

**MERIDIA - sibutramine hydrochloride monohydrate capsule**

MERIDIA<sup>®</sup>

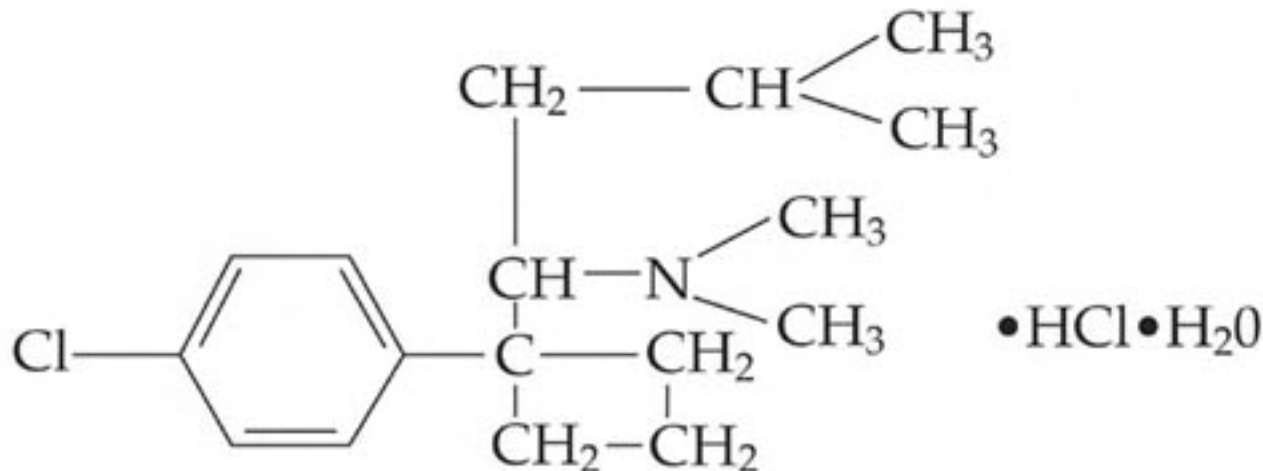
(sibutramine hydrochloride monohydrate) Capsules

CS-IV

**DESCRIPTION**

MERIDIA<sup>®</sup> (sibutramine hydrochloride monohydrate) is an orally administered agent for the treatment of obesity. Chemically, the active ingredient is a racemic mixture of the (+) and (-) enantiomers of cyclobutanemethanamine, 1-(4-chlorophenyl)-N,N-dimethyl- $\alpha$ -(2-methylpropyl)-, hydrochloride, monohydrate, and has an empirical formula of C<sub>17</sub>H<sub>29</sub>Cl<sub>2</sub>NO. Its molecular weight is 334.33.

The structural formula is shown below:



Sibutramine hydrochloride monohydrate is a white to cream crystalline powder with a solubility of 2.9 mg/mL in pH 5.2 water. Its octanol: water partition coefficient is 30.9 at pH 5.0.

Each MERIDIA capsule contains 5 mg, 10 mg, and 15 mg of sibutramine hydrochloride monohydrate. It also contains as inactive ingredients: lactose monohydrate, NF; microcrystalline cellulose, NF; colloidal silicon dioxide, NF; and magnesium stearate, NF in a hard-gelatin capsule [which contains titanium dioxide, USP; gelatin; FD&C Blue No. 2 (5- and 10-mg capsules only); D&C Yellow No. 10 (5- and 15-mg capsules only), and other inactive ingredients].

**CLINICAL PHARMACOLOGY**

**Mode of Action**

Sibutramine produces its therapeutic effects by norepinephrine, serotonin and dopamine reuptake inhibition. Sibutramine and its major pharmacologically active metabolites (M<sub>1</sub> and M<sub>2</sub>) do not act via release of monoamines.

**Pharmacodynamics**

Sibutramine exerts its pharmacological actions predominantly via its secondary (M<sub>1</sub>) and primary (M<sub>2</sub>) amine metabolites. The parent compound, sibutramine, is a potent inhibitor of serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine reuptake *in vivo*, but not *in vitro*. However, metabolites M<sub>1</sub> and M<sub>2</sub> inhibit the reuptake of these neurotransmitters both *in vitro* and *in vivo*.

In human brain tissue, M<sub>1</sub> and M<sub>2</sub> also inhibit dopamine reuptake *in vitro*, but with ~3-fold lower potency than for the reuptake inhibition of serotonin or norepinephrine.

Potencies of Sibutramine, M<sub>1</sub> and M<sub>2</sub> as In Vitro Inhibitors of Monoamine Reuptake in Human Brain Potency to Inhibit Monoamine Reuptake (K<sub>i</sub>;nM)

|                | Serotonin | Norepinephrine | Dopamine |
|----------------|-----------|----------------|----------|
| Sibutramine    | 298       | 5451           | 943      |
| M <sub>1</sub> | 15        | 20             | 49       |
| M <sub>2</sub> | 20        | 15             | 45       |

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

Sibutramine and its metabolites (M<sub>1</sub> and M<sub>2</sub>) are not serotonin, norepinephrine or dopamine releasing agents. Following chronic administration of sibutramine to rats, no depletion of brain monoamines has been observed.

