

# DATA SHEET

## REDUCTIL®

**Reductil (Sibutramine Hydrochloride) 10mg**

**Reductil (Sibutramine Hydrochloride) 15mg**

### PRESENTATION

Reductil 10mg is a blue/yellow capsule with “Reductil” and “10” printed on the capsule.

Reductil 15mg is a blue/white capsule with “Reductil” and “15” printed on the capsule.

### USES

#### Actions

Reductil (sibutramine hydrochloride) is the first orally administered serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline reuptake inhibitor (SNRI) to be used for the management of obesity.

Sibutramine produces its therapeutic effects predominantly via its active secondary and primary amine metabolites (metabolites 1 and 2 respectively), which are inhibitors of noradrenaline, serotonin (5-hydroxytryptamine; 5-HT) and dopamine reuptake. In human brain tissue, metabolites 1 and 2 are ~3-fold more potent as in vitro inhibitors of noradrenaline and serotonin reuptake than of dopamine. Plasma samples taken from sibutramine-treated volunteers caused significant inhibition of both noradrenaline reuptake (73%) and serotonin reuptake (54%) with no significant inhibition of dopamine reuptake (16%). Sibutramine and its metabolites are neither monoamine-releasing agents nor are they monoamine oxidase inhibitors. They have no affinity with a large number of neurotransmitter receptors, including serotonergic (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>), adrenergic ( $\beta_1$ ,  $\beta_2$ ,  $\beta_3$ ,  $\alpha_1$ ,  $\alpha_2$ ), dopaminergic (D<sub>1</sub>-like, D<sub>2</sub>-like), muscarinic, histaminergic (H<sub>1</sub>), benzodiazepine and NMDA receptors.

In animal models, it potently reduces body weight gain by a dual action to decrease calorie intake through enhancement of post-ingestive satiety responses and to increase energy expenditure by enhancing resting metabolic rate. It is postulated that sibutramine decreases food intake by enhancing central noradrenaline and 5-HT function mediated through  $\alpha$ -1 and 5-HT<sub>2A/2C</sub> receptors, respectively, and increases metabolic rate by enhancing peripheral noradrenaline function through  $\alpha$ -3 adrenoreceptors. In man dose-dependant reductions in bodyweight are seen following treatment with sibutramine.

## Pharmacodynamics/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 Reductil on the morbidity and mortality associated with obesity have not been established. Sibutramine's effect on weight loss was examined in double-blind, placebo-controlled obesity trials with study durations of 8 weeks to 18 months and doses ranging from 1 to 30mg once daily. A total of 8052 patients were included in these studies; 5335 patients being treated with Reductil and 2717 patients with placebo. The patients involved in these studies either had uncomplicated obesity with Body Mass Index (BMI) ranging from 27 to 40 kg/m<sup>2</sup> or were obese with comorbid condition(s) and BMI  $\geq$  27kg/m<sup>2</sup>. Weight was significantly reduced in a dose-related manner in sibutramine-treated patients compared to placebo over the dose range of 5mg to 30mg once daily. In two 12-month studies (one of these studies only involved obese patients who had lost at least 6 kg on a 4-week very low calorie diet), maximal weight loss was achieved by 6 months and statistically significant weight loss was maintained over 12 months. The amount of weight loss achieved with Reductil was consistent across studies.

Data from two 12-month studies in uncomplicated obese patients and obese patients with type 2 diabetes mellitus indicate that patients who lose at least 2 kg in the first 4 weeks with a given dose of Reductil are most likely to achieve long-term weight loss on that dose of Reductil. Approximately 75% of such patients went on to achieve a weight loss of  $\approx$ 5% of their initial bodyweight at month 12. Conversely, uncomplicated obese and obese type 2 diabetic patients, who did not lose  $\approx$ 2 kg after 4 weeks treatment with Reductil did not lose at least 5% of their initial bodyweight by month 12 (see **Dosage and Administration**).

Significant dose-related reductions in waist circumference, an indicator of intra-abdominal fat, have also been observed over 6 and 12 months treatment with Reductil in placebo-controlled clinical trials. These data were consistent with more objective measurements of abdominal visceral adiposity such as computed tomography (CT) scans; CT scans on obese patients in a 2-year study provide evidence of a significant decrease in abdominal visceral fat of 24% and in subcutaneous fat of 17% after Reductil 10 mg, compared to baseline. These changes were associated with significant reductions from baseline in mean weight, waist circumference and fasting blood glucose, insulin, C-peptide and triglycerides.

