PRODUCT MONOGRAPH

Pr MERIDIA®
sibutramine hydrochloride monohydrate
10 mg and 15 mg capsules

Anorexiant / Antiobesity Agent

Abbott Laboratories, Limited
8401 Trans-Canada Highway
St-Laurent, Qc H4S 1Z1

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sibutramine hydrochloride monohydrate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Non-medicinal Ingredients
oral	10 mg and 15 mg capsules	colloidal silicon dioxide, D&C Yellow No. 10 (15 mg capsules only), FD&C Blue No. 2 (10 mg capsules only), gelatin, lactose monohydrate, magnesium stearate, microcrystalline cellulose, printing ink, silicon dioxide, sodium lauryl sulphate, and titanium dioxide *This is a complete listing of non-medicinal ingredients.*

INDICATIONS AND CLINICAL USE

MERIDIA® (sibutramine hydrochloride monohydrate) is indicated as adjunctive therapy within a weight management program for:

- Obese patients with an initial body mass index (BMI) of 30 kg/m^2 or higher
- Obese patients with an initial BMI of 27 kg/m^2 or higher in the presence of other risk factors (e.g., controlled hypertension, type 2 diabetes, dyslipidemia, visceral fat).

Distribution restrictions

- MERIDIA® should only be prescribed to patients who have not adequately responded to an appropriate weight reducing diet alone.

Geriatrics (> 65 years of age):

For a brief discussion please see (**WARNINGS AND PRECAUTIONS** – **Special Populations** – **Geriatrics**).

Pediatrics (< 18 years of age):

For a brief discussion please see (**WARNINGS AND PRECAUTIONS** – **Special Populations** – **Pediatrics**).

BMI based on various heights and weights is presented in **Table 1**.

BMI is calculated by taking the patient's weight, in kg, divided by the patient's height, in meters, squared.

Metric conversions are as follows: pounds ÷ 2.2 = kg; feet x 0.3048 = meters; inches x 0.0254 = meters.

Table 1. Body Mass Index (BMI), kg/m^2

WEIGHT, lb (kg)	HEIGHT, ft/in (m)																
	4'10" (1.47)	**4'11" (1.50)**	**5'0" (1.52)**	**5'1" (1.55)**	**5'2" (1.57)**	**5'3" (1.60)**	**5'4" (1.63)**	**5'5" (1.65)**	**5'6" (1.68)**	**5'7" (1.70)**	**5'8" (1.73)**	**5'9" (1.75)**	**5'10" (1.78)**	**5'11" (1.80)**	**6'0" (1.83)**	**6'1" (1.85)**	**6'2" (1.88)**
120 (54.5)	25	24	23	23	22	21	21	20	19	19	18	18	17	17	16	16	15
130 (59.1)	27	26	25	25	24	23	22	22	21	20	20	19	19	18	18	17	17
140 (63.6)	29	28	27	27	26	25	24	23	23	22	21	21	20	20	19	19	18
150 (68.2)	31	30	29	28	27	27	26	25	24	24	23	22	22	21	20	20	19
160 (72.7)	34	32	31	30	29	28	28	27	26	25	24	24	23	22	22	21	21
170 (77.3)	36	34	33	32	31	30	29	28	27	27	26	25	24	24	23	22	21
180 (81.8)	38	36	35	34	33	32	31	30	29	28	27	27	26	25	24	24	23
190 (86.4)	40	38	37	36	35	34	33	32	31	30	29	28	27	27	26	25	24
200 (90.9)	42	40	39	38	37	36	34	33	32	31	30	30	29	28	27	26	26
210 (95.5)	44	43	41	40	38	37	36	35	34	33	32	31	30	29	29	28	27
220 (100.0)	46	45	43	42	40	39	38	37	36	35	34	33	32	31	30	29	28
230 (104.5)	48	47	45	44	42	41	40	38	37	36	35	34	33	32	31	30	30
240 (109.1)	50	49	47	45	44	43	41	40	39	38	37	36	35	34	33	32	31
250 (113.6)	52	51	49	47	46	44	43	42	40	39	38	37	36	35	34	33	32
260 (118.2)	54	53	51	43	48	46	45	43	42	41	40	38	37	36	35	34	33
270 (122.7)	57	55	53	51	49	48	46	45	44	42	41	40	39	38	37	36	35
280 (127.3)	59	57	55	53	51	50	48	47	45	44	43	41	40	39	38	37	36
290 (131.8)	61	59	57	55	53	51	50	48	47	46	44	43	42	41	39	38	37
300 (136.4)	63	61	59	57	55	53	52	50	49	47	46	44	43	42	41	40	39
310 (140.9)	65	63	61	59	57	55	53	52	50	49	47	46	45	43	42	41	40
320 (145.5)	67	65	63	61	59	57	55	53	52	50	49	47	46	45	43	42	41

- Patients with BMI values ≥30 may be candidates for MERIDIA® therapy.
- Patients with BMI values of 27 to 29 may be candidates for MERIDIA® therapy if they also have a concomitant risk factor (e.g., controlled hypertension, type 2 diabetes, dyslipidemia, visceral fat).

Treatment with MERIDIA® should only be given as part of a long-term integrated therapeutic approach for weight reduction and weight maintenance under the care of a physician with experience in the treatment of obesity. An appropriate approach to obesity management should include dietary and behavioral modification as well as increased physical activity. This integrated approach is essential for a lasting change in eating habits and behavior which is fundamental to the long-term maintenance of the reduced weight level once MERIDIA® is stopped. Patients should change their lifestyle while on MERIDIA® so that they are able to maintain their weight once drug treatment has ceased. They should be informed that, if they fail to do so, they may regain weight. Even after cessation of MERIDIA®, continued monitoring of the patient by the physician is recommended.

The safety and effectiveness of MERIDIA® beyond one year have not been established.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION, AND PACKAGING** section of the Product Monograph.

- MERIDIA® (sibutramine hydrochloride monohydrate) is contraindicated in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or cerebrovascular disease [stroke or transient ischemic attack (TIA)]. See (**WARNINGS AND PRECAUTIONS**).

- MERIDIA® is contraindicated in patients with inadequately controlled (>145/90 mm Hg) or unstable hypertension. See (**WARNINGS AND PRECAUTIONS**).

- MERIDIA® is contraindicated in patients with a history of, or presence of, major eating disorder such as anorexia nervosa or bulimia nervosa.

- Concomitant use of MERIDIA® with other centrally acting weight-reducing agents is contraindicated. See (**DRUG INTERACTIONS**).

- Concomitant use of MERIDIA® and a monoamine oxidase inhibitor (MAOI) is contraindicated. At least 14 days should elapse between discontinuation of a MAOI and initiation of treatment with MERIDIA®. See (**WARNINGS AND PRECAUTIONS**) and (**DRUG INTERACTIONS**).

- Concomitant use of MERIDIA® and centrally-acting drugs for the treatment of psychiatric disorders (such as antidepressants, antipsychotics) or herbal remedies (such as St John's Wort) is contraindicated. At least 14 days should elapse between discontinuation of these drugs and initiation of treatment with sibutramine hydrochloride monohydrate. A 5 week discontinuation period is required for fluoxetine. See (**DRUG INTERACTIONS**).

- MERIDIA® is contraindicated in psychiatric illness. Sibutramine has shown potential antidepressant activity in animal studies and therefore it cannot be excluded that sibutramine could induce a manic episode in bipolar patients.

WARNINGS AND PRECAUTIONS

General

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

Interaction with Monoamine Oxidase Inhibitors

MERIDIA® is a serotonin (5-hydroxytryptamine; 5-HT) and norepinephrine (NE) reuptake inhibitor and should not be used concomitantly with MAOIs. See (**CONTRAINDICATIONS**). There should be at least a 2-week interval after stopping MAOIs before commencing treatment with MERIDIA®. Treatment with MAOIs should not be initiated within 14 days of stopping MERIDIA® therapy.

Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. If concomitant treatment with MERIDIA® and SSRIs (e.g., sertraline, escitalopram oxalate, and fluoxetine) or SNRIs (e.g., venlafaxine, duloxetine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. 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 (**DRUG INTERACTIONS**).

Carcinogenesis and Mutagenesis

For a brief discussion of pre-clinical animal data, see (**TOXICOLOGY Mutagenicity and Carcinogenicity**).

Cardiovascular

Blood Pressure and Pulse Rate

MERIDIA® substantially increases blood pressure and heart rate in some patients. Blood pressure and heart rate increases were observed early in treatment with approximately 60% of those patients with significant increases being detected within the first month of therapy and approximately 90% within 4 months. Blood pressure and pulse rate should be measured prior to starting therapy with MERIDIA® and should be monitored at regular intervals thereafter. See (**DOSAGE AND ADMINISTRATION**).

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 of 4 to 5 beats per minute (bpm) relative to

placebo. The percentage of sibutramine-treated patients with sustained and clinically significant increases in systolic blood pressure (SBP) relative to placebo varied between 1.7 to 8.4%. The corresponding figures for diastolic blood pressure (DBP) were 3.8 to 8.0%. The percentage of patients on sibutramine with an increase of 10 bpm or greater at two consecutive visits was greater than on placebo and appeared to be dose-dependent (see **Table 2**). 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.

For patients who experience a sustained increase in blood pressure or pulse rate while receiving MERIDIA®, the drug should be discontinued. See (**DOSAGE AND ADMINISTRATION**). MERIDIA® should be given with caution to patients with well-controlled hypertension, and is contraindicated in patients with inadequately controlled or unstable hypertension.

Table 2. Percent Outliers

% Outliers*			
Dose	SBP	DBP	Pulse
Placebo	28.4	15.3	16.1
10 mg	30.1	19.1	29
15 mg	36.8	23.3	39.5

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

Concomitant Cardiovascular Disease

Treatment with MERIDIA® has been associated with increases in heart rate and blood pressure. Therefore, MERIDIA® is contraindicated in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or cerebrovascular disease (stroke or TIA). See (**CONTRAINDICATIONS**).