Sibutramine, M<sub>1</sub> and M<sub>2</sub> exhibit no evidence of anticholinergic or antihistaminergic actions. In addition, receptor binding profiles show that sibutramine, M<sub>1</sub> and M<sub>2</sub> have low affinity for serotonin (5-HT<sub>1</sub>, 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>), norepinephrine ( $\beta$ ,  $\beta_1$ ,  $\beta_3$ ,  $\alpha_1$  and  $\alpha_2$ ), dopamine (D<sub>1</sub> and D<sub>2</sub>), benzodiazepine, and glutamate (NMDA) receptors. These compounds also lack monoamine oxidase inhibitory activity *in vitro* and *in vivo*.

## Pharmacokinetics

### Absorption

Sibutramine is rapidly absorbed from the GI tract (T<sub>max</sub> of 1.2 hours) following oral administration and undergoes extensive first-pass metabolism in the liver (oral clearance of 1750 L/h and half-life of 1.1 h) to form the pharmacologically active mono- and dimethyl metabolites M<sub>1</sub> and M<sub>2</sub>. Peak plasma concentrations of M<sub>1</sub> and M<sub>2</sub> are reached within 3 to 4 hours. On the basis of mass balance studies, on average, at least 77% of a single oral dose of sibutramine is absorbed. The absolute bioavailability of sibutramine has not been determined.

### Distribution

Radiolabeled studies in animals indicated rapid and extensive distribution into tissues: highest concentrations of radiolabeled material were found in the eliminating organs, liver and kidney. *In vitro*, sibutramine, M<sub>1</sub> and M<sub>2</sub> are extensively bound (97%, 94% and 94%, respectively) to human plasma proteins at plasma concentrations seen following therapeutic doses.

### Metabolism

Sibutramine is metabolized in the liver principally by the cytochrome P450 (3A<sub>4</sub>) isoenzyme, to desmethyl metabolites, M<sub>1</sub> and M<sub>2</sub>. These active metabolites are further metabolized by hydroxylation and conjugation to pharmacologically inactive metabolites, M<sub>5</sub> and M<sub>6</sub>. Following oral administration of radiolabeled sibutramine, essentially all of the peak radiolabeled material in plasma was accounted for by unchanged sibutramine (3%), M<sub>1</sub> (6%), M<sub>2</sub> (12%), M<sub>5</sub> (52%), and M<sub>6</sub> (27%).

M<sub>1</sub> and M<sub>2</sub> plasma concentrations reached steady-state within four days of dosing and were approximately two-fold higher than following a single dose. The elimination half-lives of M<sub>1</sub> and M<sub>2</sub>, 14 and 16 hours, respectively, were unchanged following repeated dosing.

### Excretion

Approximately 85% (range 68-95%) of a single orally administered radiolabeled dose was excreted in urine and feces over a 15-day collection period with the majority of the dose (77%) excreted in the urine. Major metabolites in urine were M<sub>5</sub> and M<sub>6</sub>; unchanged sibutramine, M<sub>1</sub>, and M<sub>2</sub> were not detected. The primary route of excretion for M<sub>1</sub> and M<sub>2</sub> is hepatic metabolism and for M<sub>5</sub> and M<sub>6</sub> is renal excretion.

## Summary of Pharmacokinetic Parameters

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

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

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

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#### Effect of Food

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

#### Special Populations

##### Geriatric

Plasma concentrations of M<sub>1</sub> and M<sub>2</sub> were similar between elderly (ages 61 to 77 yr) and young (ages 19 to 30 yr) subjects following a single 15-mg oral sibutramine dose. Plasma concentrations of the inactive metabolites M<sub>5</sub> and M<sub>6</sub> were higher in the elderly; these differences are not likely to be of clinical significance. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

##### Pediatric

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

##### Gender

Pooled pharmacokinetic parameters from 54 young, healthy volunteers (37 males and 17 females) receiving a 15-mg oral dose of sibutramine showed the mean C<sub>max</sub> and AUC of M<sub>1</sub> and M<sub>2</sub> to be slightly ( $\leq 19\%$  and  $\leq 36\%$ , respectively) higher in females than males. Somewhat higher steady-state trough plasma levels were observed in female obese patients from a large clinical efficacy trial. However, these differences are not likely to be of clinical significance. Dosage adjustment based upon the gender of a patient is not necessary (see **DOSAGE AND ADMINISTRATION**).

##### Race

The relationship between race and steady-state trough M<sub>1</sub> and M<sub>2</sub> plasma concentrations was examined in a clinical trial in obese patients. A trend towards higher concentrations in Black patients over Caucasian patients was noted for M<sub>1</sub> and M<sub>2</sub>. However, these differences are not considered to be of clinical significance.