Double-blind, placebo-controlled obesity trials with study durations of 12 weeks to 18 months have provided evidence that the weight loss resulting from treatment with Reductil was associated with improvements in patients' glycaemic control, serum lipid profiles (similar to those seen with non-pharmacological mediated weight loss), and serum uric acid. Treatment with Reductil (5 to 20mg once daily) is associated with mean increases in blood pressure of 1 to 3mmHg and with mean increases in pulse rate of 4 to 5 beats per minute relative to placebo. These findings, which were not associated with any clinically significant outcomes, are similar in normotensives

and in patients with hypertension controlled with medication. With the latter patients, control of blood pressure was not adversely affected. Those patients who lose significant ( $\geq 5\%$  weight loss) amounts of weight on Reductil tend to have smaller increases in blood pressure and pulse rate (see **Warnings and Precautions**).

Studies in healthy volunteers indicate that Reductil does not affect the sympathoadrenal system, the hypothalamic-pituitary-end organ axes and other endocrine parameters including testosterone and postprandial cholecystokinin.

**Echocardiographic Data:** 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 with Reductil was specifically investigated in two studies using echocardiography. In the first study 209 patients (mean age, 54 years) received Reductil 15mg or placebo daily for periods of 2 weeks to 16 months (mean duration of treatment, 7.6 months). In patients without a prior history of valvular heart disease, the incidence of valvular heart disease was 3/132 (2.3%) in the sibutramine treatment group (all three cases were mild aortic insufficiency) and 2/77 (2.6%) in the placebo treatment group (one case of mild aortic insufficiency and one case of severe aortic insufficiency). In a second study, 104 patients received either sibutramine 10 mg or sibutramine 20 mg and 52 patients received placebo daily for 6 months. Echocardiography was performed at baseline and at month 6. In patients with normal valves at baseline, no sibutramine-treated patient compared to one placebo-treated patient (moderate mitral regurgitation) had valvular heart disease at month 6.

#### **The Sibutramine Cardiovascular OUTcomes (SCOUT) study**

The SCOUT study was a randomized, double-blind, placebo-controlled study, with a single-blind, sibutramine lead-in period. The study was conducted as a post approval commitment to the European regulatory authorities.

The study enrolled 10,744 and randomized 9,805 overweight or obese subjects, aged 55 years or older, at high risk of cardiovascular events (the majority who were not indicated to receive treatment with sibutramine) and was designed to evaluate the cardiovascular safety of long-term treatment with sibutramine. In the study, these cardiovascular high risk subjects were treated with sibutramine for up to 6 years and were not discontinued from treatment for inadequate weight loss response, which is not consistent with the instructions for use.

Subjects treated with sibutramine experienced a 16% increased risk of a primary outcome event of non-fatal myocardial infarction, non-fatal stroke, resuscitated cardiac arrest, or cardiovascular death (561/4906, 11.4%) compared with placebo treated subjects (490/4898, 10.0%) (hazard ratio 1.162 [95% CI 1.029, 1.311];  $p = 0.015$ ). There was however, no difference in the incidence of CV death or all-cause mortality between the treatment groups.

## **PHARMACOKINETICS**

The pharmacokinetics of sibutramine and its pharmacologically active metabolites are similar in **obese subjects** to those in **normal weight subjects**, and there is no evidence of any clinically significant difference in the pharmacokinetics of **males** and **females**. The pharmacokinetic profile observed in **elderly healthy subjects** (mean

age 70 years) is similar to that seen in **young healthy subjects**. Reductil is contraindicated in patients greater than 65 years of age (see **CONTRAINDICATIONS**). Based on steady-state trough plasma concentrations of the active metabolites of sibutramine, there was no evidence of any clinically significant pharmacokinetic difference seen between **Afro-Americans** and **Caucasians**.

### **Absorption**

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

The effect of food on steady-state kinetics of sibutramine and its two active metabolites, during long-term treatment with Reductil, will not be significant. Administration of sibutramine with food in a single dose study resulted in reduced  $C_{max}$  for each of the two active metabolites and delayed  $T_{max}$  whilst the AUCs were not significantly altered.