Pulmonary Hypertension and Cardiac Valvulopathy

Certain centrally-acting weight loss agents that cause both release and re-uptake inhibition of serotonin from nerve terminals have been associated with primary pulmonary hypertension (PPH), a rare but sometimes fatal disease, and cardiac valve dysfunction when used for more than 3 months. It is hypothesized that the mechanism by which these drugs cause PPH and cardiac valvulopathy is the release of serotonin from nerve terminals. MERIDIA® is a serotonin and norepinephrine re-uptake inhibitor and not a serotonin releasing agent. The yearly occurrence of PPH in the general population is estimated to be approximately 1-2 cases per 1,000,000 persons. Because of the low background incidence of PPH it is not yet known whether MERIDIA® may cause this condition.

The possible occurrence of cardiac valve disease was specifically investigated in clinical studies. See (**ACTION AND CLINICAL PHARMACOLOGY**). The incidence of cardiac valvulopathy in MERIDIA®-treated patients was not different from that in placebo-treated patients. In addition, in extensive postmarketing experience there has been no increase in the incidence of cardiac valve dysfunction. However, due to the limited number of patients studied, it is not yet known whether MERIDIA® may cause this condition.

In view of general concerns with anti-obesity drugs, it is important to be on the look out for symptoms such as progressive dyspnea, chest pain and ankle edema in the course of routine check-ups. The patient should be advised to consult a doctor immediately if these symptoms occur.

Dependence/Tolerance

Clinical data and postmarketing experience have not shown any evidence of drug abuse with MERIDIA®.

Hematologic

There have been reports of bleeding abnormalities associated with agents that affect serotonin reuptake. Sibutramine should be used with caution in patients treated concomitantly with drugs known to affect hemostasis or platelet function [e.g., atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid, and non-steroidal anti-inflammatory drugs (NSAIDs)]. Caution is also advised in patients with a history of bleeding disorders or those with predisposing conditions.

Hepatic/Biliary/Pancreatic

In patients with mild or moderate hepatic impairment, cautious use of MERIDIA® is advised only where the clinical benefit outweighs the risk.

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

Weight loss can precipitate or exacerbate gallstone formation.

Neurologic

Seizures/Epilepsy

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 or epilepsy. It should be discontinued in any patient who develops seizures.

Ophthalmologic

Glaucoma

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

Psychiatric

Cases of depression, psychosis, mania, suicidal ideation and suicide have been reported rarely in patients on sibutramine treatment. Special attention is therefore required in patients with a history of depression. If signs or symptoms of these psychiatric events occur during treatment with sibutramine, the discontinuation of sibutramine and commencement of an appropriate treatment should be considered.

Renal

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 (**ACTION AND CLINICAL PHARMACOLOGY**).

Special Populations

Pregnant Women

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 child-bearing potential should employ adequate contraception while taking MERIDIA®. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Labor and Delivery

The effect of MERIDIA® during labor or delivery on the mother and the fetus is unknown. The effects on later growth, development and functional maturation of the child are also unknown.

Nursing Women

It is not known whether sibutramine or its metabolites are excreted in human milk. Since no data are available on the effects of MERIDIA® in the nursing infant, MERIDIA® is not recommended for nursing mothers. Patients should be advised to notify their physician if they are breast-feeding.

Pediatrics (< 18 years of age)

The safety and effectiveness of MERIDIA® in pediatric patients under 18 years old have not been established.

Geriatrics (> 65 years of age)

The safety and effectiveness of MERIDIA® in geriatric patients over 65 years old have not been established.

Monitoring and Laboratory Tests

No specific laboratory tests are recommended.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

In placebo-controlled studies, 9.4% of patients treated with MERIDIA® (sibutramine hydrochloride monohydrate) (n=5335) and 5.9% of patients treated with placebo (n=2717) withdrew for adverse events. In placebo-controlled obesity studies, the most common events were dry mouth, anorexia, insomnia, and constipation.

Adverse Reactions During Clinical Trials

Most adverse events reported with sibutramine occurred at the start of treatment (during first four weeks). Their severity and frequency diminished over time. They were generally not serious, did not entail discontinuation of treatment and were reversible.

Adverse events in these studies occurring in ≥1% of MERIDIA®-treated patients and more frequently than in the placebo group are shown in **Table** 3:

Table 3. Events in these studies occurring in ≥1% of MERIDIA®-treated patients and more frequently than in the placebo group

BODY SYSTEM Adverse Event	Obese Patients in Placebo-Controlled Studies (% Incidence)	
	MERIDIA® 10 and 15 mg (n=4350)	Placebo (n=2717)
BODY AS A WHOLE		
Headache	15.1	13.8
Infection	13.1	12.3
Flu syndrome	7.8	6.7
Injury accident	4.8	4.3
Abdominal pain	3.9	3.9
Unevaluated reaction	3.2	2.1
Neck pain	1.6	1.6
Allergic reaction	1.1	0.9
CARDIOVASCULAR SYSTEM		
Hypertension	2.3	1.8
Tachycardia	2.2	0.5
Vasodilation	1.6	0.8
Migraine	1.8	1.5
Palpitations	1.6	0.8
DIGESTIVE SYSTEM		
Constipation	11	5.1
Nausea	4.6	2.3
Appetite increase	3.7	2.4
Anorexia	3.5	1.8
Dyspepsia	3.0	2.9
Gastroenteritis	2.3	1.8
Gastritis	1.7	1.4
Vomit	1.5	1.2
Rectal Disorder	1.5	0.5
Flatulence	1.3	1.2
MUSCULOSKELETAL SYSTEM		
Arthralgia	3.8	3.7
Joint disorder	1.1	0.8
Tenosynovitis	1	0.4

BODY SYSTEM Adverse Event	Obese Patients in Placebo-Controlled Studies (% Incidence)	
	MERIDIA® 10 and 15 mg (n=4350)	Placebo (n=2717)
NERVOUS SYSTEM		
Dry mouth	15.9	3
Insomnia	7.3	3.9
Dizziness	4.9	3.2
Nervousness	3.2	1.8
Depression	2.8	2.4
Anxiety	2.6	2.2
Paresthesia	1.2	0.8
Vertigo	1.1	0.7
RESPIRATORY SYSTEM		
Pharyngitis	9.2	8.4
SKIN & APPENDAGES		
Sweat	4.3	0.9
Rash	3.4	2.8
Eczema	1.2	0.8
Herpes simplex	1.4	1.1
SPECIAL SENSES		
Conjunctivitis	1.1	0.7
UROGENITAL SYSTEM		
Metrorrhagia	1.2	0.8
Cystitis	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 (N=6420).

Body as a Whole:	asthenia, back pain, chest pain, fever, pain;
Digestive System:	diarrhea, flatulence, hemorrhoid aggravation, periodontal abscess, thirst;
Metabolic and Nutritional Disorders:	general edema, peripheral edema;
Musculoskeletal System:	arthritis, tendon disease;
Nervous System:	hypertonia, labile emotions, neuralgia, somnolence;
Respiratory System:	bronchitis, dyspnea, increased cough, laryngitis, rhinitis, sinusitis;
Skin and Appendages:	acne, pruritus;
Special Senses:	taste perversion;

Urogenital System:	dysmenorrhea, menstrual disorder, urinary tract infection;

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following additional adverse events were reported with an incidence of ≥ 0.1% to < 1.0% in patients exposed to MERIDIA® in controlled and uncontrolled studies (N=6420).

Body as a Whole;	abdominal enlargement, abnormal laboratory test, abscess, accidental injury, altered hormone level, carcinoma, cellulitis, chills, feverish chills, cyst, facial edema, halitosis, hangover, hernia, inflammation, malaise, monilia, mucous membrane disease, rigid neck, neoplasm, substernal chest pain, pelvic pain, photosensitivity, shock, unexpected benefit;
Cardiovascular System:	angina pectoris, arrhythmia, bradycardia, bundle branch block, cardiovascular disease, cerebrovascular accident, abnormal ECG, supraventricular extrasystoles, ventricular extrasystoles, atrial fibrillation, hemorrhage, hypotension, postural hypotension, cerebral ischemia, phlebitis, syncope, vascular disorder, peripheral vascular disorder, varicose veins;
Digestive System:	cheilitis, cholelithiasis, colitis, dysphagia, tongue edema, enteritis, eructation, esophagitis, increased GGT, gastrointestinal disorder, gingivitis, glossitis, gastro-intestinal hemorrhage, rectal hemorrhage, fatty liver, abnormal liver function, oral monilia, nausea and vomiting, bilary pain, stomatitis, abnormal stools, tongue disorder, tooth caries, mouth ulcer, stomach ulcer;
Endocrine System:	goiter, hyperthyroidism, thyroid disorder;
Hemic and Lymphatic System:	anemia, hypochromatic anemia, iron deficiency anemia, ecchymosis, eosinophilia, leukocytosis, leukopenia, lymphadenopathy, lymphocytosis, monocytosis, abnormal red blood cells, thrombocythemia, thrombocytopenia;
Metabolic and Nutritional Disorders:	alcohol intolerance, bilirubinemia, increased BUN, increased creatine phosphokinase, increased creatinine, dehydration, diabetes mellitus, edema, gout, hypercholesteremia, hyperglycemia, hyperkalemia, hyperlipidemia, hyperuricemia, hypoglycemia, hypokalemia, increased alkaline phosphatase, increased SGOT, increased SGPT, increased weight;
Musculoskeletal System:	rheumatoid arthritis, arthrosis, bone disorder, bursitis, leg cramps, myasthenia, myopathy, osteoporosis, bone pain;