##### Renal Insufficiency

The disposition of sibutramine metabolites (M<sub>1</sub>, M<sub>2</sub>, M<sub>5</sub> and M<sub>6</sub>) following a single oral dose of sibutramine was studied in patients with varying degrees of renal function. Sibutramine itself was not measurable.

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

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

##### Hepatic Insufficiency

In 12 patients with moderate hepatic impairment receiving a single 15-mg oral dose of sibutramine, the combined AUCs of M<sub>1</sub> and M<sub>2</sub> were increased by 24% compared to healthy subjects while M<sub>5</sub> and M<sub>6</sub> plasma concentrations were unchanged. The observed differences in M<sub>1</sub> and M<sub>2</sub> concentrations do not warrant dosage adjustment in patients with mild to moderate hepatic impairment. Sibutramine should not be used in patients with severe hepatic dysfunction.

##### Drug-Drug Interactions

*In vitro* studies indicated that the cytochrome P450 (3A<sub>4</sub>)-mediated metabolism of sibutramine was inhibited by ketoconazole and to a lesser extent by erythromycin. Phase 1 clinical trials were conducted to assess the interactions of sibutramine with drugs that are substrates and/or inhibitors of various cytochrome P450 isozymes. The potential for studied interactions is described below.

#### Ketoconazole

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

#### Erythromycin

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

#### Cimetidine

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

#### Simvastatin

Steady-state pharmacokinetics of sibutramine and metabolites  $M_1$  and  $M_2$  were evaluated in 27 healthy volunteers after the administration of simvastatin 20 mg once daily in the evening and sibutramine 15 mg once daily in the morning for 7 days. Simvastatin had no significant effect on plasma  $C_{max}$  and AUC of  $M_2$  or  $M_1$  and  $M_2$  combined. The  $C_{max}$  (16%) and AUC (12%) of  $M_1$  were slightly decreased. Simvastatin slightly decreased sibutramine  $C_{max}$  (14%) and AUC (21%). Sibutramine increased the AUC (7%) of the pharmacologically active moiety, simvastatin acid and reduced the  $C_{max}$  (25%) and AUC (15%) of inactive simvastatin.

#### Omeprazole

Steady-state pharmacokinetics of sibutramine and metabolites  $M_1$  and  $M_2$  were evaluated in 26 healthy volunteers after the co-administration of omeprazole 20 mg once daily and sibutramine 15 mg once daily for 7 days. Omeprazole slightly increased plasma  $C_{max}$  and AUC of  $M_1$  and  $M_2$  combined (approximately 15%).  $M_2$   $C_{max}$  and AUC were not significantly affected whereas  $M_1$   $C_{max}$  (30%) and AUC (40%) were modestly increased. Plasma  $C_{max}$  (57%) and AUC (67%) of unchanged sibutramine were moderately increased. Sibutramine had no significant effect on omeprazole pharmacokinetics.

#### Olanzapine

Steady-state pharmacokinetics of sibutramine and metabolites  $M_1$  and  $M_2$  were evaluated in 24 healthy volunteers after the co-administration of sibutramine 15 mg once daily with olanzapine 5 mg twice daily for 3 days and 10 mg once daily thereafter for 7 days. Olanzapine had no significant effect on plasma  $C_{max}$  and AUC of  $M_2$  and  $M_1$  and  $M_2$  combined, or the AUC of  $M_1$ . Olanzapine slightly increased  $M_1$   $C_{max}$  (19%), and moderately increased sibutramine  $C_{max}$  (47%) and AUC (63%). Sibutramine had no significant effect on olanzapine pharmacokinetics.

#### Lorazepam

Steady-state pharmacokinetics of sibutramine and metabolites  $M_1$  and  $M_2$  after sibutramine 15 mg once daily for 11 days were compared in 25 healthy volunteers in the presence or absence of lorazepam 2 mg twice daily for 3 days plus one morning dose. Lorazepam had no significant effect on the pharmacokinetics of sibutramine metabolites  $M_1$  and  $M_2$ . Sibutramine had no significant effect on lorazepam pharmacokinetics.

#### Drugs Highly Bound to Plasma Proteins

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

#### CLINICAL STUDIES

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

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

Analysis of the data in three long-term ( $\geq 6$  months) obesity trials indicates that patients who lose at least 4 pounds in the first 4 weeks of therapy with a given dose of sibutramine are most likely to achieve significant long-term weight loss on that dose of sibutramine. Approximately 60% of such patients went on to achieve a placebo-subtracted weight loss of  $\geq 5\%$  of their initial body weight by month 6. Conversely, of those patients on a given dose of sibutramine who did not lose at least 4 pounds in the first 4 weeks of therapy, approximately 80% did not go on to achieve a placebo-subtracted weight loss of  $\geq 5\%$  of their initial body weight on that dose by month 6.