### **Distribution**

In vitro, sibutramine and its metabolites 1 and 2 are extensively bound (97%, 94% and 94%, respectively) to human plasma proteins at plasma concentrations seen following therapeutic doses. Radiolabeled studies in animals indicated rapid and extensive distribution into tissues: highest concentrations of radiolabeled material were found in the eliminating organs, liver and kidney. Tissue distribution was unaffected by pregnancy, with relatively low transfer to the foetus.

### **Metabolism**

Sibutramine is metabolised in the liver principally by the cytochrome P450 isoenzyme CYP3A4 to, principally, two demethylated active metabolites which are secondary and primary amines. These active metabolites are further metabolised to pharmacologically inactive conjugated hydroxy-metabolites. Based on in-vitro studies there was no indication of sibutramine's affinity for the CYP2D6 isoenzyme - a low capacity enzyme involved in pharmacokinetic interactions of numerous drugs. Further in-vitro studies revealed that sibutramine had no significant effect on the activity of the major P450 isoenzymes, including CYP3A4.

In-vivo, co-administration of CYP3A4 inhibitors (ie ketoconazole or erythromycin) with Reductil increased plasma concentrations of the active metabolites and this was accompanied by recorded modest increase in heart rate.

The high capacity of the CYP3A4 and the low therapeutic dose of sibutramine suggest a relatively low potential for sibutramine to affect the metabolism of other drugs metabolised by this isoenzyme. However, caution should be exercised on concomitant administration of Reductil with drugs that affect CYP3A4 isoenzyme activity (see **Interactions**).

The plasma concentrations of the active metabolites reached steady-state within four days of dosing and were approximately two-fold higher than following a single dose. The elimination half-lives of the secondary- and primary amine metabolites (14 and 16 hours, respectively) were unchanged following repeated dosing.

### **Elimination**

Approximately 85% (range 68-95%) of a single orally administered radiolabeled dose was excreted in urine and faeces over a 15-day collection period with the majority of the dose (77%) excreted in the urine. Major metabolites in urine were two inactive conjugated hydroxy-metabolites; unchanged sibutramine, and the active secondary and primary amine metabolites were not detected. The primary route of excretion for the active metabolites is hepatic metabolism and for the inactive hydroxy-metabolites is renal excretion. The plasma levels of the two active metabolites (ie the secondary and primary amine metabolites) peaked in 3 hours ( $T_{max}$ ) with elimination  $t_{1/2}$  of 14 hours and 16 hours respectively. Linear kinetics have been demonstrated over the dose range 10mg to 30mg. Steady-state for the two active metabolites was achieved within 4 days with an approximate two-fold accumulation.

### **Renal Impairment**

The disposition of sibutramine metabolites 1, 2, 5 and 6 was studied in patients with varying degrees of renal function. Sibutramine itself was not measurable.

The AUCs of active metabolites 1 and 2 were generally not affected by renal impairment, except that that AUC of metabolite 2 in end-stage renal disease patients on dialysis was approximately half of that measured in normal subjects ( $CL_{cr} \geq 80$  mL/min). The AUCs of inactive metabolites 5 and 6 increased 2-3 fold in patients with moderate impairment ( $30 \text{ mL/min} < CL_{cr} \leq 60 \text{ mL/min}$ ), 8-11 fold in patients with severe impairment ( $CL_{cr} \leq 30 \text{ mL/min}$ ), and 22-33 fold in patients with end-stage renal disease on dialysis as compared to normal subjects. Approximately 1% of the oral dose was recovered in the dialysate as a combination of metabolites 5 and 6 during hemodialysis process, while metabolites 1 and 2 were not measurable in the dialysate.

Sibutramine should be used with caution in patients with mild to moderate renal impairment. Sibutramine should not be used in patients with severe renal impairment, including end-stage renal disease patients on dialysis (see **Warnings and Precautions**).

### **Hepatic Impairment**

In a study, with patients with moderate hepatic impairment receiving a single 15mg oral dose of sibutramine, the combined AUCs of the two active metabolites were increased by 24% compared to healthy subjects while plasma concentrations of the two inactive hydroxy-metabolites were unchanged. The observed differences in concentrations of the active metabolites do not warrant dosage adjustment in patients with mild to moderate hepatic impairment. Reductil should be used with caution in patients with mild to moderate hepatic impairment. Reductil should not be used in patients with severe hepatic dysfunction.