Nervous System:	agitation, akathisia, amnesia, apathy, ataxia, CNS stimulation, confusion, convulsions, leg cramps, psychotic depression, abnormal dream, euphoria, hostility, hypesthesia, hyperkinesis, decreased libido, increased libido, myoclonus, neuritis, neurosis, facial paralysis, circumoral paresthesia, personality disorder, sleep disorder, abnormal thinking, torticollis, tremor, twitch;
Respiratory System:	apnea, asthma, epistaxis, hyperventilation, lung disorder, pneumonia, respiratory disorder, increased sputum, altered voice;
Skin and Appendages:	alopecia, angioedema, contact dermatitis, ear disorder, fungal dermatitis, furunculosis, hair disorder, herpes zoster, skin hypertrophy, nail disorder, skin neoplasm, skin nodule, psoriasis, papular macular rash, pustular rash, vesicular rash, skin disorder, skin discolor, dry skin, urticaria, skin ulcer;
Special Senses:	amblyopia, cataract, deaf, dry eye, eye disorder, glaucoma, eye hemorrhage, iritis, lacrimation disorder, otitis externa, otitis media, ear pain, eye pain, parosmia, retinal disorder, tinnitus, vestibular disorder, abnormal vision;
Urogenital System:	albuminuria, amenorrhea, breast enlargement, dysuria, abnormal ejaculation, epididymitis, vaginal hemorrhage, hematuria, impotence, urinary incontinence;

Other Notable Adverse Events

Seizures

Convulsions were reported as an adverse event in four of 5335 (0.1%) MERIDIA®-treated patients and in none of 2717 placebo-treated patients in placebo-controlled pre-marketing obesity studies. Three of the four patients with seizures had potentially predisposing factors (one had a prior history of epilepsy; two had a subsequent diagnoses of brain tumor). The incidence in all subjects who received MERIDIA® (four of 8,208 subjects) was less than 0.1%.

Ecchymosis/Bleeding Disorders

Ecchymosis (bruising) was observed in 0.7% of MERIDIA®-treated patients and in 0.5% 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.

Henoch-Schönlein purpura

A patient in a pre-marketing placebo-controlled obesity study who developed an acute vasculitic rash with edema following hospitalisation for septicemia (secondary to an infected hand blister) was diagnosed with Henoch-Schönlein (anaphylactoid) purpura. The relationship of the event to

MERIDIA® was considered unlikely and possibly related to intravenous antibiotics (flucloxacillin).

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 normalised. The patient made a full recovery.

Mesangiocapillary glomerulonephritis

Mesangiocapillary glomerulonephritis was diagnosed in one obese patient approximately five weeks following cessation of treatment with MERIDIA® due to migraine-like headaches. The patient presented with breathlessness, edema and headaches and a diagnosis of right ventricular failure with hypertension was made with evidence of slight biochemical renal impairment. The patient was hospitalised and renal biopsy revealed mesangiocapillary glomerulonephritis, leading to a diagnosis of acute nephritic syndrome and accelerated hypertension. It was considered unlikely that this histological pattern represented drug-induced renal damage.

Immune system disorders

Allergic hypersensitivity reactions ranging from mild skin eruptions and urticaria to angioedema and anaphylaxis have been reported.

Psychotic episode

In placebo-controlled pre-marketing studies, there was one case of a psychotic episode occurring on discontinuation of MERIDIA® in a patient who may have been predisposed to psychosis. The patient was withdrawn from the study because of increased heart rate and hypertension, and was admitted to hospital two days later with delusions and visual and auditory hallucinations. The episode resolved within five days with haloperidol and benztropine mesylate treatment.

Abnormal Hematologic and Clinical Chemistry Findings

Altered Laboratory Findings

Reversible increases in liver enzymes. The incidence of abnormal liver function tests (LFTs) in placebo-controlled studies was low (sibutramine 0.5%; placebo 0.2%), transient and without clinical sequelae.

Thrombocytopenia

Abnormalities in platelet count were recorded in a small number of obese patients in placebo-controlled trials; all cases resolved without clinical sequelae.

Post-Market Adverse Drug Reactions

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: abnormal dreams, abnormal ejaculation/(orgasm), 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, psychosis, mania, suicidal ideation and suicide, 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, metrorrhagia, 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, torsades de pointes, transient ischemic attack, tremor, twitch, urinary retention, urticaria, vascular headache, ventricular tachycardia, ventricular extrasystoles, ventricular fibrillation, vertigo, yawn.

DRUG INTERACTIONS

Serious Drug Interactions

- Concomitant use of MERIDIA® (sibutramine hydrochloride monohydrate) with other centrally acting weight-reducing agents is contraindicated. See (**CONTRAINDICATIONS**).
- Concomitant use of MERIDIA® and a monoamine oxidase inhibitor (MAOI) is contraindicated. At least 14 days should elapse between discontinuation of a MAOI and initiation of treatment with MERIDIA®. See (**WARNINGS AND PRECAUTIONS**) and (**CONTRAINDICATIONS**).
- Concomitant use of sibutramine hydrochloride monohydrate and centrally-acting drugs for the treatment of psychiatric disorders (such as antidepressants, antipsychotics) or herbal remedies (such as St John's Wort) is contraindicated. At least 14 days should elapse between discontinuation of these drugs and initiation of treatment with sibutramine hydrochloride monohydrate. A 5 week discontinuation period is required for fluoxetine. See (**CONTRAINDICATIONS**).

CNS Active Drugs

The use of MERIDIA® in combination with other CNS-active drugs 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 AND PRECAUTIONS**).

Monoamine oxidase inhibitors (MAOIs)

In patients receiving 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.

Selective Serotonin Reuptake Inhibitors/ Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

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, co-administration of MERIDIA® with other serotonergic agents is contraindicated. See (**CONTRAINDICATIONS**). At least 5 weeks should elapse between discontinuation of fluoxetine and initiation of treatment with MERIDIA®.

Drugs that Inhibit Cytochrome P450(3A4) Metabolism

Sibutramine and its active metabolites (M_1 and M_2) are eliminated primarily via metabolism by the cytochrome P450(3A4) isoenzyme. Caution should be exercised on concomitant administration of MERIDIA® with drugs which effect CYP3A4 enzyme activity. Clinical drug interaction studies were conducted using the cytochrome P450(3A4) inhibitors ketoconazole and erythromycin.

Erythromycin:

Co-administration of sibutramine with erythromycin resulted in a 2-fold increase in mean C_{max} of unchanged plasma sibutramine, and 10% and 12% increases in C_{max} and AUC, respectively, of its active metabolite (M_2). Mean systolic and diastolic blood pressure increased by up to 9.6 and 6.7 mm Hg, respectively, compared to sibutramine treatment alone. Mean pulse rate increased by up to 9.3 bpm compared to sibutramine treatment alone (14.7 bpm above baseline).

Ketoconazole:

Co-administration of sibutramine with ketoconazole resulted in a 3-fold increase in mean C_{max} of unchanged plasma sibutramine, and 58% and 36% increases in AUC and C_{max}, respectively, of its active metabolite (M_1). Mean heart rate increased by up to 2.5 bpm more than on sibutramine alone (9.5 bpm over baseline).

Drugs That May Raise Blood Pressure and/or Heart Rate

Concomitant use of MERIDIA® and other agents that may raise blood pressure or heart rate have not been evaluated. These include certain decongestants, cough, cold and allergy medications that contain agents such as phenylpropanolamine (no longer available in Canada), ephedrine, or pseudoephedrine and certain anti-inflammatory agents (e.g. NSAIDs). Caution should be used when prescribing MERIDIA® to patients who use these medications.

Cimetidine

Concomitant administration of cimetidine 400 mg twice daily and sibutramine 15 mg once daily for seven 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

At single doses, there was no additional impairment of cognitive or psychomotor performance when sibutramine was administered concomitantly with alcohol. However, the consumption of alcohol is not compatible with the recommended dietary measures as a general rule. The concomitant use of sibutramine with 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 MERIDIA®.

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.

Drug-Food Interactions

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.

Drug-Herb Interactions

Concomitant use of MERIDIA® and St John's Wort is contraindicated. At least 14 days should elapse between discontinuation of these drugs and initiation of treatment with MERIDIA®.

Drug-Laboratory Interactions

There is no evidence that sibutramine and its metabolites interfere with the results of standard laboratory tests.

DOSAGE AND ADMINISTRATION

Treatment with MERIDIA® (sibutramine hydrochloride monohydrate) should only be given as part of an integrated therapeutic approach for weight reduction and weight maintenance under the care of a physician with experience in the treatment of obesity.

MERIDIA® substantially increases blood pressure and heart rate in some patients. Therefore, regular monitoring of blood pressure and heart rate is required when prescribing MERIDIA®. In the first three months of treatment, these parameters should be checked at least every 2 weeks, thereafter, regularly at one to three month intervals. Blood pressure and heart rate changes should be taken into account when making decisions regarding monitoring intervals.

- Treatment should be discontinued in patients who have an increase, at two consecutive visits, in systolic or diastolic blood pressure of ≥ 10 mm Hg or in resting heart rate of ≥ 10 bpm.
- In previously well-controlled hypertensive patients, if blood pressure exceeds 145/90 mm Hg at two consecutive readings, treatment should be discontinued.

The use of a standardized blood pressure measurement technique as described in the 1999 Canadian recommendations for the management of hypertension from the Canadian

Hypertension Society[1] is recommended when assessing blood pressure in order to ensure reliable and accurate results. The guidelines recommend measurement with a mercury manometer using a cuff with an appropriate bladder width:

Arm Circumference	Type of BP Cuff
19 to 31 cm	Regular Cuff
30 to 45 cm	Large Cuff
over 45 cm	Tight Cuff

Recommended Dose and Dosage Adjustment

Adults

The recommended dose is MERIDIA® 10 mg once daily, taken in the morning. The capsule should be swallowed whole and can be taken with or without food.

