

# REDUCTIL CAPSULES

## Composition

### Reductil 10 mg

Each capsule contains:

#### *Active Ingredient*

Sibutramine hydrochloride monohydrate 10 mg  
(equivalent to 8.37 mg sibutramine)

#### *Other Ingredients*

##### **Capsule Content**

Lactose, microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide.

##### **Capsule Shell, Body and Printing**

Gelatin, shellac, titanium dioxide, indigo carmine, quinoline yellow, iron oxide black, sodium lauryl sulfate, soya lecithin, dimeticone.

### Reductil 15 mg

Each capsule contains:

#### *Active Ingredient*

Sibutramine hydrochloride monohydrate 15 mg  
(equivalent to 12.55 mg sibutramine)

#### *Other Ingredients*

##### **Capsule Content**

Lactose, microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide.

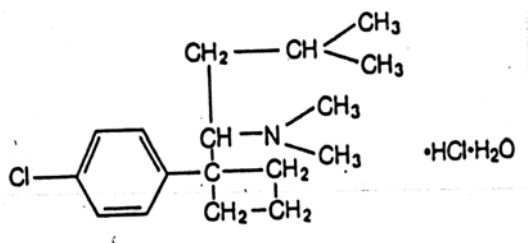
##### **Capsule Shell, Body and Printing**

Gelatin, shellac, titanium dioxide, indigo carmine, iron oxide black, sodium lauryl sulfate, soya lecithin, dimeticone.

## Description

Reductil (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  $C_{17}H_{29}Cl_2NO$ . Its molecular weight is 334.33.

The structural formula is shown below:



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

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

### Distribution

Radiolabeled studies in animals indicated rapid and extensive distribution into tissues; 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 fetus. *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 4 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> (ng/mL)	T <sub>max</sub> (h)	AUC* (ng*h/mL)	T <sup>1/2</sup> (h)
<b>Metabolite M<sub>1</sub></b>				
Target Population:				
Obese Subjects (N=18)	4.0 (4.2) 3.2 - 4.8	3.6 (28) 3.1 - 4.1	25.5 (63) 18.1 - 32.9	---
Special Population:				
Moderate Hepatic Impairment (n=12)	2.2 (36) 1.8 - 2.7	3.3 (33) 2.7 - 3.9	18.7 (65) 11.9 - 25.5	---
<b>Metabolite M<sub>2</sub></b>				
Target Population:				
Obese Subjects (n=18)	6.4 (28) 5.6 - 7.2	3.5 (17) 3.2 - 3.8	92.1 (26) 81.2 - 103	17.2 (58) 12.5 - 21.8
Special Population:				
Moderate Hepatic Impairment (n=12)	4.3 (37) 3.4 - 5.2	3.8 (34) 3.1 - 4.5	90.5 (27) 76.9 - 104	22.7 (30) 18.9 - 26.5

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

### Effect of Food

Administration of a single 20 mg dose of sibutramine with a standard breakfast resulted in reduced peak M<sub>1</sub> and M<sub>2</sub> concentrations (by 27% and 32%, respectively) and delayed the time to peak by approximately 3 hours. However, the AUCs of M<sub>1</sub> and M<sub>2</sub> were not significantly altered.

### Special Population

#### Geriatrics

Plasma concentration 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  $C_{max}$  and AUC of  $M_1$  and  $M_2$  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.

### *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 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.

Sibutramine should not be used in patients with severe hepatic dysfunction.

### *Renal Insufficiency*

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

Sibutramine should not be used in patients with severe renal impairment.

## **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 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 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 3 long term ( $\geq 6$  months) obesity trial 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 Asorptiometry (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 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 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 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 (n)	5 (n)	10 (n)	15 (n)	20 (n)

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

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

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

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

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

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.