## Indications

Reductil 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. Reductil is recommended for obese patients with body mass index  $\geq 30\text{kg/m}^2$ , or  $\geq 27\text{kg/m}^2$  in the presence of other obesity-related risk factors (e.g., diabetes, dyslipidaemia, hypertension).

Reductil may only be prescribed to patients who have not adequately responded to an appropriate weight-reducing regimen alone (hypocaloric diet and/or exercise) i.e patients who have difficulty achieving or maintaining  $>5\%$  weight loss within 3 months.

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

Reductil is not intended for use in obese children under 18 years as safety and efficacy in this population has not been established.

Reductil is not intended for use in elderly patients over 65 years of age as safety and efficacy in this population has not been established.

## DOSAGE AND ADMINISTRATION

The recommended starting dose of Reductil is one 10mg capsule administered once daily with or without food. If there is inadequate weight loss (ie less than 2kg) after 4 weeks, the dose may be increased to one 15mg capsule once daily provided 10mg was well tolerated. Treatment must be discontinued in patients who have not responded to the 15 mg dose (defined as less than 2 kg weight loss after 4 weeks treatment). Blood pressure and heart rate changes should be taken into account when deciding to increase the dose. (see **Warnings and Precautions**). Doses above 15mg daily are not recommended. In most of the clinical trials, Reductil was given in the morning.

**Elderly Patients:** Reductil is contraindicated for elderly patients over 65 years of age (see **Contraindications/Warnings & Precautions**).

**Children:** Reductil is contraindicated for children under 18 years of age.

**Duration of Treatment:** Patients who have demonstrated an adequate response to Reductil (ie weight loss of  $\geq 2\text{kg}$  within 4 weeks at a defined dose), usually achieve maximal weight loss (5% -10% of initial body weight) after completing 6 months continuous treatment with Reductil. Current data supports that maximal weight loss is maintained when treatment with Reductil is extended to 1 year. Studies involving more than 1-year administration of Reductil to patients are ongoing.

Treatment must be discontinued in patients who have not responded adequately, i.e whose weight loss stabilizes at less than 5% of their initial bodyweight or whose weight loss within 3 months after starting therapy has been less than 5% of their

initial bodyweight. Treatment should not be continued in patients who regain 3kg or more after previously achieved weight loss (see **Warnings and Precautions**).

In patients with associated co-morbid conditions, it is recommended that treatment with Reductil should only be continued if it can be shown the weight loss induced is associated with clinical benefits, such as improvements in lipid profile in patients with dyslipidemia or improvements in glycemic control in patients with diabetes mellitus.

## CONTRAINDICATIONS

Reductil is contraindicated in patients:

- With a history of coronary artery disease (e.g. stable or unstable angina, history of myocardial infarction), congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or cerebrovascular disease (stroke or TIA)
- With inadequately controlled hypertension (>145/90 mmHg) (see **Warnings and Precautions**)
- Patients above 65 years of age
- With known hypersensitivity to sibutramine hydrochloride or any of the inactive ingredients of Reductil
- With organic causes of obesity
- Who have history of major eating disorders such as anorexia nervosa or bulimia nervosa
- With psychiatric illness. Sibutramine has shown potential antidepressant activity in animal studies and, therefore it cannot be excluded that sibutramine could induce a manic episode in bipolar patients
- With Gilles de la Tourette's syndrome
- Using, or have used during the past two weeks monoamine oxidase inhibitors, other centrally-acting drugs for the treatment of either psychiatric disorders (such as antidepressants, antipsychotics) or weight reduction, or tryptophan for sleep disturbances. (see **PRECAUTIONS**)
- With hyperthyroidism
- With severe liver impairment
- With severe renal impairment, including end stage renal disease patients on dialysis.
- With benign prostatic hyperplasia with urinary retention
- With pheochromocytoma
- With narrow angle glaucoma
- With a history of drug, medication or alcohol abuse
- Who are pregnant or breastfeeding
- Children and young adults up to the age of 18 years, owing to insufficient data

## WARNINGS AND PRECAUTIONS

### Cardiovascular Parameters

#### **BLOOD PRESSURE AND PULSE RATE MUST BE MONITORED IN ALL PATIENTS ON REDUCTIL AS SIBUTRAMINE HAS CAUSED CLINICALLY RELEVANT INCREASES IN BLOOD PRESSURE IN SOME PATIENTS.**

In the first three months of treatment, these parameters should be checked at least every 2 weeks; between month 4 and 6 these parameters should be checked once monthly and thereafter, regularly at maximum intervals of three months. Treatment must be discontinued in patients who have an increase, at two consecutive visits, in resting heart rate of  $\geq 10$  bpm or systolic/diastolic blood pressure of  $\geq 10$  mm Hg. In previously well-controlled hypertensive patients, if blood pressure exceeds 145/90 mmHg at two consecutive readings, treatment must be discontinued.