In those patients with an inadequate response to MERIDIA® 10 mg (less than 4 lbs (1.8 kg) weight loss after 4 weeks treatment), the dose may be increased to 1 capsule of MERIDIA® 15 mg once daily, provided that MERIDIA® 10 mg was well tolerated. 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.

Duration of treatment

Physicians should re-evaluate the patient's weight management plan and consider discontinuation of MERIDIA® in patients who have not achieved a clinically significant weight loss (at least 5% of initial body weight) within a period of three to six months. Continuation of treatment beyond six months should only be considered for those patients who continue to lose weight or maintain their weight loss.

In patients with associated co-morbid conditions, such as Type 2 diabetes or dyslipidemia, it is recommended that treatment with MERIDIA® should only be continued if it can be shown that the weight loss induced is associated with clinical benefits.

The safety and effectiveness of treatment with MERIDIA® beyond one year has not been established.

[1] Feldman RD, 1999 Canadian recommendations for the management of hypertension. Task force for the development of the 1999 Canadian recommendations for the management of hypertension CMAJ 1999; 161 Suppl. 12:S1-S17.

Missed Dose

If a dose of MERIDIA® is missed, patients should take the next dose the next morning. However, patients should not take an extra capsule to "make up" for the dose that was missed.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There are a number of reports of overdose in humans (including accidental ingestion by children as young as 18 months) where doses of up to 500 mg MERIDIA® (sibutramine hydrochloride monohydrate) were ingested. A heart rate of 160 bpm was observed in one patient who took 500 mg MERIDIA®. Except in one case of multiple drug intoxication with alcohol (where the patient died, possibly due to inhalation of vomit), there were no complications and the individuals made a full recovery.

Treatment

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; cardiac and vital sign monitoring is recommended; general symptomatic and supportive measures should be instituted.

Early administration of activated charcoal may delay the absorption of MERIDIA®; gastric lavage may be of benefit. Excessive CNS stimulation or seizures may require treatment with an anticonvulsant. Cautious use of β-blockers may be indicated to control elevated blood pressure or tachycardia. In managing overdose, consider the possibility of multiple drug involvement. 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

MERIDIA® (sibutramine hydrochloride monohydrate) has been shown to reduce body weight by dual actions: reduction of food intake through enhancement of satiety, and increase of energy expenditure by induction of thermogenesis. MERIDIA® produces its therapeutic effects primarily by serotonin and norepinephrine reuptake inhibition.

Pharmacodynamics

MERIDIA® 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 (NE) 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*. Sibutramine and its metabolites (M_1 and M_2) do not cause the release of serotonin, norepinephrine or dopamine (DA). In human brain tissue, M_1 and M_2 also inhibit DA reuptake *in vitro*, but with ~3-fold lower potency than for the reuptake inhibition of serotonin or norepinephrine (see **Table 4**).

Table 4. Potencies of Sibutramine, M_1 and M_2 as *In Vitro* Inhibors of Monoamine Reuptake in Human Brain Potency to Inhibit Monoamine Reuptake (Ki ; 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%. Inhibition of dopamine reuptake was not significant.

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 5-HT, (5-HT_1, 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}), NE (β, β_1, β_3, α_1 and α_2), DA (D_1 and D_2), benzodiazepine, and glutamate (NMDA) receptors. These compounds also lack monoamine oxidase inhibitory activity *in vitro* and *in vivo*.

Pharmacokinetics

A summary of pharmacokinetic parameters is presented in **Table 5**.

Table 5. Summary of Sibutramine's 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 M_2				
Target Population:				
Obese Subjects (n=18)	6.4 (28)	3.5 (17)	92.1 (26)	17.2 (58)
	5.6 - 7.2	3.2 - 3.8	81.2 - 103	12.5 - 21.8
Special Population:				
Moderate Hepatic Impairment (n=12)	4.3 (37)	3.8 (34)	90.5 (27)	22.7 (30)
	3.4 - 5.2	3.1 - 4.5	76.9 - 104	18.9 - 26.5

† Calculated only up to 24 hours for M_1.

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. Tissue distribution was unaffected by pregnancy, with relatively low transfer to the foetus. *In vitro*, sibutramine, M_1 and M_2 are extensively bound (97%, 94% and 94%, respectively) to human plasma proteins at plasma concentrations seen following therapeutic doses.

Metabolism

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

in plasma was accounted for by unchanged sibutramine (3%), M_1 (6%), M_2 (12%), M_5 (52%), and M_6 (27%). M_1 and M_2 plasma concentrations reached steady-state within four days of dosing and were approximately two-fold higher than following a single dose. The elimination half-lives of M_1 and M_2, 14 and 16 hours, respectively, were unchanged following repeated dosing.

Excretion

Approximately 85% (range 68 to 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.

Special Populations and Conditions

Pediatrics and Geriatrics

Due to insufficient safety and efficacy data, MERIDIA® is not recommended for use in patients <18 or >65 years old.

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.

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.

Renal Insufficiency

The disposition of sibutramine metabolites (M_1, M_2, M_5 and M_6) was studied in patients with varying degrees of renal function. Sibutramine itself was not measurable.

The AUCs of the active metabolites M_1 and M_2 were generally not affected by renal impairment, except that the AUC of M_2 in end-stage renal disease patients on dialysis was approximately half of that measured in normal subjects (CLcr ≥ 80 mL/min). The AUCs of inactive metabolites M_5 and M_6 increased 2-3 fold in patients with moderate impairment (30 mL/min < CLcr ≤ 60 mL/min), 8-11 fold in patients with severe impairment (CLcr ≤ 30 mL/min), and 22-33 fold in patients with end-stage renal disease on dialysis as compared to normal subjects. Approximately 1% of the oral dose was recovered in the dialysate as a combination of M_5 and M_6 during 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.

STORAGE AND STABILITY

Store between 15 and 25°C, protect from light and high humidity.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MERIDIA® (sibutramine hydrochloride monohydrate) capsules contain 10 mg or 15 mg sibutramine hydrochloride monohydrate and are supplied as follows:

- 10 mg, blue/white capsules imprinted with “MERIDIA” on the cap and “-10-” on the body, in PVC-Foil blisters containing 30 capsules and in HDPE bottles containing 100 capsules.
- 15 mg, yellow/white capsules imprinted with “MERIDIA” on the cap and “-15-” on the body, in PVC-Foil blisters containing 30 capsules and in HDPE bottles containing 100 capsules.

Listing of Non-Medicinal Ingredients

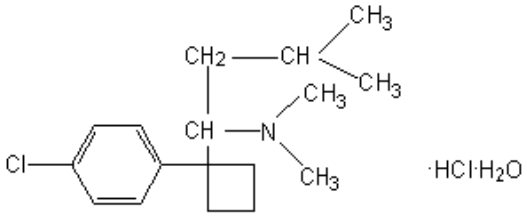
In addition to sibutramine hydrochloride monohydrate, each capsule contains the following inactive ingredients: colloidal silicon dioxide, D&C Yellow No. 10 (15 mg capsules only), FD&C Blue No. 2 (10 mg capsules only), gelatin, lactose monohydrate, magnesium stearate, microcrystalline cellulose, printing ink, silicon dioxide, sodium lauryl sulphate, and titanium dioxide.

Do not use beyond expiry date indicated on the package.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	sibutramine hydrochloride monohydrate
Chemical name:	cyclobutanemethanamine, 1-(4-chlorophenyl)-N,N-dimethyl-α-(2-methylpropyl)-, hydrochloride, monohydrate(±)
Molecular formula and molecular mass:	$C_{17}H_{26}ClN \cdot HCl \cdot H_2O$ 334.33
Structural formula:	
Physicochemical properties:	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.

CLINICAL TRIALS

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

Analysis of the data in three long-term (≥6 months) obesity trials indicates that patients who lose at least 4 pounds (1.8 kg) in the first 4 weeks of therapy with a given dose of sibutramine

hydrochloride monohydrate are most likely to achieve significant long-term weight loss on that dose of sibutramine hydrochloride monohydrate. Approximately 60% of such patients went on to achieve a placebo-subtracted weight loss of ≥5% of their initial body weight by month six. Conversely, of those patients on a given dose of sibutramine hydrochloride monohydrate who did not lose at least 4 pounds (1.8 kg) 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 six.

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 hydrochloride monohydrate, Dual Energy X-Ray Absorptiometry (DEXA) assessment of changes in body composition showed that total body fat mass decreased by 4 lbs (1.8 kg) in the sibutramine hydrochloride monohydrate group versus 0.4 lbs (0.2 kg) in the placebo group ($p<0.001$). Similarly, truncal (android) fat mass decreased by 1.3 lbs (0.6 kg) in the sibutramine hydrochloride monohydrate group versus 0.2 lbs (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 hydrochloride monohydrate positively affects glycemia, serum lipid profiles, and serum uric acid in obese patients who respond by losing weight. Treatment with sibutramine hydrochloride monohydrate (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 (bpm) 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 hydrochloride monohydrate tend to have smaller increases in blood pressure and pulse rate. See (**WARNINGS AND PRECAUTIONS**).

In Study I, a 6-month, double-blind, placebo-controlled study in obese patients, Study II, a 1-year, double-blind, placebo-controlled study in obese patients, and Study III, a 1-year, double-blind, placebo-controlled study in obese patients who lost at least 13.2 lbs (6 kg) on a 4-week very low calorie diet (VLCD), sibutramine hydrochloride monohydrate produced significant reductions in weight, as shown in **Table 6**. In the two 1-year studies, maximal weight loss was achieved by 6 months and statistically significant weight loss was maintained over 12 months.

