

# Obenil<sup>®</sup>

Sibutramine HCl Monohydrate  
*Antiobesity*

---

## COMPOSITION

**Obenil<sup>®</sup> 5:** Each capsule contains Sibutramine HCl Monohydrate INN 5 mg.

## PHARMACOLOGY

Sibutramine produces its therapeutic effect by norepinephrine, serotonin and dopamine reuptake inhibition. 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 and norepinephrine reuptake in vivo. However metabolites M<sub>1</sub> and M<sub>2</sub> inhibit the reuptake of these neurotransmitters both in vivo and in vitro.

## PHARMACOKINETICS

*Absorption:* Sibutramine is rapidly absorbed from the GI tract (T<sub>max</sub> : 1.2 hrs.) following oral administration and undergoes extensive first-pass metabolism in the liver (Oral clearance 1750 L/hr; half life: 1.1 hr) to form pharmacologically active mono- and di-desmethyl metabolites M<sub>1</sub> and M<sub>2</sub> are reached within 3 to 4 hrs. On an average, at least 77% of a single oral dose of Sibutramine is absorbed.

*Distribution:* Radiolabeled studies in animals indicated rapid and extensive distribution into tissues: highest concentrations of radiolabeled materials 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 (3A4) 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 active metabolites, M<sub>5</sub> and M<sub>6</sub>.

*Elimination:* Approximately 85% (range, 68% to 95%) of single oral dose was excreted in urine and feces over a 15-day collection period with the majority of the dose (77%) excreted in the urine. 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.

## INDICATION

**Obenil<sup>®</sup> 5** (Sibutramine) is used in the management of obesity, including weight loss and management of weight loss. It should be used in conjunction with a reduced caloric diet.

**Obenil<sup>®</sup> 5** (Sibutramine) is recommended for obese patients with an initial body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> or  $\geq 27$  kg/m<sup>2</sup> in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia) BMI is calculated by taking the patient's weight, in kg and dividing by the patient's height in meters, squared. Metric conversion is as follows:

Pounds  $\div$  2.2 = kg; inches  $\times$  0.0254 = meters.

## **DOSAGE AND ADMINISTRATION**

The recommended starting dose is 10 mg once daily 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. 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. Analysis of numerous variables has indicated that 60% of patients who lose at least 4 lbs 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. Conversely, 80% of patients who do not lose at least 4 lbs in the first 4 weeks of treatment with a given dose 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 lbs in the first 4 weeks of treatment, consider reevaluation of therapy which may include increase in the dose or discontinuation of Sibutramine. The safety and efficacy of Sibutramine have not been determined beyond 1 year at this time.

## **CONTRAINDICATION AND PRECAUTION**

Patients receiving monoamine oxidase inhibitors (MAOIs), hypersensitivity to Sibutramine or any of the active ingredients of Sibutramine; patients with anorexia nervosa, patients taking other centrally acting appetite - suppressant drugs. Give with caution to those patients with a history of hypertension and do not give to patients with uncontrolled or poorly controlled hypertension. Use caution when prescribing Sibutramine with other agents that may raise blood pressure or heart rate including certain decongestant, cough, cold and allergy medications that contain agents such as phenylpropanolamine, ephedrine or pseudoephedrine.

## **SIDE EFFECT**

Commonly reported side-effects of Sibutramine are dry mouth, headache, insomnia and constipation; diarrhoea, dizziness, drowsiness and rhinitis have also occurred. Less frequently reported side-effects include dysmenorrhoea, oedema, influenza-like symptoms and depression. Abnormal bleeding, acute interstitial nephritis, emotional lability, migraine, seizures and skin rashes have been reported rarely. Clinically significant increase in heart rate and blood pressure may occur. Sibutramine may decrease salivary flow and therefore increase the risk of dental caries, periodontal diseases, or other oral disorders. It may also produce mydriasis. Increase in liver enzyme have been reported.

## **DRUG INTERACTION**

Sibutramine should not be given concurrently with, or within at least two weeks of stopping an MAOI; at least two weeks should elapse between discontinuation of Sibutramine and starting therapy with an MAOI. There is a risk of the serotonin syndrome developing if Sibutramine is administered together with other serotonergic drug such as selective serotonin reuptake inhibitors (SSRIs), Sumatriptan, Lithium, Pethidine, Fentanyl, Dextromethorphan and Pentazocine. Sibutramine should not be used with other drugs that may increase heart rate or blood pressure such as Ephedrine,

Phenylpropanolamine, and Pseudoephedrine (which are ingredients of some cough and cold remedies). Alcohol should be avoided. Inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as Ketoconazole and Erythromycin, may increase plasma concentrations of Sibutramine.

#### **USE IN PREGNANCY AND LACTATION**

The use of Sibutramine is not recommended during pregnancy. Women of child-bearing potential should use adequate contraception while taking this drug. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. It is not known whether Sibutramine or its active metabolites are excreted in breast milk. It is not recommended for use in nursing mothers. Patients should be advised to notify their physician if they are breast-feeding.

#### **STORAGE CONDITION**

Store in a cool and dry place. Protect from light and moisture.

#### **HOW SUPPLIED:**

**Obenil<sup>®</sup> 5:** Each box contains 3 x 10 capsules in blister pack.