In the obese patient, blood pressure should be determined using an appropriate cuff size based on arm circumference, measurement in the seated position and taking measurements in both arms (at least initially).

In patients with sleep apnea syndrome particular care should be taken in monitoring blood pressure.

#### **Duration of Treatment:**

Treatment must be discontinued in non-diabetic patients who have not responded adequately within 3 months, i.e. whose weight loss stabilizes at less than 5% of their initial bodyweight. Treatment must be discontinued for diabetic patients whose weight loss within 6 months after starting therapy has been less than 5% of their initial bodyweight. Treatment should not be continued in patients who regain 3kg or more after previously achieving successful weight loss (see **DOSAGE AND ADMINISTRATION**).

#### **Concurrent Cardiovascular Disease**

See **Contraindications**.

#### **Primary Pulmonary Hypertension**

Although sibutramine has not been associated with primary pulmonary hypertension, certain centrally-acting weight loss agents that cause release of serotonin from nerve terminals (a different mechanism of action than sibutramine) have been associated with pulmonary hypertension. It is therefore important, in view of general concerns with anti-obesity drugs, to check for symptoms such as progressive dyspnoea, chest pain and ankle oedema in the course of routine monitoring of patients. The patient should be advised to consult a doctor immediately if these symptoms occur.

#### **Psychiatric Disorders**

Cases of psychosis, mania, suicidal ideation and suicide have been reported in patients taking sibutramine. If these events occur, treatment with sibutramine must be discontinued.

Cases of depression have been reported in patients taking sibutramine. If this event occurs during treatment with sibutramine, discontinuation should be considered.

### **Hepatic Impairment**

Patients with mild to moderate hepatic impairment showed a 24% increase in bioavailability of sibutramine. Reductil should be used with caution in these patients. Sibutramine should not be used in patients with severe hepatic impairment (see **Contraindications**).

### **Renal Impairment**

Although only inactive metabolites are excreted by the renal route, Reductil should be used with caution in patients with mild to moderate renal impairment. Reductil should not be used in patients with severe renal impairment, including end stage renal disease on dialysis (see **Pharmacokinetics: Renal Impairment**).

### **Bleeding Disorders**

In common with other agents that inhibit serotonin reuptake, there is a potential for an increased risk of bleeding in patients taking sibutramine. Sibutramine should be used with caution in patients predisposed to bleeding events and those taking concomitant medications known to affect haemostasis or platelet function.

### **Seizures**

Seizures were reported in <0.1% of patients treated with Reductil in controlled studies. Reductil should be given with caution to patients with a history of seizures.

### **Motor or Verbal Tics**

Reductil should be given with caution to patients who have a family history of motor or verbal tics.

### **Gallstones**

Weight loss can precipitate or exacerbate gallstone formation.

### **Ophthalmic**

Sibutramine should be given with caution to patients with glaucoma and those who are at risk of raised intraocular pressure e.g. family history.

### **Use in Pregnancy**

Whilst reproduction studies in animals have shown that Reductil is not teratogenic, the safety of Reductil in pregnant women has not been established and therefore the use of Reductil during pregnancy is contraindicated. Women of child-bearing potential should employ adequate contraception while taking Reductil (see **INTERACTIONS – Oral contraceptives**). Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during treatment with Reductil.

### **Use During Lactation**

It is not known whether sibutramine or its metabolites are excreted in human breast milk and therefore administration of Reductil is contraindicated during lactation.

### **Use in Children**

The safety and effectiveness of Reductil in children and young adults up to the age of 18 years is contraindicated, owing to insufficient data.

### **Use in Elderly**

Use in patients above 65 years of age is contraindicated, owing to insufficient data.

### **Effects on Ability to Drive and Use Machines**

Reductil was shown not to affect psychomotor or cognitive performance in studies involving healthy volunteers. As centrally-active medication may have the potential to impair judgement, thinking and motor skills, patients should be cautioned that their ability to drive a vehicle or operate hazardous machinery may be impaired when taking Reductil.