Table 6. Mean Weight Loss (lbs, [kg]) in the Six-Month and One-Year Trials.

		MERIDIA® (mg)			
Study/Patient Group	**Placebo**	**5**	**10**	**15**	**20**
	(n)	**(n)**	**(n)**	**(n)**	**(n)**
Study I					
All patients*	2.0[0.9]	6.6[3.0]	9.7[4.4]	12.1[5.5]	13.6[6.2]
	(142)	(148)	(148)	(150)	(145)
Completers**	2.9[1.3]	8.1[3.7]	12.1[5.5]	15.4[7.0]	18.0[8.2]
	(84)	(103)	(95)	(94)	(89)
Early responders***	8.5[3.9]	13.0[5.9]	16.0[7.3]	18.2[8.3]	20.1[9.1]
	(17)	(60)	(64)	(73)	(76)
Study II					
All patients*	3.5[1.6]	—	9.8[4.5]	14.0[6.4]	—
	(157)	—	(154)	(152)	—
Completers**	4.8[2.2]	—	13.6[6.2]	15.2[6.9]	—
	(76)	—	(80)	(93)	—
Early responders***	10.7[4.9]	—	18.2[8.3]	18.8[8.6]	—
	(24)	—	(57)	(76)	—
Study III					
All patients*	15.2[6.9]	—	28.4[12.9]	—	—
	(78)	—	(81)	—	—
Completers**	16.7[7.6]	—	29.7[13.5]	—	—
	(48)	—	(60)	—	—
Early responders***	21.5[9.8]	—	33.0[15]	—	—
	(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 I) or one-year period of dosing and have data recorded for the month 6 (Study I) or month 12 visit.

*** Data for patients who lost at least 4 lbs (1.8 kg) 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 (7.7 kg) for sibutramine and 16.3 lbs (7.4 kg) for placebo.

Weight loss was dose-related, and peaked at 3 to 6 months. The weight loss was essentially maintained with continued sibutramine hydrochloride monohydrate treatment over 12 months.

Sibutramine hydrochloride monohydrate induced weight loss has been accompanied by beneficial changes in serum uric acid and lipids that are similar to those seen with nonpharmacologically-mediated weight loss.

Cardiac valve dysfunction

Certain centrally-acting weight loss agents that cause both release and re-uptake inhibition of serotonin from nerve terminals have been associated with cardiac valve dysfunction when used for more than 3 months. It is hypothesized that the mechanism by which these drugs cause cardiac valvulopathy is the release of serotonin from nerve terminals. Sibutramine hydrochloride monohydrate is a serotonin and norepinephrine re-uptake inhibitor and not a releasing agent. The possible occurrence of cardiac valve disease was specifically investigated in clinical studies. In one study 2-D and color Doppler echocardiography were performed on 210 patients (mean age, 54 years) receiving sibutramine hydrochloride monohydrate 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 a second study, 104 patients received either sibutramine 10 mg or sibutramine 20 mg and 52 patients received placebo daily for 6 months. Echocardiography was performed at baseline and at month 6. In patients with normal valves at baseline, no sibutramine-treated patient compared to one placebo-treated patient (moderate mitral regurgitation) had valvular heart disease at month 6.

The incidence of cardiac valvulopathy in sibutramine hydrochloride monohydrate-treated patients was not different from that in placebo-treated patients. In addition, in extensive postmarketing experience there has been no increase in the incidence of cardiac valve dysfunction. However, due to the limited number of patients studied, it is not yet known whether sibutramine hydrochloride monohydrate may cause this condition.

DETAILED PHARMACOLOGY

Monoamine Reuptake Profile

A poor [^{3}H]monoamine uptake inhibitor *in vitro*, sibutramine's actions are predominantly mediated *in vivo* by its secondary amine (BTS 54 354, metabolite 1) and primary amine (BTS 54 505, metabolite 2) metabolites, both excellent norepinephrine (NE) and serotonin (5-HT) uptake inhibitors, *in vitro* and *in vivo*. Sibutramine also gives rise to a range of 4 hydroxylated metabolites in various species (mouse, rat, guinea pig, dog, monkey) including 2 inactive aglycone glucuronide conjugates (metabolites 5 and 6).

In vivo and *in vitro*, salts of metabolites 3 (maleate) and 6 (hydrochloride) are potent monoamine reuptake inhibitors, whereas 5 (fumarate) is moderately active and 4 (fumarate) is weak. In man, sibutramine exerts its monoamine reuptake inhibition almost exclusively via BTS 54 354 (1) and BTS 54 505 (2), since metabolite 3 has not been identified in human plasma and metabolites 5 and 6 have only been detected as glucuronides.

Effects of Food Intake, Energy Expenditure and Body Weight

Acute sibutramine administration produced a clear dose-dependent food intake reduction in lean growing rats, genetically obese Zucker rats and obese rats fed a high fat diet. Good evidence suggests that this effect was mediated by enhancing natural satiety responses. Sibutramine likely produced these effects (via BTS 54 354 and BTS 54 505), by enhanced central NE and 5-HT function exerted through β_1 and 5-$HT_{2A/2C}$ receptors, respectively. 5-HT release is not a mechanism of action. Unlike d-fenfluramine, neither sibutramine nor its active metabolites, at pharmacologically-relevant concentrations, increase [^{3}H]5-HT overflow from brain slices. Furthermore, the sibutramine food intake effect cannot be mediated directly by receptor activation.

Sibutramine, BTS 54 354 and BTS 54 505 have no affinity for noradrenergic or 5-hydroxytryptaminergic receptors, including β_1 and 5-$HT_{2A/2C}$. Consistent with the hypothesized NE and 5-HT reuptake mechanism of action, both sibutramine, BTS 54 354 and BTS 54 505 are approximately equipotent in reducing food intake. In addition, the (+)sibutramine enantiomer, a more potent *in vivo* monoamine reuptake inhibitor, is also about 10 times more potent in reducing food intake than is (-)-enantiomer. Additionally, sibutramine appears to increase energy expenditure. In repeat-dose studies, there was a consistent food intake reduction effect at the treatment start, but its duration was variable. Despite this, reductions in body weight gain were found in all experiments. Corroborating this observation, sibutramine was shown to be thermogenic (increases oxygen consumption and body temperature). At thermoneutral ambient temperatures, in lean and obese rats the effect was both dose-dependent and prolonged (>6h at 10 mg/kg). Moderately selective β_1- and β_2-adrenoceptors antagonists, (atenolol and ICI 118,55,1 respectively), given at low doses (i.e., producing β_1- and β_2-blockade), did not modify sibutramine-induced thermogenesis. High doses (i.e., β_1-, β_2- and β_3-blockade) abolished the response. Therefore, *in vivo*, sibutramine putatively enhances thermogenesis by increasing peripheral β_3-mediated noradrenergic activation, via reuptake inhibition. Direct β_3-adrenoceptor action can be discounted because sibutramine and its metabolites have no adrenergic receptor affinity, including β_3.

Behavioral CNS Effects

Sibutramine is neither sedative nor activating in rats at 6 mg/kg, a dose that potently inhibits food intake and enhances thermogenesis. Increasing the dose to ≥ 30 mg/kg, however, results in behavioral activation and stereotypy.

Effects on Central Dopaminergic Function

The monoamine uptake inhibition profiles of BTS 54 354 and BTS 54 505 *in vitro* indicate an overall rank order of potency of NE>5-HT≈DA (dopamine) whereas *ex vivo* studies indicate NE>5-HT>DA. This latter ranking has been confirmed using plasma from animals and man after acute or repeated sibutramine treatment to examine the effects of sibutramine's *in vivo* metabolites on radiolabeled monoamine uptake *in vitro*.

High dose sibutramine is behaviorally activating. However, its pharmacological profile differs from DA activating stimulants such as d-amphetamine and methamphetamine. Sibutramine, BTS 54 354 and BTS 54 505 did not (with one exception) increase [^{3}H]DA release from rat striatal slices, nor elevate 3-methoxytyramine in rat striatum. As for behavioral markers, these compounds did not induce circling in unilateral nigrostriatal lesioned rats at pharmacologically-relevant doses, or generalise in rats trained to discriminate d-amphetamine from saline in a 2-choice lever-pressing model. By comparison, methamphetamine, was potently active, while bupropion, a weak selective DA reuptake inhibitor antidepressant, was active only in the behavioral tests. Psychomotor stimulation, reward and reinforcement effects of stimulants are associated with enhanced limbic DA release. Thus, nucleus accumbens extracellular DA concentrations were determined by intracerebral microdialysis following sibutramine, bupropion and d-amphetamine.

Sibutramine produced slow-onset, dose-dependent, moderate increases in limbic DA levels. By contrast, d-amphetamine evoked a rapid flood of DA release (at 3 mg/kg doses about 15 times greater than sibutramine); bupropion (at pharmacologically-relevant doses) also rapidly elevated limbic DA considerably more than sibutramine, but markedly less than d-amphetamine.

Other Effects on CNS Function

Sibutramine, BTS 54 354 and BTS 54 505 are relatively potent anticonvulsants against maximal electroshock seizures in rodents, but are ineffective against bicuculline. Consistent with an NE and 5-HT reuptake inhibitor profile, sibutramine is active in the Porsolt test. Repeated sibutramine administration down-regulates monoamine receptors β_1, α_2, 5-HT_{1A}. Unaltered receptors are: α_1; 5-HT_2; 5-HT reuptake sites; D_1; D_2.

Cardiovascular System Effects

Sibutramine produces less cardiovascular effects than either the tricyclic antidepressants or sympathomimetics. Sibutramine's effects on blood pressure (BP) and heart rate (HR) are consistent with peripheral catecholamine reuptake inhibition.