<b>Combined Analysis (11 Studies) of Percentage Change in Serum Lipids (N)-LOCF</b>				
Category	TG	CHOL	LDL-C	HDL-C
All Placebo	0.53 (475)	-1.53 (475)	-0.09 (233)	-0.56 (248)
<5% Weight Loss	4.52 (382)	-0.42 (382)	-0.70 (205)	-0.71 (217)
≥5% Weight Loss	-15.30 (92)	-6.23 (92)	-6.19 (27)	0.94 (30)
All Sibutramine	-8.75 (1164)	-2.21 (1165)	-1.85 (642)	4.13 (664)
<5% Weight Loss	-0.54 (547)	0.17 (548)	-0.37 (320)	3.19 (331)
≥5% Weight Loss	-16.59 (612)	-4.87 (612)	-4.56 (612)	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

Sibutramine induced weight loss has been accompanied by reductions in serum uric acid. In one study, serum uric acid has been identified as an independent risk factor for death from coronary artery disease.

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 3 months; there were no cases of valvular heart disease.

### Indications

Reductil is indicated as adjunctive therapy within a weight management programme for:

- 1) Patients with obesity due to energy imbalance whose body mass index (BMI) is 30 kg/m<sup>2</sup> or higher.
- 2) Overweight patients with a BMI of 27 kg/m<sup>2</sup> or higher due to energy imbalance, if other obesity-related risk factors such as type II diabetes or dyslipidemia are present.

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

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

BMI	25	26	27	28	29	30	31	32	33	34	35	40	
WEIGHT (lbs)													
	4'10"	119	124	129	134	138	143	149	153	158	163	167	191
	4'11"	124	128	133	138	143	148	154	158	164	169	173	198
	5'	128	133	138	143	148	153	159	164	169	175	179	204
	5'1"	132	137	143	148	153	158	165	169	175	180	185	211
	5'2"	136	142	147	153	158	164	170	175	181	186	191	218
H	5'3"	141	146	152	158	163	169	175	181	187	192	197	225
	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
	5'6"	155	161	167	173	179	186	192	199	205	211	216	247
I	5'7"	159	166	172	178	185	191	198	205	211	218	223	255
	5'8"	164	171	177	184	190	197	204	211	218	224	230	262
G	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
H	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
T	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

Reductil is contraindicated in patients with hypersensitivity to sibutramine or to any other ingredient of the preparation.

Reductil is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs). (See Warnings).

Reductil is contraindicated in patients who have anorexia nervosa.

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

### Warnings

**Note**

*The duration of treatment is limited to one year.*

*Treatment with sibutramine should only be given as part of an integrated therapeutic approach for weight reduction under care of a physician experienced in the treatment of obesity. An appropriate approach to obesity management should include dietary and behavioral modifications 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 therapy is complete.*

**Blood Pressure and Pulse**

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

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 pre-marketing 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 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 sibutramine and should be monitored at regular intervals thereafter. For patients who experience a sustained increase in blood pressure or pulse rate while receiving sibutramine, either dose reduction or discontinuation should be considered. Sibutramine 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.

**Potential Interaction with Monoamine Oxidase Inhibitors (MAOI)**

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

**Concomitant Cardiovascular Disease**

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



**Glaucoma**

Because sibutramine 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 sibutramine.

***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).

**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 2 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.

**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 2 years generating combined maximum plasma AUC's of the 2 major active metabolites equivalent to 0.5 and 21 times, respectively, those following the maximum daily human dose (20 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.

**Teratogenicity**

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 43 times those following the maximum human dose (20 mg). In rabbits dosed at 3, 15, or 75 mg/kg/day, plasma AUC's greater than approximately 5 times those following the maximum human dose 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.

**Effect on Fertility and Reproduction**

In rats, there were no effects on fertility at doses generating combined plasma AUC's of the two major active metabolites up to 43 times those following the maximum human dose (20 mg). At 13 times the human combined AUC, there was maternal toxicity, and the dam's 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.

**Use in Pregnancy**

No adequate and well controlled studies with sibutramine have been conducted in pregnant women. The use of sibutramine during pregnancy is not recommended. Women of child-bearing potential should employ adequate contraception while taking

sibutramine. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

#### ***Use During Lactation***

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

#### ***Use in Pediatrics***

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

#### ***Use in the Elderly***

Clinical studies of sibutramine did not include sufficient numbers of patients aged over 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 under *Pharmacokinetics*).