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

**Carcinogenicity:** There was no evidence of carcinogenicity in mice (up to 20 mg/kg/day for 2 years) or in female rats (up to 9 mg/kg/day for 2 years). In male rats there was a higher incidence of benign tumours of the testicular interstitial cells; such tumours are commonly seen in rats and are hormonally mediated. The relevance of these tumours to humans is not known.

**Mutagenicity:** In vitro and in vivo assays found sibutramine to be non-mutagenic. 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 other in vitro and in vivo assays.

**Impairment of Fertility:** In rats, there were no effects on fertility at doses generating combined plasma AUCs 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 dams' nest-building behaviour was impaired, leading to a higher incidence of perinatal mortality; there was no such effect at approximately 4 times the human combined AUC.

### **ADVERSE EFFECTS**

Most adverse effects occurred at the start of treatment (during the first 4 weeks). Their severity and frequency diminished over time. They were generally not serious, did not entail discontinuation of treatment, and were reversible.

The side effects are listed below by body system.

<b>Body system</b>	<b>Incidence</b>	<b>Undesirable effects</b>
Cardiovascular system (cf. “cardiovascular changes”)	Common	Tachycardia Palpitations Raised blood pressure/hypertension Vasodilation (hot flush)
Gastrointestinal system	Very common	Loss of appetite Constipation
	Common	Nausea Haemorrhoid aggravation
Central nervous system	Very common	Dry mouth Insomnia
	Common	Light-headedness Paraesthesia Headache Anxiety
Skin	Common	Sweating
Sensory functions	Common	Taste perversion

Incidence: “Very common”  $\geq 10\%$ ; “Common”  $\geq 1\%$  and  $< 10\%$

The following clinically significant adverse events occurred in individual cases under treatment with sibutramine:

- Acute interstitial nephritis
- Mesangiocapillary glomerulonephritis
- Henoch-Schönlein purpura
- Seizures
- Thrombocytopenia
- Reversible increases in liver enzymes
- Acute psychotic attack after treatment in one patient with schizo-affective disorder which presumably existed prior to treatment

Withdrawal symptoms such as headache and increased appetite have rarely been observed. There is no evidence of a withdrawal or abstinence syndrome or mood swings on cessation of treatment.

#### **Increased Blood Pressure and Pulse in Pre-Marketing Clinical Trials**

A mean increase in resting systolic and diastolic blood pressure of 2-3 mm Hg, and a mean increase in pulse of 3-7 beats per minute have been observed in pre-marketing clinical trials. Higher increases in blood pressure and pulse have been observed in some patients.

Clinically significant increases in blood pressure and pulse tend to occur early on in treatment (first 4-12 weeks). Therapy must be discontinued in such cases (see **WARNINGS AND PRECAUTIONS**).

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

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

### **Cardiac disorders**

Atrial fibrillation

### **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 psychosis, mania, suicidal ideation and suicide have been reported in patients on sibutramine treatment. If any of these events occur, treatment with sibutramine must be discontinued.

Cases of depression have been reported in patients on sibutramine treatment. If this event occurs during treatment with sibutramine, discontinuation should be considered.

### **Nervous system disorders**

Seizures, transient short-term memory disturbance

### **Eye disorders**

Blurred vision

### **Gastrointestinal disorders**

Diarrhoea, vomiting, dyspepsia, gastritis

### **Skin and subcutaneous tissue disorders**

Alopecia, rash, urticaria, bruising, ecchymosis

### **Renal and urinary disorders**

Acute interstitial nephritis, urinary retention

### **Reproductive system disorders**

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

### **Altered laboratory findings**

Reversible increases in liver enzymes.

### **Laboratory Test Findings:**

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

## **INTERACTIONS**

**CNS Active Drugs:** The use of Reductil is contraindicated in patients with concomitant use of other centrally-acting agents for weight reduction or the treatment of psychiatric disorders. (see **Contraindications**).

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 known as “serotonin syndrome”. Because Reductil inhibits serotonin reuptake, Reductil 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 Reductil. Similarly, at least 2 weeks should elapse between discontinuation of Reductil and initiation of treatment with a MAOI.