Sibutramine (3×10^{-6} to 10^{-4} g/mL) inhibited spontaneously-beating and electrically-stimulated guinea-pig atria *in vitro*. This effect was ~7-fold weaker than that produced by amitriptyline (3×10^{-7} to 10^{-5} g/mL).

Acute effects on blood pressure, heart rate and electrocardiogram

In spontaneously hypertensive rats (SHR), sibutramine (1 or 3 mg/kg orally) produced small, but significant, BP and HR reductions at 1.5 and 5 hours; 25% of the rats died at the higher dose. In a second experiment, however, a 3 mg/kg single oral dose of either sibutramine, BTS 54 354 or BTS 54 505 had no effect on BP and HR. 50% of the rats died. In normotensive rats, sibutramine (1 or 3 mg/kg orally) produced only transient bradycardia (3 mg/kg). In a second experiment, sibutramine 3 mg/kg orally, BTS 54 354 or BTS 54 505 evoked significant bradycardia 1.5 hours post-dose.

In anaesthetised normotensive rats, sibutramine (3 and 30 mg/kg intravenous) had no significant effect on BP, but reduced HR by ~25%, prolonged R-R interval and elevated T-waves at the higher dose. Sibutramine only marginally attenuated S-waves depression produced by continuous isoprenaline infusion (1 µg/kg/min intravenous), unlike amitriptyline which markedly enhanced isoprenaline's effect. In normotensive, pithed rats, sibutramine (1.5 or 5 mg/kg intravenous) produced a rise in BP and a small increase in HR, with minor variations in the P-Q interval. Sibutramine's pressor effects were qualitatively similar to (but ~10-fold less potent than,) d-amphetamine (0.2 mg/kg intravenous), but of longer duration. Positive chronotropic effects were less. Reserpine pretreatment markedly attenuated both compounds' effects. In anaesthetized dogs, sibutramine had little effect on mean BP, HR, electrocardiogram (ECG) at 0.03 and 0.1 mg/kg intravenous. At 0.3 mg/kg intravenous, there was a slight increase in mean BP and a decrease in HR. At 1 to 10 mg/kg intravenous, the changes were more marked, with a transient dose-dependent decrease in BP and an increase in HR succeeded by a slight BP increase and a more prolonged fall in HR. The ECG was unaffected at doses < 3 mg/kg. At 3 and 10 mg/kg intravenous, there were transient decreases in the P-R interval and an increase in the QRS wave height. At 10 mg/kg, P-wave height slightly increased in one of three dogs.

Effects On The Renal System (in Water-loaded Animals)

In mice, doses ≤10 mg/kg, had no effect on urine volume, sodium and potassium excretion. At 3 and 10 mg/kg chloride excretion was increased. In rats at 1 mg/kg, urine volume was increased 2 and 3 hours after dosing; electrolyte excretion was unaltered. At 3 and 10 mg/kg, urine volume was increased at all time-points; sodium and chloride excretion was enhanced. In dogs, 3 mg/kg sibutramine increased urine volume two hours after dosing; electrolytes were unaltered.

TOXICOLOGY

Acute Toxicity

Species	Strain	Initial Group	Route	Doses (mg/kg/day)	Duration (weeks)	Results
Mouse	Charles River CD1	5M+5F	Oral	single dose 12.5, 25, 50, 100, 150, 200	2	NOEL 12.5. At >25 hyperactivity. At 100 stereotyped behavior, motor, posture disturbances, dyspnea, rales. Max non-lethal ♂: 50, ♀: 200. Min lethal ♂: 200 ♀: >200.
Rat	Charles River CD	5M+5F	Oral	single dose 12.5, 25, 50, 100, 150	222	NOEL 12.5. > 25 hyperactivity. >100-150 ↑ respiration, dyspnea, rales, lacrimation, urinary stains depression, GI irritation, hepatomegaly. Max non-lethal ♂: 100, ♀: 50. Min lethal ♂: 150, ♀: 100.
	Charles River CD	5M+5F	Intra-peritoneal	single dose 6.25, 12.5, 25, 50, 75		At ≥ 12.5 hyperactivity; >25 GI irritation, adhesions, centrilobar hepatocyte enlargement; >75 behavioral, motor changes, tremor, convulsions, depression
	Crl:CD [SD]BR	5M+5F	Inhalation	0.017, 0.063, 0.431 0.017, 0.063, (mg/L)		NOEL 0. At 0.017 exaggerated startle response, piloerection; ≥ 0.431 ejaculation, rhinitis, aggression, self-inflicted injuries, hepatocellular necrosis, micro vacuolation, plureal congestion, edema. Max. non-lethal 0.063. Min. lethal 0.431. Higher inhaled doses (1.013) produced ataxia, convulsions, respiratory distress.
Dog	Beagle	1M+1F	Oral	3, 10, 20, 40	2	NOEL 3. At 10: ↑ or ↓ activity, stereotyped head, mouth movements, ↑ salivation, mydriasis. At 40: ♀ convulsions, ♂ 20 & 40 emesis. Max. non-lethal ♂: 40, ♀: 20. Min. lethal ♂: > 40, ♀: 40.
Monkey	Cynomolgus	1M+1F (2M+2F, 50 mg only)	Oral	Sequential doses from 1 to 100	2	NOAEL 10. At > 20 mg mydriasis. At > 30, ↑ activity, excitability; visual disturbance. Max. non-lethal ♂ 20, ♀ 100. Min. lethal ♂: >50, ♀: >100.

NOEL: No Observable Effect Level

NOAEL: No Observable Adverse Effect Level

Long-Term Toxicity

Species	Strain	Initial Group	Route	Doses (mg/kg/day)	Duration (weeks)	Results
Mouse	Charles River CD1	10M + 10F	Oral	6.25, 12.5, 25.0	313	Reduced body weight gain, ↑ absolute liver weight, at all doses. ↑ activity disturbed hepatic glycogen distribution (♂), at all doses, magnitude is dose-related.
	Charles River CD1	12M + 12F	Oral	3.2, 8, 20, 50		≥ 3.2, ↑ salivary acinar cell cytoplasmic vacuolation (♀) ≥ 8, hyperactivity, ↓ periportal, hepatic glycogen, enlarged centrilobar hepatocytes. At 50 slow dyspnea, rales
Rat	Charles River CD	5M+5F	Oral	3, 10, 30	226	All doses: ↓ relative organ weights, cholesterol; For ♂ hemoconcentration, ↑ coagulation times, ↓ triglycerides; ↑ myeloid cells, bilirubin, ALP. At ≥3 ↓ body weight, food consumption. At ↑ 30, macroscopic gastric irritation.
	Charles River CD	20M+20F	Oral	3.2, 8, 20		↑ myeloid/eyrthroid ratio, Hb (20); ↓ serum Cr, Na, K, Ca (♂20) glucose, protein, urea, liver enzymes, bilirubin (♀). ↑ relative kidney, salivary uterus weights (at 20); hepatocyte vacuolation. Subpleural macrophage aggregates in ♂.
Dog	Beagle	1M+1F	Oral	10	10d	At ≥ 10, ↑ serum AST, ALT, bilirubin, ↓ protein, active or subdued behavior, ↑ salivation
				15	8d	
				20 to 10	9d	At ≥ 15, intestinal, fecal blood, interstitial hemorrhage, hemoconcentration, reduced eating At 20, ↓ rectal temp., behavioral changes.
	Beagle	4M+4F	Oral	10 to 15 titrated max tolerated dose: increased after 6 wks	24	Stereotyped movements, behavioral changes, ↓ body, absolute and relative liver, relative kidney weights, ↓ rectal temp., ↓ urine volume, ↑ myeloid/eyrthroid ratio, mydriasis, inhibited pupillary response.

Species	Strain	Initial Group	Route	Doses (mg/kg/day)	Duration (weeks)	Results
Monkey	Cynomolgus	1M	Oral	10	8d	At ≥ 10, mydriasis,
		1F		15	7d	At ≥ 15, excitability ↓ body weight, ↓ food consumption
				20	4d	At ≥ 20, hepatocellular fat vacuolation
				30	56	At 30 visual disturbances
	Cynomolgus	4M+4F	Oral	1, 3, 10	13	Occasional emesis, initial body weight loss, ↓ body weight loss.
				10	7d	
	Cynomolgus	5M+5F	Oral	1, 3, 10	52	Hyperactivity, agitation, lipsmacking, subdued, reduced activity, ↓ body weight, eating

Mutagenicity and Carcinogenicity

Mutagenicity

Assay	Sibutramine	BTS 54 345 (metabolite 1)	BTS 54 505 (metabolite 2)	BTS 58 726 Process intermediate	BTS 64 472 (metabolite 5)	BTS 65 400 (metabolite 6)
In vitro						
Bacterial mutagenicity test (Ames test) Salmonella typhimurium	-ve	Weakly +ve, (unactivated)	Weakly +ve, (unactivated)	-ve, +ve 2nd test (unactivated)	-ve	-ve
± metabolic activation	yes	yes	yes	yes	no	no
V9 mammalian cell mutation assay 6-thioguanineresistance	-ve	-ve	-ve	-ve	-ve	-ve
± metabolic activation	yes	yes	yes	yes	no	no
Mammalian HeLA S3 cell DNA repair assay	ND	-ve	-ve	-ve	-ve	-ve
± metabolic activation		yes	yes	yes	no	no
Human lymphocyte clastogenicity assay	-ve	-ve	-ve	-ve	-ve	-ve
± metabolic activation	yes	yes	yes	no	no	no

Assay	Sibutramine	BTS 54 345 (metabolite 1)	BTS 54 505 (metabolite 2)	BTS 58 726 Process intermediate	BTS 64 472 (metabolite 5)	BTS 65 400 (metabolite 6)
In vivo						
Micronucleus assay in mice cyclophosphamide negative control	-ve	-ve	-ve	-ve	ND	ND
Rat liver DNA repair assay	ND	-ve	-ve	ND	ND	ND

BTS 54 345 hydrochloride salt of metabolite 1

BTS 54 505 hydrochloride salt of metabolite 2

BTS 59 482 maleate salt of metabolite 3

BTS 64 472 fumarate salt of the aglycone of metabolite 5

BTS 64 473 fumarate salt of the aglycone of metabolite 4

BTS 65 400 hydrochloride salt of the aglycone of metabolite 6

ND: Not Done

Carcinogenicity

Species	Strain	Initial Group	Route	Doses (mg/kg/day)	Duration (weeks)	Results
Mouse	Charles River CD1	52M 52F	Oral in Diet	0, 1.25, 5, 20	95-104	No effect on overall benign and malignant tumor incidence, survival. ↓ in stomach adenocarcinoma in males. Slight increase in serous cell vacuolation in males.
Rat	Charles River CD	52M+52F	Oral in Diet	0, 1, 3, 9	104	No effect on overall benign and malignant tumor incidence, survival. Small ↑ in benign testicular interstitial-cell tumors, and ↓ mammary fibroadenomas (♀).