Significant dose-related reductions in waist circumference, an indicator of intra-abdominal fat, have also been observed over 6 and 12 months in placebo-controlled clinical trials. In a 12-week placebo-controlled study of non-insulin dependent diabetes mellitus patients randomized to placebo or 15 mg per day of sibutramine, Dual Energy X-Ray Absorptiometry (DEXA) assessment of changes in body composition showed that total body fat mass decreased by 1.8 kg in the sibutramine group versus 0.2 kg in the placebo group ( $p < 0.001$ ). Similarly, truncal (android) fat mass decreased by 0.6 kg in the sibutramine group versus 0.1 kg in the placebo group ( $p < 0.01$ ). The changes in lean mass, fasting blood sugar, and HbA<sub>1c</sub> were not statistically significantly different between the two groups.

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

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

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

| Study/Patient Group | Sibutramine (mg) |              |              |               |               |
|---------------------|------------------|--------------|--------------|---------------|---------------|
|                     | Placebo<br>(n)   | 5<br>(n)     | 10<br>(n)    | 15<br>(n)     | 20<br>(n)     |
| <b>Study 1</b>      |                  |              |              |               |               |
| All patients*       | 2.0<br>(142)     | 6.6<br>(148) | 9.7<br>(148) | 12.1<br>(150) | 13.6<br>(145) |
| Completers**        | 2.9<br>(84)      | 8.1<br>(103) | 12.1<br>(95) | 15.4<br>(94)  | 18.0<br>(89)  |
| Early responders*** | 8.5<br>(17)      | 13.0<br>(60) | 16.0<br>(64) | 18.2<br>(73)  | 20.1<br>(76)  |
| <b>Study 2</b>      |                  |              |              |               |               |
| All patients*       | 3.5<br>(157)     |              | 9.8<br>(154) | 14.0<br>(152) |               |
| Completers**        | 4.8<br>(76)      |              | 13.6<br>(80) | 15.2<br>(93)  |               |
| Early responders*** | 10.7<br>(24)     |              | 18.2<br>(57) | 18.8<br>(76)  |               |
| <b>Study 3****</b>  |                  |              |              |               |               |
| All patients*       | 15.2<br>(78)     |              | 28.4<br>(81) |               |               |
| Completers**        | 16.7<br>(48)     |              | 29.7<br>(60) |               |               |
| Early responders*** | 21.5<br>(22)     |              | 33.0<br>(46) |               |               |

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

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

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

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

Maintenance of weight loss with sibutramine was examined in a 2-year, double-blind, placebo-controlled trial. After a 6-month run-in phase in which all patients received sibutramine 10 mg (mean weight loss, 26 lbs.), patients were randomized to sibutramine (10 to 20 mg, 352 patients) or placebo (115 patients). The mean weight loss from initial body weight to endpoint was 21 lbs. and 12 lbs. for sibutramine and placebo patients, respectively. A statistically significantly ( $p < 0.001$ ) greater proportion of sibutramine treated patients, 75%, 62%, and 43%, maintained at least 80% of their initial weight loss at 12, 18, and 24 months, respectively, compared with the placebo group (38%, 23%, and 16%). Also 67%, 37%, 17%, and 9% of sibutramine treated patients compared with 49%, 19%, 5%, and 3% of placebo patients lost  $\geq 5\%$ ,  $\geq 10\%$ ,  $\geq 15\%$ , and  $\geq 20\%$ , respectively, of their initial body weight at endpoint. From endpoint to the post-study follow-up visit (about 1 month), weight regain was approximately 4 lbs for the sibutramine patients and approximately 2 lbs for the placebo patients.

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

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

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

Baseline mean values:

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

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

TG: Triglycerides, CHOL: Cholesterol, LDL-C Low Density Lipoprotein-Cholesterol

HDL-C: High Density Lipoprotein-Cholesterol

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

The effect of sibutramine 15 mg once daily on measures of 24-hour blood pressure was evaluated in a 12-week placebo-controlled study. Twenty-six male and female, primarily Caucasian individuals with an average BMI of 34 kg/m<sup>2</sup> and an average age of 39 years underwent 24-hour ambulatory blood pressure monitoring (ABPM). The mean changes from baseline to Week 12 in various measures of ABPM are shown in the following table.

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

Normal diurnal variation of blood pressure was maintained.



**INDICATIONS AND USAGE**

MERIDIA is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet. MERIDIA is recommended for obese patients with an initial body mass index  $\geq 30 \text{ kg/m}^2$ , or  $\geq 27 \text{ kg/m}^2$  in the presence of other risk factors (e.g., diabetes, dyslipidemia, controlled hypertension).