The simultaneous use of several drugs, each of which increases levels of serotonin in the brain, may give rise to serotonin syndrome. Serotonin syndrome occurs rarely in cases with the simultaneous use of a selective serotonin reuptake inhibitor (SSRI) together with certain agents such as lithium, or tryptophan or antimigraine drugs (eg sumatriptan succinate and dihydroergotamine) or with certain opioids (eg dextromethorphan, pethidine, pentazocine and fentanyl), or in cases of simultaneous use of two SSRIs.

As Reductil inhibits serotonin reuptake, it should not be administered with other serotonergic agents such as those listed above.

**Drugs That May Raise Blood Pressure and/or Heart Rate:** Concomitant use of Reductil 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 and certain anti-inflammatory agents (eg NSAIDs). Caution should be used when prescribing Reductil to patients who use these medications.

**Drugs That Affect Cytochrome P450(CYP3A4 Isoenzyme) Metabolism:** The data indicate that there is a potential for drug interactions to occur between drugs which affect the CYP3A4 isoenzyme of cytochrome P450 (see **Pharmacokinetics; Metabolism**), however, the magnitude appears to be small. Caution should therefore be exercised on concomitant administration of Reductil with drugs which either inhibit (eg ketoconazole, erythromycin, troleandomycin and cyclosporin) or induce (eg rifampicin, macrolide antibiotics, phenytoin, carbamazepine, phenobarbitone and dexamethasone) CYP3A4 isoenzyme activity.

Co-administration of ketoconazole or erythromycin with sibutramine increased plasma concentrations (AUC) of sibutramine metabolites (23% or 10% respectively) in an interaction study. Mean heart rate increased by up to 2.5 beats per minute more than on sibutramine alone.

**Cimetidine:** Studies in healthy volunteers indicated that the concomitant administration of Reductil (15mg once daily) and cimetidine (400mg twice daily) caused a marginal clinically insignificant increase in  $C_{max}$  and AUC of the active metabolites of sibutramine.

**Alcohol:** At single doses, there was no impairment of cognitive or psychomotor performance when Reductil was administered concomitantly with alcohol. However, the consumption of alcohol is not compatible with the recommended dietary measures as a rule. The concomitant use of Reductil with excess alcohol is not recommended.

**Oral Contraceptives:** The suppression of ovulation by oral contraceptives was not inhibited by Reductil. No clinically significant systemic interaction was observed;

therefore, no requirement for alternative contraceptive precautions are needed when patients taking oral contraceptives are concurrently prescribed sibutramine.

**Drugs Highly Bound to Plasma Proteins:** Although sibutramine and its two active metabolites 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.

**Orlistat:** No data on the concomitant use of Reductil and orlistat are available.

## **OVERDOSAGE**

There is very limited experience of overdosing 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 overdose, such as, airway establishment as needed, cardiac and vital sign monitoring and general symptomatic and supportive measures. 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. Cautious use of  $\beta$ -blockers may be indicated to control elevated blood pressure or tachycardia. The benefits of forced diuresis and haemodialysis are unknown.

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

## **PHARMACEUTICAL PRECAUTIONS**

### **Shelf Life**

3 years

### **Special Precautions for Storage**

Store below 25°C.

### **Medicine Classification**

Prescription Medicine

### **Package Quantities**

Blister pack of 30 capsules.

### **Further Information**

Reductil is in the Intensive Medicines Monitoring Programme (IMMP).

Each Reductil capsule contains 10mg, or 15mg of sibutramine hydrochloride. It also contains as inactive ingredients: lactose, cellulose - microcrystalline, silica- colloidal anhydrous and magnesium stearate in a hard-gelatin capsule [which contains gelatin, sodium lauryl sulfate, titanium dioxide, shellac, lecithin, dimethicone, propylene glycol, indigo carmine CI73015, iron oxide black CI77499 and quinidine yellow CI47005 (10mg capsules only)]

Chemically, sibutramine hydrochloride monohydrate is a racemic mixture of the (+) and (-) enantiomers of  $\underline{N}$ -{1-[1-(4-chlorophenyl) cyclobutyl]-3-methylbutyl}- $\underline{N,N}$ -dimethylamine hydrochloride, monohydrate, and has an empirical formula of  $C_{17}H_{29}Cl_2NO$ . Its molecular weight is 334.33. CAS Number: 125494-59-9. The INN for the free base is 'sibutramine'. The CAS Number for sibutramine free base is CAS 106650-56-0.

Sibutramine hydrochloride 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.

### **Name and Address**

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### **Date of Preparation**

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