Reproduction and Teratology

Segment	Species/ Strain	Initial Group	Route	Doses (mg/kg/day)	Duration (days or weeks)	Results
I: Fertility and General Reproduction Performance	Rat Charles River COBS CD	12M 24F	Oral Gavage	0, 1, 3, 10 0, 1, 3, 10	60d prior to mating until sacrifice. 14d prior to mating until Caesarean section or weaning of F_1 generation.	At 10: toxicity for F_0 ♂ and ♀. Evidence of embryo- and feto-toxicity at high doses. F_1: ↓ size but no behavioral effects. At 3: slight embryotoxicity, no fetotoxicity, pup body weight lower for first 6 weeks.
II: Embryotoxicity	Rat Charles River COBS CD	14 to 40F	Oral	0, 1, 3, 10	Day 7 to 17 post-coitum	At > 10, some evidence of maternotoxicity. No evidence of embryo- feto-toxicity or teratogenicity. No effect on F_1 physical or behavioral development.
II: Embryotoxicity	Rabbit Dutch Belted	14 to 16F	Oral	0, 3, 15, 75	Day 7 to 19 post-coitum	At 75, marked maternotoxicity, (4 deaths), GI irritation. Slight fetotoxicity at 75, slight ↓ weight. Supernumery ribs seen, but no overall effect in drug related birth defect incidence.
II: Embryotoxicity	Rabbit New Zealand White	13 to 16F were mated	Oral	0, 3, 12, 50	Day 7 to 19 post-coitum	CNS effects in dams at 12, 50, weight loss at 50. ↑ incidence of 13th rib and pelvic girdle displacement, likely from maternal stress. Species-specific cardiac abnormalities seen. No evidence of teratogenicity.
II: Embryotoxicity	Rabbit New Zealand White	32 or 33F	Oral	0, 12, 24	Day 6 to day 18 of gestation	At 24, CNS effects in dams, significant weight loss at 24. No embryo- or feto-toxicity. At 24, ↑ small aorta artery, 13th rib malformations. At 12, similar, smaller non-significant effect.
III: Peri-/Post-Natal	Rat Charles River CD	25F	Oral	0, 0.1, 1, 3, 10	Day 17 of gestation to day 21 of lactation	NOEL systemic F_0 maternal toxicity, 0.1. NOEL F_1 behavioral, developmental parameters, 1.0. NOEL F_1 reproductive capacity, 3.0. Cannibalisation, dam aggressiveness seen at original high dose (10), contributing to F1 mortality.
III: Peri- and Post-Natal Utilizing Cross-Fostering	Rat Charles River CD	25F	Oral	0, 3	Day 17 of gestation to day 21 of lactation	Evidence of direct drug adverse effects on pup mortality to lactation Day 4. Cross-fostered control pups had ↓ body weight, indicative of maternal drug toxicity.

NOEL: No Observable Effect Level

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PART III: CONSUMER INFORMATION

PrMERIDIA®
sibutramine hydrochloride monohydrate

This leaflet is PART III of a three-part "Product Monograph" published when MERIDIA® was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about MERIDIA®. Contact your doctor or pharmacist if you have any questions about the drug.

The manufacturer of MERIDIA® offers a free weight management program, myDECISION™. To learn more about this program please visit the web site at www.mydecision.ca.

ABOUT THIS MEDICATION

What the medication is used for:

MERIDIA® (sibutramine hydrochloride monohydrate) is a once-daily prescription medication for weight loss and weight maintenance. It is to be used as part of a comprehensive weight management program supervised by your doctor, that includes a reduced calorie diet and appropriate physical activity. You will lose more weight if you increase your physical activity, in addition to eating sensibly. MERIDIA® can only be prescribed by a medical doctor.

MERIDIA® is for patients whose excess weight, in the opinion of their doctor, presents a health risk. MERIDIA® may be right for you if you are considerably overweight [a Body Mass Index (BMI) of 30 kg/m2 or greater]. MERIDIA® may also be right for you if you are overweight (a BMI of 27 kg/m^2 or greater) in the presence of other risk factors (e.g., high blood pressure, diabetes, high cholesterol, large waist measurement). BMI is not a direct measurement of fat and therefore, these guidelines do not apply to athletes and pregnant women.

Your doctor may be equally concerned about where you are carrying your excess weight. Visceral fat, fat stored in your abdomen, is a significant health risk. The best indicator of visceral fat is abdominal circumference. This is measured at a point midway between your waist and below your ribcage. To be a health concern, a woman's abdominal circumference would exceed 88 cm or 35 inches or for men greater than 102 cm or 40 inches.

How to determine your Body Mass Index (BMI):

BMI according to a variety of weights and heights is presented in the Table at the end of this leaflet. The BMI is calculated by dividing your weight in kilograms by your height in meters squared. To use this chart:

Find the weight closest to your weight in the left-hand column.

Then move across the top row to find the height closest to your height.

The number where these two meet is your BMI. (For example, a person who weighs 180 lbs and is 5'5", would have a BMI of 30, as would a person 6'0" and 220 lbs, or a person 5'1" and 160 lbs).

What it does:

MERIDIA® works by making you feel full sooner. MERIDIA® is not an amphetamine-type drug. Hunger will continue to tell you when to eat, but MERIDIA® will help you to be satisfied to eat less food.

MERIDIA® is prescribed to help you to be more successful losing and maintaining your weight loss, but you still need to do your part. 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.

Why should MERIDIA® be used as part of a weight management program?

Your excess weight is a result of a surplus of energy. The energy that you consume as food has been greater than the energy that you expend such as through physical activity. To lose weight and to maintain a weight loss you need to reverse this imbalance. As you increase your physical activity and decrease the amount of food you eat, you increase the energy deficit and the amount of fat you can lose. MERIDIA® makes it easier for you to be successful. You must do your part.

How long does it take for MERIDIA® to begin to work?

Every person will respond differently to MERIDIA® when used as part of a comprehensive weight-loss program. If you do your part, MERIDIA® will help. You may be able to lose 4 or more pounds (1.8 kg or more) in the first month you take MERIDIA®. If you find that you do not lose at least 4 pounds (1.8 kg) during the first month, your doctor may re-evaluate your situation. This may include a review of your entire weight management program, including your menu choices and level of physical activity. Your doctor may advise you to make other food choices or increase your physical activity. Alternatively your doctor may decide that it is appropriate to change your dose of MERIDIA® if your blood pressure and heart rate did not increase significantly.

Most people who lose weight on MERIDIA® lose it in the first 6 months of treatment. Your doctor may consider discontinuation of MERIDIA® if you have not achieved a clinically significant weight loss (at least 5% of initial body weight) within a period of three to six months.

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 3.5 lbs.

In order to achieve long-term maintenance of weight loss, you must change your lifestyle while taking MERIDIA® so that you are able to maintain your weight upon cessation of drug treatment. When MERIDIA® therapy is stopped, most patients will regain weight unless they have changed their eating habits, as well as increased their level of physical activity.

When it should not be used:

MERIDIA® must not be taken by people who:

- Are, in the opinion of their doctor, not medically at risk because of their excess weight.
- Have a diagnosis of coronary artery disease and/or who have angina pectoris (heart-related chest pain).
- Have arrhythmias (irregular heart beats).
- Have had a prior heart attack.
- Have a diagnosis of congestive heart failure.
- Have had a stroke or symptoms of a stroke [transient ischemic attacks (TIAs)].
- Have uncontrolled or poorly controlled high blood pressure because MERIDIA® substantially increases blood pressure in some patients.
- Have a diagnosis of depression or any other psychiatric illness.
- Are taking prescription medications for depression or any other psychiatric illnesses
- Are taking prescription medicines called monoamine oxidase inhibitors (MAOIs) for depression, Parkinson's Disease, or any other disorder [for example: Eldepryl® (no longer available in Canada), Parnate®, Nardil®, Manerix
- Are taking other medications that regulate the neurotransmitter serotonin in the brain (for example: Prozac®, Zoloft®, Effexor®, Luvox®, or Paxil®), including herbal remedies (such as St John's Wort).
- 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.
- Are suffering from anorexia nervosa or bulimia nervosa.
- Have had prior allergic reactions to MERIDIA® or sibutramine.
- Have severe liver disease
- Have any kidney disease.
- Are pregnant or planning to become pregnant.
- Are breast-feeding their infants.
- Have had seizures (epilepsy or convulsions).
- Have an eye disorder called narrow angle glaucoma.
- Are under 18 years of age.
- Are over 65 years of age.