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

BMI is calculated by taking the patient's weight, in kg, and dividing by the patient's height, in meters, squared. Metric conversions are as follows: pounds  $\div 2.2 = \text{kg}$ ; inches  $\times 0.0254 = \text{meters}$ .

| BMI    | 25           | 26  | 27  | 28  | 29  | 30  | 31  | 32  | 33  | 34  | 35  | 40  |
|--------|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|        | WEIGHT (lbs) |     |     |     |     |     |     |     |     |     |     |     |
| 4'10"  | 119          | 124 | 129 | 134 | 138 | 143 | 149 | 153 | 158 | 163 | 167 | 191 |
| 4'11"  | 124          | 128 | 133 | 138 | 143 | 148 | 154 | 158 | 164 | 169 | 173 | 198 |
| 5'     | 128          | 133 | 138 | 143 | 148 | 153 | 159 | 164 | 169 | 175 | 179 | 204 |
| 5'1"   | 132          | 137 | 143 | 148 | 153 | 158 | 165 | 169 | 175 | 180 | 185 | 211 |
| 5'2"   | 136          | 142 | 147 | 153 | 158 | 164 | 170 | 175 | 181 | 186 | 191 | 218 |
| 5'3"   | 141          | 146 | 152 | 158 | 163 | 169 | 175 | 181 | 187 | 192 | 197 | 225 |
| H 5'4" | 145          | 151 | 157 | 163 | 169 | 174 | 181 | 187 | 193 | 199 | 204 | 232 |
| E 5'5" | 150          | 156 | 162 | 168 | 174 | 180 | 187 | 193 | 199 | 205 | 210 | 240 |
| I 5'6" | 155          | 161 | 167 | 173 | 179 | 186 | 192 | 199 | 205 | 211 | 216 | 247 |
| G 5'7" | 159          | 166 | 172 | 178 | 185 | 191 | 198 | 205 | 211 | 218 | 223 | 255 |
| H 5'8" | 164          | 171 | 177 | 184 | 190 | 197 | 204 | 211 | 218 | 224 | 230 | 262 |
| T 5'9" | 169          | 176 | 182 | 189 | 196 | 203 | 210 | 217 | 224 | 231 | 236 | 270 |
| 5'10"  | 174          | 181 | 188 | 195 | 202 | 207 | 216 | 223 | 230 | 237 | 243 | 278 |
| 5'11"  | 179          | 186 | 193 | 200 | 208 | 215 | 222 | 230 | 237 | 244 | 250 | 286 |
| 6'     | 184          | 191 | 199 | 206 | 213 | 221 | 228 | 236 | 244 | 251 | 258 | 294 |
| 6'1"   | 189          | 197 | 204 | 212 | 219 | 227 | 236 | 243 | 251 | 258 | 265 | 302 |
| 6'2"   | 194          | 202 | 210 | 218 | 225 | 233 | 241 | 250 | 258 | 265 | 272 | 311 |
| 6'3"   | 200          | 208 | 216 | 224 | 232 | 240 | 248 | 256 | 264 | 272 | 279 | 319 |

**CONTRAINDICATIONS**

MERIDIA is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs) (see **WARNINGS**).  
 MERIDIA is contraindicated in patients with hypersensitivity to sibutramine or any of the inactive ingredients of MERIDIA.  
 MERIDIA is contraindicated in patients who have a major eating disorder (anorexia nervosa or bulimia nervosa).  
 MERIDIA is contraindicated in patients taking other centrally acting weight loss drugs.

**WARNINGS**

**Blood Pressure and Pulse**

**MERIDIA SUBSTANTIALLY INCREASES BLOOD PRESSURE AND/OR PULSE RATE IN SOME PATIENTS. REGULAR MONITORING OF BLOOD PRESSURE AND PULSE RATE IS REQUIRED WHEN PRESCRIBING MERIDIA.**

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

Percent Outliers in Studies 1 and 2

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

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

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### **Potential Interaction With Monoamine Oxidase Inhibitors**

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

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

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

### **Concomitant Cardiovascular Disease**

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

### **Glaucoma**

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

### **Miscellaneous**

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

## **PRECAUTIONS**

### **Pulmonary Hypertension**

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

### **Seizures**

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

### **Bleeding**

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

### **Gallstones**

Weight loss can precipitate or exacerbate gallstone formation.

### **Renal Impairment**

MERIDIA should be used with caution in patients with mild to moderate renal impairment. MERIDIA should not be used in patients with severe renal impairment, including those with end stage renal disease on dialysis (see **Pharmacokinetics-Special Populations-Renal Insufficiency**).

### **Hepatic Dysfunction**

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

### **Interference With Cognitive and Motor Performance**

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



### **Information For Patients**

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

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

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

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

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

### **Drug Interactions**

#### **CNS Active Drugs:**

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

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

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

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

#### **Drugs That May Raise Blood Pressure and/or Heart Rate**

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

#### **Alcohol**

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

#### **Oral Contraceptives**

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

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### **Carcinogenicity**

Sibutramine was administered in the diet to mice (1.25, 5 or 20 mg/kg/day) and rats (1, 3, or 9 mg/kg/day) for two years generating combined maximum plasma AUC's of the two major active metabolites equivalent to 0.4 and 16 times, respectively, those following a daily human dose of 15 mg. There was no evidence of carcinogenicity in mice or in female rats. In male rats there was a higher incidence of benign tumors of the testicular interstitial cells; such tumors are commonly seen in rats and are hormonally mediated. The relevance of these tumors to humans is not known.