#### ***Use in Patients with Impairment of Hepatic Function***

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 (see also *Pharmacokinetics*).

#### ***Use in Patients with Impairment of Renal Function***

The effect of renal disease has not been studied. However, since sibutramine and its active metabolites M<sub>1</sub> and M<sub>2</sub> are eliminated by hepatic metabolism, renal disease is unlikely to have a significant effect on their disposition. Elimination of the inactive metabolites M<sub>5</sub> and M<sub>6</sub>, which are renally excreted, may be affected in this population.

Sibutramine, should not be used in patients with severe renal impairment (see under *Pharmacokinetics*).

#### **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 obesity studies, the most common events were dry mouth, anorexia, insomnia, and constipation. 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.

BODY SYSTEM Adverse Event	Obese Patients in Placebo-Controlled Studies	
	Sibutramine (n=2068) % Incidence	Placebo (n=884) % Incidence

BODY AS A WHOLE		
Headache	30.3	18.6
Back Pain	8.2	5.5
Flu syndrome	8.2	5.8
Injury accident	5.9	4.1
Asthemia	5.9	5.3
Abdominal pain	4.5	3.6
Chest pain	1.8	1.2
Neck pain	1.6	1.1
Allergic reaction	1.5	0.8
CARDIOVASCULAR SYSTEM		
Tachycardia	2.6	0.6
Vasodilation (hot flush)	2.4	0.9
Migraine	2.4	2.0
Hypertension/increased blood pressure	2.1	0.9
Palpitation	2.0	0.8
DIGESTIVE SYSTEM		
Anorexia	13.0	3.5
Constipation	11.5	6.0
Increased appetite	8.7	2.7
Nausea	5.9	2.8
Dyspepsia	5.0	2.6
Gastritis	1.7	1.2
Vomiting	1.5	1.4
Rectal disorder	1.2	0.5
METABOLIC & NUTRITIONAL		
Thirst	1.7	0.9
Generalized edema	1.2	0.8
MUSCULOSKELETAL SYSTEM		
Arthralgia	5.9	5.0
Myalgia	1.9	1.1
Tenosynovitis	1.2	0.5
Joint disorder	1.1	0.6
NERVOUS SYSTEM		
Dry mouth	17.2	4.2
Insomnia	10.7	4.5
Dizziness	7.0	3.4
Nervousness	5.2	2.9
Anxiety	4.5	3.4
Depression	4.3	2.5
Paresthesia	2.0	0.5
Somnolence	1.7	0.9
CNS stimulation	1.5	0.5
Emotional lability	1.3	0.6

Obese Patients in Placebo-Controlled Studies

	Sibutramine (n=2068)	Placebo (n=884)
<u>Adverse Event</u>	<u>% Incidence</u>	<u>% Incidence</u>

## RESPIRATORY SYSTEM

Rhinitis	10.2	7.1
Paryngitis	10.0	8.4
Sinusitis	5.0	2.6
Cough Increase	3.8	3.3
Laryngitis	1.3	0.9

## SKIN &amp; APPENDAGES

Rash	3.8	2.5
Sweating	2.5	0.9
Herpes simplex	1.3	1.0
Acne	1.0	0.8

## SPECIAL SENSES

Taste perversion	2.2	0.8
Ear disorder	1.7	0.9
Ear pain	1.1	0.7

## UROGENITAL SYSTEM

Dysmenorrhea	3.5	1.4
Urinary tract infection	2.3	2.0
Vaginal monilla	1.2	0.5
Metrorrhagia	1.0	0.8

**Other Notable Adverse Events**

**Seizures:** Convulsions were reported in an adverse event in 3 of 2068 (0.1%) sibutramine-treated patients and in none of 884 placebo-treated patients in placebo-controlled premarketing obesity studies. Two of the 3 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 (3 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 pre-marketing 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 pre-marketing studies. After discontinuation of the medication, dialysis and oral corticosteroids were administered; renal function normalized. The patient made a full recovery.