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 the medicinal ingredient is:

sibutramine hydrochloride monohydrate

What the non-medicinal ingredients are:

MERIDIA® contains the following non-medicinal ingredients: colloidal silicon dioxide, D&C Yellow No. 10 (15 mg capsules only), FD&C Blue No. 2 (10 mg capsules only), gelatin, lactose monohydrate, magnesium stearate, microcrystalline cellulose, printing ink, silicon dioxide, sodium lauryl sulphate, and titanium dioxide.

What dosage forms it comes in:

10 and 15 mg Capsules

WARNINGS AND PRECAUTIONS

BEFORE you use MERIDIA® talk to your doctor or pharmacist if:

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, any psychiatric illness, 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 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 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®.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with MERIDIA® include:

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 that are sometimes used to treat depression or Parkinson's Disease [for example: Eldepryl® (no longer available in Canada), Nardil®, Parnate®, Manerix®]. 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® must 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® (no longer available in Canada), Serzone® (no longer available in Canada), Nardil®, Parnate®, Paxil®, Prozac®, Zoloft®, Ludiomil® (no longer available in Canada), Asendin™ (no longer available in Canada), Elavil®, Etrafon® (no longer available in Canada), Norpramin®, Sinequan®, Surmontil®, Tofranil®, Triavil™ (no longer available in Canada), Luvox®, Anafranil®, Manerix®], drugs for migraine headache therapy (Imitrex®, Maxalt®, Zomig®, Amerge®) 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 serotonin 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.

MERIDIA® must not be taken with medications used to treat depression or other psychiatric illnesses.

MERIDIA® must not be taken with St. John's Wort.

Many over-the-counter decongestants, cough, cold and allergy remedies, containing medicines such as phenylpropanolamine (no longer available in Canada), ephedrine, or pseudoephedrine, as well as certain anti-inflammatory drugs (e.g. NSAIDS) 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®.

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

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. In addition, alcohol will increase your caloric intake without providing nutritional value, making it more difficult to lose weight.

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.

Will MERIDIA® affect the effectiveness of birth control pills?

No.

PROPER USE OF THIS MEDICATION

Usual dose:

The recommended dose, as directed by your physician, should be taken once daily in the morning. MERIDIA® should be swallowed whole. You may take MERIDIA® on an empty stomach or after a meal.

How long should I take MERIDIA®?

You should continue to take MERIDIA® while you are losing weight or continuing to maintain your weight loss. Your doctor will determine how long you should take MERIDIA®. Follow your doctor's advice.

The safety and effectiveness of MERIDIA® when taken for more than one year have not been determined.

Overdose:

In the case of an overdose, immediately speak with your doctor and/or go to the nearest emergency room for immediate medical

attention. If you are unable to reach a doctor or emergency room, call your local Poison Information Center (see the front page of your local phone directory).

Missed Dose:

If you forget to take a dose of MERIDIA®, take the next dose the next morning. Do not take an extra capsule to "make up" for the dose that you missed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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, anorexia, insomnia (inability to fall asleep) and constipation. Other side effects that may occur include: 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®.

Does MERIDIA® affect blood pressure or heart rate?

MERIDIA® substantially increases blood pressure and heart rate in some patients. Blood pressure increases may be smaller or less likely to occur if you succeed in losing weight.

Because increases in blood pressure are not experienced as a bothersome side effect, you will have to have your blood pressure checked on a regular basis while you are taking MERIDIA®. Your blood pressure and pulse should be measured prior to starting MERIDIA®, and you will be required to visit your doctor for follow-up every two weeks during the first three months of therapy and once every 1-3 months thereafter for as long as you are taking MERIDIA®. If you experience a significant increase in blood pressure or heart rate while taking MERIDIA®, your doctor may decide to decrease the dose or discontinue MERIDIA®.

If you have well controlled high blood pressure, before starting to take MERIDIA® you will also have to have your blood pressure checked on a regular basis by your doctor. You should not take MERIDIA® if you have uncontrolled or poorly controlled high blood pressure.

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 MERIDIA® studies were examined by doctors who used cardiac ultrasound testing to carefully look at heart valve structure and function. In one study, 104 patients received MERIDIA® for 6 months. None of the patients had heart valve disease at 6 months. 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. In extensive postmarketing experience in other countries, including the U.S.A., there has been no increase in the incidence of cardiac valve disease. However, due to the limited number of patients studied, it is not yet known whether MERIDIA® may cause this condition.

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 symptoms in the **SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM** Table below, stop taking MERIDIA® and notify your doctor immediately.

What about physician follow-up visits?

You should make sure you see your doctor as directed for regular follow-up visits where your doctor can follow your body weight, and carefully monitor your blood pressure and overall health as you try to lose weight and maintain weight loss. You will be required to visit your doctor once every two weeks for the first three months of MERIDIA® therapy and once every 1-3 months thereafter for as long as you are taking this medication.

What about driving a car or dangerous work activities?

Any drug that affects the central nervous system has the potential to impair judgement, thinking, coordination or motor skills. 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 while driving or operating dangerous machinery.

You should check with your doctor if you have any questions with regard to your work and the use of MERIDIA®.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate emergency medical treatment**
		Only if severe	**In all cases**	
Common	Increase in blood pressure;		✓	
	Increase in heart rate;		✓	
	Light-headedness;	✓		
	Abdominal pain;	✓		
	Nausea.	✓		
Uncommon	Possible signs of serotonin syndrome: Rapid heart beats (over 100 beats per minute), restlessness, blackout spells, disorientation, mental confusion, anxiety, tremors, loss of muscle coordination, muscle stiffness or rigidity, high fever, dilated pupils, shivering, sweating, vomiting;			✓
	Chest Pain;		✓	
	Pounding or irregular heartbeats;		✓	
	Seizures;			✓
	Bleed or bruise easily;		✓	
	Trouble breathing/shortness of breath;		✓	
	Depression.		✓	

Additional side effects reported during post-marketing surveillance:

- Mental illnesses (thoughts of suicide, suicide and loss of contact with reality)

This is not a complete list of side effects. For any unexpected effects while taking MERIDIA®, contact your doctor or pharmacist.

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.

Does MERIDIA® cause primary pulmonary hypertension (PPH)?

Certain other weight loss drugs have been associated with primary pulmonary hypertension (PPH), a rare but sometimes fatal disease. MERIDIA® works in a slightly different way from those weight loss medications. 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.

HOW TO STORE IT

MERIDIA® should be stored at normal room temperature (15 to 25°C). Never leave MERIDIA® in hot or moist places.

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

Never take more MERIDIA® than prescribed by your doctor.

You should never share MERIDIA® with a friend.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: *CanadaVigilance@hc-sc.gc.ca*

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and
Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information on this product, please contact the number below, 1-800-361-7852, or visit the website at www.abbott.ca.

This leaflet was prepared by
Abbott Laboratories, Limited
Saint-Laurent, Quebec, H4S 1Z1

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WEIGHT, lb (kg)	HEIGHT, ft/in (m)																	
	4'10" (1.47)	**4'11" (1.50)**	**5'0" (1.52)**	**5'1" (1.55)**	**5'2" (1.57)**	**5'3" (1.60)**	**5'4" (1.63)**	**5'5" (1.65)**	**5'6" (1.68)**	**5'7" (1.70)**	**5'8" (1.73)**	**5'9" (1.75)**	**5'10" (1.78)**	**5'11" (1.80)**	**6'0" (1.83)**	**6'1" (1.85)**	**6'2" (1.88)**
120 (54.5)	25	24	23	23	22	21	21	20	19	19	18	18	17	17	16	16	15
130 (59.1)	27	26	25	25	24	23	22	22	21	20	20	19	19	18	18	17	17
140 (63.6)	29	28	27	27	26	25	24	23	23	22	21	21	20	20	19	19	18
150 (68.2)	31	30	29	28	27	27	26	25	24	24	23	22	22	21	20	20	19
160 (72.7)	34	32	31	30	29	28	28	27	26	25	24	24	23	22	22	21	21
170 (77.3)	36	34	33	32	31	30	29	28	27	27	26	25	24	24	23	22	21
180 (81.8)	38	36	35	34	33	32	31	30	29	28	27	27	26	25	24	24	23
190 (86.4)	40	38	37	36	35	34	33	32	31	30	29	28	27	27	26	25	24
200 (90.9)	42	40	39	38	37	36	34	33	32	31	30	30	29	28	27	26	26
210 (95.5)	44	43	41	40	38	37	36	35	34	33	32	31	30	29	29	28	27
220 (100.0)	46	45	43	42	40	39	38	37	36	35	34	33	32	31	30	29	28
230 (104.5)	48	47	45	44	42	41	40	38	37	36	35	34	33	32	31	30	30
240 (109.1)	50	49	47	45	44	43	41	40	39	38	37	36	35	34	33	32	31
250 (113.6)	52	51	49	47	46	44	43	42	40	39	38	37	36	35	34	33	32
260 (118.2)	54	53	51	43	48	46	45	43	42	41	40	38	37	36	35	34	33
270 (122.7)	57	55	53	51	49	48	46	45	44	42	41	40	39	38	37	36	35
280 (127.3)	59	57	55	53	51	50	48	47	45	44	43	41	40	39	38	37	36
290 (131.8)	61	59	57	55	53	51	50	48	47	46	44	43	42	41	39	38	37
300 (136.4)	63	61	59	57	55	53	52	50	49	47	46	44	43	42	41	40	39
310 (140.9)	65	63	61	59	57	55	53	52	50	49	47	46	45	43	42	41	40
320 (145.5)	67	65	63	61	59	57	55	53	52	50	49	47	46	45	43	42	41

- Patients with BMI values ≥30 may be candidates for MERIDIA® therapy.
- Patients with BMI values of 27 to 29 may be candidates for MERIDIA® therapy if they also have a concomitant risk factor (e.g., high blood pressure, diabetes, high cholesterol, large waist measurement).