### Mutagenicity

Sibutramine was not mutagenic in the Ames test, *in vitro* Chinese hamster V79 cell mutation assay, *in vitro* clastogenicity assay in human lymphocytes or micronucleus assay in mice. Its two major active metabolites were found to have equivocal bacterial mutagenic activity in the Ames test. However, both metabolites gave consistently negative results in the *in vitro* Chinese hamster V79 cell mutation assay, *in vitro* clastogenicity assay in human lymphocytes, *in vitro* DNA-repair assay in HeLa cells, micronucleus assay in mice and *in vivo* unscheduled DNA-synthesis assay in rat hepatocytes.

### Impairment of Fertility

In rats, there were no effects on fertility at doses generating combined plasma AUC's of the two major active metabolites up to 32 times those following a human dose of 15 mg. At 13 times the human combined AUC, there was maternal toxicity, and the dams' nest-building behavior was impaired, leading to a higher incidence of perinatal mortality; there was no effect at approximately 4 times the human combined AUC.

### Pregnancy

#### Teratogenic Effects

#### Pregnancy Category C

Radiolabeled studies in animals indicated that tissue distribution was unaffected by pregnancy, with relatively low transfer to the fetus. In rats, there was no evidence of teratogenicity at doses of 1, 3, or 10 mg/kg/day generating combined plasma AUC's of the two major active metabolites up to approximately 32 times those following the human dose of 15 mg. In rabbits dosed at 3, 15, or 75 mg/kg/day, plasma AUC's greater than approximately 5 times those following the human dose of 15 mg caused maternal toxicity. At markedly toxic doses, Dutch Belted rabbits had a slightly higher than control incidence of pups with a broad short snout, short rounded pinnae, short tail and, in some, shorter thickened long bones in the limbs; at comparably high doses in New Zealand White rabbits, one study showed a slightly higher than control incidence of pups with cardiovascular anomalies while a second study showed a lower incidence than in the control group.

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

### Nursing Mothers

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

### Pediatric Use

The efficacy of sibutramine in adolescents who are obese has not been adequately studied.

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

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

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

### Geriatric Use

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

### ADVERSE REACTIONS

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

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

Obese Patients in Placebo-Controlled Studies

| <b>BODY SYSTEM</b>                    | <b>Sibutramine<br/>(n = 2068)</b> | <b>Placebo<br/>(n = 884)</b> |
|---------------------------------------|-----------------------------------|------------------------------|
| <b>Adverse Event</b>                  | <b>% Incidence</b>                | <b>% Incidence</b>           |
| <b>BODY AS A WHOLE:</b>               |                                   |                              |
| Headache                              | 30.3                              | 18.6                         |
| Back pain                             | 8.2                               | 5.5                          |
| Flu syndrome                          | 8.2                               | 5.8                          |
| Injury accident                       | 5.9                               | 4.1                          |
| Asthenia                              | 5.9                               | 5.3                          |
| Abdominal pain                        | 4.5                               | 3.6                          |
| Chest pain                            | 1.8                               | 1.2                          |
| Neck pain                             | 1.6                               | 1.1                          |
| Allergic reaction                     | 1.5                               | 0.8                          |
| <b>CARDIOVASCULAR SYSTEM</b>          |                                   |                              |
| Tachycardia                           | 2.6                               | 0.6                          |
| Vasodilation                          | 2.4                               | 0.9                          |
| Migraine                              | 2.4                               | 2.0                          |
| Hypertension/increased blood pressure | 2.1                               | 0.9                          |
| Palpitation                           | 2.0                               | 0.8                          |
| <b>DIGESTIVE SYSTEM</b>               |                                   |                              |
| Anorexia                              | 13.0                              | 3.5                          |
| Constipation                          | 11.5                              | 6.0                          |
| Increased appetite                    | 8.7                               | 2.7                          |
| Nausea                                | 5.9                               | 2.8                          |
| Dyspepsia                             | 5.0                               | 2.6                          |
| Gastritis                             | 1.7                               | 1.2                          |
| Vomiting                              | 1.5                               | 1.4                          |
| Rectal disorder                       | 1.2                               | 0.5                          |
| <b>METABOLIC &amp; NUTRITIONAL</b>    |                                   |                              |
| Thirst                                | 1.7                               | 0.9                          |
| Generalized edema                     | 1.2                               | 0.8                          |
| <b>MUSCULOSKELETAL SYSTEM</b>         |                                   |                              |
| Arthralgia                            | 5.9                               | 5.0                          |
| Myalgia                               | 1.9                               | 1.1                          |
| Tenosynovitis                         | 1.2                               | 0.5                          |
| Joint disorder                        | 1.1                               | 0.6                          |
| <b>NERVOUS SYSTEM</b>                 |                                   |                              |
| Dry mouth                             | 17.2                              | 4.2                          |
| Insomnia                              | 10.7                              | 4.5                          |
| Dizziness                             | 7.0                               | 3.4                          |
| Nervousness                           | 5.2                               | 2.9                          |
| Anxiety                               | 4.5                               | 3.4                          |
| Depression                            | 4.3                               | 2.5                          |
| Paresthesia                           | 2.0                               | 0.5                          |
| Somnolence                            | 1.7                               | 0.9                          |
| CNS stimulation                       | 1.5                               | 0.5                          |
| Emotional lability                    | 1.3                               | 0.6                          |
| <b>RESPIRATORY SYSTEM</b>             |                                   |                              |
| Rhinitis                              | 10.2                              | 7.1                          |

