever, shivering, sweating, vomiting and increased heart rate.

The metabolism of MERIDIA may be inhibited by ketoconazole (an anti-fungal medicine) and to a lesser degree erythromycin (an antibiotic medicine). You need to make sure your doctor knows you are taking these medicines before you take MERIDIA. If, while taking MERIDIA, your doctor decides to put you on ketoconazole or erythromycin, you should remind him or her that you are also on MERIDIA.

Many over-the-counter cough and cold remedies, as well as certain allergy products and decongestants, contain medicines such as phenylpropanolamine, ephedrine, or pseudoephedrine that may increase blood pressure or heart rate. Before taking these medications on your own, you should check with your doctor to make sure it is all right to take these medicines if you are already taking MERIDIA.

Your doctor may advise you to take a certain type of cough, cold, decongestant or allergy medicine that will not interact with MERIDIA.

When should I call my doctor?

It is important that you call your doctor immediately if you experience any symptoms or feelings that make you concerned about your health or a possible drug side effect. Let your doctor advise you on your concerns. If you experience any of the following symptoms, stop taking MERIDIA and notify your doctor immediately: trouble breathing, shortness of breath, chest pain, angina, rapid heart beats over 100 beats a minute, pounding or irregular heart beats, restlessness, lightheadedness, blackout spells, disorientation, depression, mental confusion, anxiety, nervousness, tremors, loss of muscle coordination, muscle stiffness or muscle rigidity, high fever, pain in the eyes, dilated pupils, shivering, sweating, abdominal pain, nausea or vomiting, or other symptoms that concern you.

Is MERIDIA a controlled substance?

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

What weight-loss results have been observed with MERIDIA?

Patients treated with MERIDIA while on a reduced calorie diet, showed a significant weight-loss during the first 6 months of treatment, and significant weight loss was maintained for one year. In one 12-month study, the average weight loss in patients taking MERIDIA, 10 mg daily, was about 10 lbs. and in those taking 15 mg daily was about 14 lbs. The average weight loss in persons on only a reduced calorie diet was 3½ lbs.

What are some of the more common side effects of MERIDIA?

MERIDIA, like all medications, may cause side effects. In studies the most common side effects were: dry mouth, constipation, and insomnia (inability to fall asleep). Other side effects that may occur include: headache, increased sweating, an increase in blood pressure, and an increase in heart rate. These side effects are generally mild, and have usually not caused people to stop taking MERIDIA. If you develop a symptom that you think might be a side effect, stop taking MERIDIA and notify your doctor immediately so he or she can advise you on what to do.

Can MERIDIA affect blood pressure or heart rate?

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

On average, small increases in blood pressure and small increases in heart rate were seen in overweight people who took MERIDIA in scientifically controlled studies. You should make sure you see your doctor as directed for regular follow-up visits. Your blood pressure and pulse should be measured prior to starting therapy with MERIDIA and should be monitored at regular intervals thereafter. If you experience an increase in blood pressure or heart rate while taking MERIDIA, your doctor may decide to decrease the dose or discontinue MERIDIA.

If you have high blood pressure that is controlled by medication or diet, your doctor may choose to prescribe MERIDIA for you as part of a comprehensive weight-management program. MERIDIA should not be taken by people who have uncontrolled or poorly controlled high blood pressure.

Are there any severe side effects?

Certain weight-loss drugs have been associated with pulmonary hypertension (PPH), a rare but sometimes fatal disease. In clinical studies, no cases of PPH have been reported with MERIDIA. Because this disease is so rare, however, it is not known whether or not MERIDIA may cause this disease.

The first symptom of PPH is usually shortness of breath. If you experience new or worsening shortness of breath, or if you experience chest pain, fainting, or swelling of your feet, ankles, or legs, stop taking MERIDIA, and notify your doctor immediately.

Does MERIDIA cause damage to the heart valves?