**Altered Laboratory Findings:** Abnormal liver function tests, including increases in AST, (aspartate aminotransferase) ALT (alanine aminotransferase), GGT(gamma glutamyl transferase), LDH (lactate dehydrogenase), alkaline phosphate 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  $\geq$  2mg/dL; ALT, AST,GGT, LDH or alkaline phosphatase  $\geq$  3x 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.

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

**Body as a Whole:** fever.

**Digestive System:** diarrhea, flatulence, gastroenteritis, tooth disorder.

**Metabolic and Nutritional:** peripheral edema.

**Muculoskeletal System:** arthritis.

**Nervous System:** agitation, leg cramps, hypertonia, thinking abnormal.

**Respiratory system:** bronchitis, dyspnea.

**Skin and Appendages:** pruritus.

**Special Senses:** amblyopia.

**Urogenital System:** menstrual disorder.

**Miscellaneous:**

Chest pain, hemorrhoid aggravation, light-headedness.

**Reactions from Postmarketing Surveillance or Phase IV Clinical Trials**

Additionally clinically significant adverse events seen in clinical studies and during postmarketing surveillance are listed below by body system.

**Blood and lymphatic system disorders**

Thrombocytopenia.

**Immune system disorders**

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

**Psychiatric disorders**

Cases of depression, suicidal ideation and suicide have been reported rarely in patients on sibutramine treatment. However, a relationship has not been established between the occurrence of depression and/or suicidal ideation and the use of sibutramine. If depression occurs during treatment with sibutramine, further evaluation may be necessary.

**Nervous system disorders**

Seizures.

**Eye disorders**

Blurred vision.

**Gastrointestinal disorders**

Diarrhea, vomiting.

**Skin and subcutaneous tissue disorders**

Rash, urticaria.

**Renal and urinary disorders**

Acute interstitial nephritis, urinary retention.

**Reproductive system disorders**

Abnormal ejaculation (orgasm), impotence, menstrual cycle disorders.

**Altered laboratory findings**

Reversible increase in liver enzymes.

**Precautions**

**Pulmonary Hypertension**

Certain centrally-acting weight loss agents that cause release of serotonin from nerve terminals have been associated with pulmonary hypertension (PPH), a rare but lethal disease. In pre-marketing clinical studies, no cases of PPH have been reported with

sibutramine. Because of the low incidence of this disease in the underlying population, however, it is not known whether or not sibutramine may cause this disease.

### **Seizures**

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

### **Gallstones**

Weight loss can precipitate or exacerbate gallstone formation.

### **Renal/Hepatic Dysfunction**

Patients with severe renal impairment or severe hepatic dysfunction have not been systematically studied; sibutramine 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.

### **Bleeding disorders**

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.

### **Other**

Blood pressure and pulse rate should be monitored in all patients on sibutramine in the first 2 months of treatment; these parameters should be checked at least every 2 weeks, thereafter, once a month.

In hypertensive patients whose blood pressure is properly controlled ( $\leq 145/90$  mm Hg) these checks must be carried with the utmost care and, if necessary, at shorter intervals. Patients whose blood pressure levels exceed 145/90 mm Hg at 2 consecutive readings are to be withdrawn from therapy.

Caution should be exercised in the following:

Patients suffering from bulimia nervosa.

Patients suffering from psychiatric illness.

Patients with Gilles de la Tourette's syndrome.

Patients suffering from benign prostatic hyperplasia with urinary retention.

Patients with pheochromocytoma.

Patients with a history of drug, medication, or alcohol abuse.

### **Drug Interactions**

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

**Sibutramine/Monoamine Oxidase Inhibitors (MAOIs):** 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, sibutramine should not be used concomitantly with MAOI (see Contraindications). At least 2 weeks should

elapse between discontinuation of a MAOI and initiation of treatment with sibutramine. Similarly, at least 2 weeks should elapse between discontinuation of sibutramine and initiation of treatment with MAOI.

### **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 (SSRI) and agents for migraine therapy, (such as sumatriptan succinate) and dihydroergotamine, certain opioids (such as dexamethorphan), meperidine (pethidine), 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 it should not be administered with other serotonergic agents such as those listed above.