|                              |      |     |
|------------------------------|------|-----|
| Pharyngitis                  | 10.0 | 8.4 |
| Sinusitis                    | 5.0  | 2.6 |
| Cough increase               | 3.8  | 3.3 |
| Laryngitis                   | 1.3  | 0.9 |
| <b>SKIN &amp; APPENDAGES</b> |      |     |
| Rash                         | 3.8  | 2.5 |
| Sweating                     | 2.5  | 0.9 |
| Herpes simplex               | 1.3  | 1.0 |
| Acne                         | 1.0  | 0.8 |
| <b>SPECIAL SENSES</b>        |      |     |
| Taste perversion             | 2.2  | 0.8 |
| Ear disorder                 | 1.7  | 0.9 |
| Ear pain                     | 1.1  | 0.7 |
| <b>UROGENITAL SYSTEM</b>     |      |     |
| Dysmenorrhea                 | 3.5  | 1.4 |
| Urinary tract infection      | 2.3  | 2.0 |
| Vaginal monilia              | 1.2  | 0.5 |
| Metrorrhagia                 | 1.0  | 0.8 |

The following additional adverse events were reported in  $\geq 1\%$  of all patients who received sibutramine in controlled and uncontrolled premarketing studies.

**Body as a Whole**

fever.

**Digestive System**

diarrhea, flatulence, gastroenteritis, tooth disorder.

**Metabolic and Nutritional**

peripheral edema.

**Musculoskeletal System**

arthritis.

**Nervous System**

agitation, leg cramps, hypertonia, thinking abnormal.

**Respiratory System**

bronchitis, dyspnea.

**Skin and Appendages**

pruritus.

**Special Senses**

amblyopia.

**Urogenital System**

menstrual disorders.

**Other Adverse Events**

**Clinical Studies**

**Seizures**

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

#### Ecchymosis/Bleeding Disorders

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

#### Interstitial Nephritis

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

#### Altered Laboratory Findings

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

#### Postmarketing Reports

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

#### Psychiatric

Cases of depression, psychosis, mania, suicidal ideation and suicide have been reported rarely in patients on sibutramine treatment. However, a relationship has not been established between these events and the use of sibutramine. If any of these events should occur during treatment with sibutramine, discontinuation should be considered.

#### Hypersensitivity

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

#### Other Postmarketing Reported Events:

##### Body as a Whole

anaphylactic shock, anaphylactoid reaction, chest pressure, chest tightness, facial edema, limb pain, sudden unexplained death.

##### Cardiovascular System

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

##### Digestive System

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

##### Endocrine System

goiter, hyperthyroidism, hypothyroidism.

##### Hemic and Lymphatic System

anemia, leukopenia, lymphadenopathy, petechiae, thrombocytopenia.

##### Metabolic and Nutritional

hyperglycemia, hypoglycemia.

##### Musculoskeletal System

arthrosis, bursitis.

##### Nervous System

abnormal dreams, abnormal gait, amnesia, anger, cerebrovascular accident, concentration impaired, confusion, depression aggravated, Gilles de la Tourette's syndrome, hypesthesia, libido decreased, libido increased, mood changes, nightmares, short term memory loss, speech disorder, transient ischemic attack, tremor, twitch, vertigo.



#### Respiratory System

epistaxis, nasal congestion, respiratory disorder, yawn.

#### Skin and Appendages

alopecia, dermatitis, photosensitivity (skin), urticaria.

#### Special Senses

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

#### Urogenital System

abnormal ejaculation, hematuria, impotence, increased urinary frequency, micturition difficulty, urinary retention.

### DRUG ABUSE AND DEPENDENCE

#### Controlled Substance

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

#### Abuse and Physical and Psychological Dependence

Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., drug development of tolerance, incrementation of doses, drug seeking behavior).

### OVERDOSAGE

#### Overdose Management

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

### DOSAGE AND ADMINISTRATION

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

Doses above 15 mg daily are not recommended. In most of the clinical trials, MERIDIA was given in the morning.

Analysis of numerous variables has indicated that approximately 60% of patients who lose at least 4 pounds in the first 4 weeks of treatment with a given dose of MERIDIA in combination with a reduced-calorie diet lose at least 5% (placebo-subtracted) of their initial body weight by the end of 6 months to 1 year of treatment on that dose of MERIDIA. Conversely, approximately 80% of patients who do not lose at least 4 pounds in the first 4 weeks of treatment with a given dose of MERIDIA do not lose at least 5% (placebo-subtracted) of their initial body weight by the end of 6 months to 1 year of treatment on that dose. If a patient has not lost at least 4 pounds in the first 4 weeks of treatment, the physician should consider reevaluation of therapy which may include increasing the dose or discontinuation of MERIDIA.