Certain weight-loss drugs have been associated with cardiac valve dysfunction (heart valve disease). Patients in two studies were examined by doctors who used cardiac ultrasound testing to carefully look at heart valve structure and function. In one study, 25 patients were examined before treatment with MERIDIA and again after three months of treatment. None of the patients had heart valve disease. In another study, patients who had received either MERIDIA or placebo (sugar pills) for periods of two weeks to 16 months were examined. Three out of 132 patients (2.3%) who had taken MERIDIA and two out of 77 patients (2.6%) who had taken placebo were found to have heart valve disease. You should discuss this further with your doctor.

Will MERIDIA change the way I need to take my nutritional supplements?

Non-drug nutritional supplements, like vitamins, minerals and amino acids (with the exception of tryptophan) can be used along with MERIDIA. You should make sure your doctor knows what nutritional supplements you are taking and why you are taking them. You should not take MERIDIA if you are taking tryptophan. You should not use herbal or over-the-counter weight-loss products while taking MERIDIA.

What about drinking alcoholic beverages?

MERIDIA may increase the sedative effects of alcohol. It is important that you let your doctor know how often, and what type of alcoholic beverages you drink. Your doctor can advise you best as to whether you should drink alcoholic beverages while on MERIDIA.

What about drinking coffee, tea and caffeinated beverages?

MERIDIA can be safely taken with moderate use of coffee, tea or caffeinated beverages. You should check with your doctor to make sure that you do not have a medical condition that can be aggravated by these beverages independent of being on MERIDIA. You should check with your doctor if you consume a great deal of caffeinated beverages or use over-the-counter pills that contain caffeine.

What if I develop allergic reactions?

Stop taking MERIDIA and notify your doctor immediately if you develop a skin rash, hives or other allergic reactions.

What if I am pregnant or nursing?

MERIDIA should not be used by pregnant women or nursing mothers. You should notify your doctor immediately if you become pregnant or plan to become pregnant.

What about sexual activity and potential pregnancy?

Women of child bearing potential should use an effective birth control method while taking MERIDIA. Check with your doctor to make sure you are on a medically safe and effective birth control method while taking MERIDIA.

Will MERIDIA affect the effectiveness of birth control pills?

No.

What about driving a car or dangerous work activities?

MERIDIA should not interfere with your ability to drive your car. However, you should be on the alert for any signs of fatigue, sedation, or lack of alertness. You should be very careful about using alcohol before you drive as MERIDIA may increase the sedative effects of alcohol.

MERIDIA was studied in healthy people and did not affect their coordination or impair their judgment. However, MERIDIA has the potential to impair judgment, thinking, coordination or motor skills. You should check with your doctor if you have any questions with regard to your work and the use of MERIDIA.

How should I keep and use MERIDIA?

MERIDIA should be stored at normal room temperature (about 60 to 85°F). Never leave MERIDIA in hot or moist places.

It is important to keep MERIDIA in a safe area where children cannot get it.

If your child swallows MERIDIA, immediately speak with your doctor and/or take your child to the emergency room for immediate medical attention. If you are unable to reach a doctor or emergency room, call the poison control center at 1-800-764-7661.

Never take more MERIDIA than prescribed by your doctor.

You should never share MERIDIA with a friend.

SAVE THIS PATIENT INFORMATION SHEET ON MERIDIA. YOU SHOULD KEEP THIS SHEET TO REFER BACK TO FROM TIME TO TIME. KEEP IT IN A SAFE PLACE WHERE YOU CAN FIND IT. YOU MAY WISH TO BRING THIS SHEET WITH YOU EVERY TIME YOU VISIT YOUR DOCTOR. IT MAY HELP YOU WITH YOUR DISCUSSIONS WITH YOUR DOCTOR.

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

This patient information sheet is intended for information only. It is not a substitute for your doctor's instructions. Notify your doctor immediately of any questions or concerns. Never take extra doses of MERIDIA.

For additional information on MERIDIA and weight management, please talk with your doctor, nurse, pharmacist, other health care professional or call 1-800-633-9110.

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