**Sibutramine/Other Centrally Acting Drugs for the Treatment of Mental Disorders or for Sleep Disturbances:** Care should be exercised upon concomitant use of sibutramine with centrally acting drugs for the treatment of mental disorders (such as antidepressants, antipsychotics), for sleep disturbances (tryptophan), since sibutramine inhibits serotonin reuptake.

**Sibutramine/Drugs That May Raise Blood Pressure and/or Heart Rate:** Concomitant use of sibutramine 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, ephedrine, or pseudoephedrine. Caution should be used when prescribing sibutramine to patients who use these medications.

**Sibutramine/Drugs That Inhibit Cytochrome P450(3A<sub>4</sub>) Metabolism:** *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.

Clinical interaction trials were conducted on these substrates. The data indicate that there is a potential for such interactions, but the magnitude appears to be small.

**Sibutramine/Ketoconazole:** Concomitant administration of 200 mg doses of ketoconazole twice daily and 20 mg sibutramine once daily for 7 days in 12 uncomplicated obese subjects resulted in moderate increases in AUC and C<sub>max</sub> of 58% and 36% for M<sub>1</sub> and of 20% and 19% for M<sub>2</sub>, respectively.

**Sibutramine/Erythromycin:** The steady-state pharmacokinetics of sibutramine and metabolites M<sub>1</sub> and M<sub>2</sub> were evaluated in 12 uncomplicated obese subjects following concomitant administration of 500 mg of erythromycin 3 times daily and 20 mg of sibutramine once daily for 7 days. Concomitant erythromycin resulted in small increases in the AUC (less than 14%) for M<sub>1</sub> and M<sub>2</sub>. A small reduction in C<sub>max</sub> for M<sub>1</sub> (11%) and a slight increase in C<sub>max</sub> for M<sub>2</sub> (10%) were observed.

**Sibutramine/Other Cytochrome P450(3A<sub>4</sub>) Inhibitors (e.g., Troleandomycin/Cyclosporin);** Cautions should also be exercised in concomitant administration of sibutramine with troleandomycin or cyclosporin which inhibit cytochrome P450 (3A) enzyme activity, leading to increased plasma concentrations of sibutramine.

**Sibutramine/ Cytochrome P450(3A<sub>4</sub>) Inducers (e.g., Rifampicin, Phenytoin, Carbamazepine, Phenobarbital, Dexamethasone):** Caution should be exercised upon concomitant administration of sibutramine with cytochrome P450(3A<sub>4</sub>) inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, dexamethasone) since these agents may lead to acceleration of sibutramine metabolism.

**Sibutramine/Cimetidine:** Concomitant administration of cimetidine 400 mg twice daily and sibutramine 15 mg once daily for 7 days in 12 volunteers resulted in small

increases in combined ( $M_1$  and  $M_2$ ) plasma  $C_{max}$  (3.4%) and AUC (7.3%); these differences are unlikely to be of clinical significance.

**Sibutramine/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 sibutramine and excess alcohol is not recommended.

**Sibutramine/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.

**Sibutramine/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.

### Information for Patients

Physicians should instruct their patients to read the patient package insert before starting therapy with Reductil 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, 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.

### Dosage and Administration

The recommended starting dose of Reductil is 10 mg administered once daily in the morning swallowed whole with a glass of water. The capsule can be taken with or without food. If there is inadequate weight loss, the dose may be titrated after 4 weeks to a total of 15 mg once daily. Blood pressure and heart rate changes should be taken into account when making decisions regarding dose titration (see Precautions).

Doses above 15 mg daily are not recommended. In most clinical trials, sibutramine 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 sibutramine 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 sibutramine. 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 sibutramine 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 sibutramine.

If no response is seen after 3 months, the treatment should be stopped.

The safety and effectiveness of sibutramine as demonstrated in double-blind, placebo-controlled trials, have not been determined beyond 1 year at this time. Therefore, the duration of treatment is limited to one year.

## **Overdosage**

### *Human Experience/Manifestations*

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

### *Management*

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

## **Presentation**

Packs of 28 capsules.

## **Manufacturer**

Teva Pharmaceutical Industries Ltd  
P.O.Box 3190, Petach-Tikva