The safety and effectiveness of MERIDIA, as demonstrated in double-blind, placebo-controlled trials, have not been determined beyond 2 years at this time.

### HOW SUPPLIED

MERIDIA<sup>®</sup> (sibutramine hydrochloride monohydrate) Capsules contain 5 mg, 10 mg, or 15 mg sibutramine hydrochloride monohydrate and are supplied as follows:

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

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

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

#### Storage

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

Manufactured for Abbott Laboratories, North Chicago, IL 60064 USA by KNOLL LLC B.V. Jayuya, PR, 00664.  
IMITREX is a registered trademark of Glaxo Group Limited.  
Sibutramine is covered by US Patent Nos. 4,746,680; 4,929,629; and 5,436,272.  
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**MERIDIA®**  
**(mer-ID-dee-uh)**  
**(sibutramine hydrochloride monohydrate) Capsules CS-IV**

### **PATIENT INFORMATION**

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

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

Some people taking MERIDIA can have a large increase in blood pressure or heart rate (pulse). Do not take MERIDIA if your blood pressure is not well controlled. Contact your doctor if you experience an increase in blood pressure while taking MERIDIA. Your doctor should check your blood pressure and heart rate before you start MERIDIA and continue checking it regularly while you are using MERIDIA. It is important to have regular check-ups while taking MERIDIA.

#### **What is MERIDIA?**

MERIDIA is a medicine that may help obese people, as determined by their doctor, lose weight and keep weight off. MERIDIA may help with weight loss because it affects areas of the brain that control hunger. You should use MERIDIA with a low calorie diet. The use of MERIDIA for more than 2 years has not been studied. MERIDIA has not been studied in children under 16 years of age.

#### **Who should not take MERIDIA?**

Do not take MERIDIA if you:

- have uncontrolled or poorly controlled high blood pressure.
- **are taking or have taken a medicine called a monoamine oxidase inhibitor (MAOI).** Ask your doctor or pharmacist if you are not sure if any of your medicines are MAOIs. Do not take MAOIs for at least 2 weeks before using MERIDIA. Do not take MAOIs for at least 2 weeks after stopping MERIDIA.
- **have an eating disorder called anorexia nervosa or bulimia nervosa.**
- **are taking weight loss medicines to control your appetite.**
- **are allergic to MERIDIA.** The active ingredient is sibutramine hydrochloride monohydrate. See the end of this leaflet for a complete list of ingredients in MERIDIA.

#### **How should I take MERIDIA?**

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

#### **What should I avoid while taking MERIDIA?**

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

- **have high blood pressure.**
- **have or had heart problems** such as a heart attack, heart failure, chest pain or an irregular heartbeat.
- **had a stroke or stroke symptoms.**
- **have liver or kidney problems.**

- **have an eye problem called glaucoma.**
- **have a thyroid problem (hypothyroidism).**
- **have or had seizures (convulsions, fits).**
- **have bleeding problems.**
- **have or had gallstones.**
- **have depression.**
- **are over age 65.**
- **are under age 16.**
- **are pregnant or planning to become pregnant.** The effects of MERIDIA on your unborn baby are not known. If you can become pregnant, you should use birth control while taking MERIDIA. Tell your doctor right away if you get pregnant while taking MERIDIA.
- **are breastfeeding.** It is not known if MERIDIA passes into your milk. The effects of MERIDIA on your baby are not known. You should not breastfeed while taking MERIDIA.

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

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

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

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

#### **What are the possible side effects of MERIDIA?**

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

The following serious side effects have been reported with MERIDIA:

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

- feel weak, restless, confused, or anxious
- lose consciousness
- have a fever, vomiting, sweating, shivering or shaking
- have a fast heartbeat

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

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

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

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

MERIDIA is a controlled substance (CIV). This means that MERIDIA can be a target for people who abuse prescription medicines.

Keep your MERIDIA in a safe place. Selling or giving away MERIDIA is against the law.

#### **How should I store MERIDIA?**

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

#### **General information about MERIDIA.**

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

This leaflet summarizes the most important information about MERIDIA. If you would like more information, talk to your doctor.

You can also ask your doctor or pharmacist for information that is written for health professionals.

For more information call Abbott Laboratories at 1-800-633-9110 or visit [www.Meridia.net](http://www.Meridia.net).

#### **What are the ingredients in MERIDIA?**

Active Ingredient: sibutramine hydrochloride monohydrate Inactive Ingredients: lactose monohydrate, NF; microcrystalline cellulose, NF; colloidal silicon dioxide, NF; and magnesium stearate, NF in a hard-gelatin capsule [which contains titanium dioxide, USP; gelatin; FD&C Blue No. 2 (5- and 10-mg capsules only); D&C Yellow No. 10 (5- and 15-mg capsules only), and other inactive ingredients].

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Revised: 04/2009