National PBM Drug Monograph

Sibutramine (Meridia)

August 2005

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

Sibutramine is approved for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet. The Department of Veterans Affairs National Center for Health Promotion and Disease Prevention has developed and implemented the Managing Overweight/Obesity for Veterans Everywhere (MOVE) program. The intention of MOVE is to address obesity through a multidisciplinary approach incorporating nutrition, exercise, behavior modification and medical management. Pharmacotherapy for obesity is included in MOVE after patients have tried dietary and behavior interventions for 6-months.

Sibutramine is taken orally as 10 mg or 15 mg daily. Its systemic absorption in extensive and the parent compound is rapidly converted to active metabolites (M_1 and M_2) which inhibit the reuptake of norepinephrine and serotonin within the hypothalamic areas involved in the regulation of eating behavior. Sibutramine is thought to induce weight loss by enhancing the feeling of satiety and stimulating thermogenesis.

Sibutramine's efficacy and safety have been subjected to systematic reviews and meta-analysis by the Cochrane group, NICE, and an independent group. The reviews have found that sibutramine resulted in a greater mean difference in weight loss from placebo (sibutramine – placebo) ranging between 2.5 to 5 kg after 1year of treatment. The mean difference in the percent of body weight lost also favored sibutramine, 4.6%. The differences in the percentage of patients (sibutramine – placebo) achieving a $\geq$5% or $\geq$10% weight loss were 19% to 34% and 12% to 31%, respectively. After 2 years, weight regain by patients treated with sibutramine was less than that regained by patients taking placebo.

Sibutramine has also been shown to improve cardiovascular risk factors such as lipid and glycemic profiles. The impact of these improvements on cardiovascular and other clinical outcomes and mortality is unknown. The Sibutramine Cardiovascular OUTcome (SCOUT) study, a 5-year prospective study, is currently underway and is designed to evaluate cardiovascular and metabolic outcomes as they relate to weight loss attributed to sibutramine.

Insomnia, nausea, dry mouth, and constipation are frequently reported with sibutramine. Sibutramine may result in dangerous elevations in blood pressure or heart rate, thus these parameters should be monitored and sibutramine should not be prescribed to patients with uncontrolled or poorly controlled hypertension or uncontrolled or poorly controlled hypertension.

The annual cost of sibutramine 10 mg and 15 mg capsules to the VA is $667 and $861. One cost-effective analysis determined that 3 patients need to be treated in order for 1 patient to lose 5% of his/her body weight after 1 year at a cost of $1835 to $2372.

It is recommended that sibutramine remain off of the VA National and VISN Formularies. Prescribers from a MOVE program (or a similar multidisciplinary weight loss program) may prescribe sibutramine to patients meeting its criteria-for-use and they must complete a non-formulary request. All patients prescribed sibutramine must be enrolled in the VA PBM/Strategic Health safety registry.

Introduction[1]

Obesity is the second most preventable cause of death in the United States affecting 31% of adults between the ages of 20 to 70 years. Obesity is a risk factor for hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, stroke, musculoskeletal disorders, and sleep apnea. The total cost of obesity in 1995 was estimated to be $99 billion.

In 2003, the Department of Veterans Affairs National Center for Health Promotion and Disease Prevention developed the Managing Overweight/Obesity for Veterans Everywhere (MOVE) program. The intention of MOVE is to address obesity through a multidisciplinary approach incorporating nutrition, exercise, behavior modification and medical management. Pharmacotherapy for obesity is included in MOVE after patients have tried dietary and behavior interventions for 6-months.

Sibutramine and orlistat, two FDA-approved prescription weight loss drugs, are not currently on the VA National Formulary and the PBM has been asked to review their formulary status so that they may be more accessible to patients in the MOVE program.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating sibutramine for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[2]

Sibutramine, through two active metabolites (M_1 and M_2), inhibits the reuptake of norepinephrine and serotonin within the hypothalamic areas involved in the regulation of eating behavior. Sibutramine does not directly affect the neuronal release of serotonin, norepinephrine, or dopamine, thus differentiating it from anorectic agents such as fenfluramine and amphetamines. Sibutramine is thought to induce weight loss by enhancing the feeling of satiety and stimulating thermogenesis.

Table 1. Sibutramine, M_1 and M_2 Pharmacokinetics

Parameter	Sibutramine	M_1	M_2
Metabolism	First pass; CYP3A4	Hydroxylation, conjugation	Hydroxylation, conjugation
Elimination	Urine 77%; fecal	Urine, feces	Urine, feces
Half-life	1.1 hours	14 hours	16 hours
Protein Binding	97%	94%	94%
Bioavailability	77%	-	-

FDA Approved Indication(s) and Off-label Uses[2]

Management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet. A recently published study reported that sibutramine significantly decreased binge eating episodes in patients with an eating disorder.

Current VA National Formulary Alternatives

There are no agents currently on the VA National Formulary specifically intended for weight loss or maintenance of weight loss.

Dosage and Administration[2]

Sibutramine's recommended starting dose is 10 mg taken once a day with or without food. After four weeks if the patient's weight loss has not been adequate, the dose can be increased to 15 mg taken once daily. Patients who do not tolerate an initial dose of 10 mg daily can be tried on 5 mg daily. Patients who do not obtain a 4 pound weight loss in the first 4 weeks of treatment on a therapeutic dose should be reevaluated. Doses greater than 15 mg per day are not recommended by the manufacturer. Sibutramine has not been studied in clinical trials with respect to safety and efficacy beyond 2 years.

Sibutramine has not been systematically studied in patients with severe hepatic dysfunction or renal impairment and should not be used by such patients.

Clinical trials with sibutramine did not include sufficient numbers of subjects 65 years or older to determine if older patients differ from younger patients with respect to efficacy or safety. Sibutramine should be used cautiously by older patients.

Efficacy[3-8]

Efficacy Measures

Common methodologies used in the clinical trials

- Inclusion criteria: Body Mass Index (BMI: weight in kg divided by height in m^2) $\geq$30 kg/m^2 or a BMI $\geq$27 kg/m^2 with at least one obesity related co-morbidity
- A placebo-controlled run-in phase that included dietary interventions.
- Only those patients meeting predetermined criteria were randomized to placebo or sibutramine

Primary outcomes

- Percent of baseline weight lost
- Number of kilograms (kg) lost
- Percent of patients losing 5% or 10% of initial body weight

Secondary Outcomes

- Change in blood pressure and heart rate
- Change in cholesterol concentration
- Change in BMI
- Change in waist circumference or waist:hip ratio

Summary of efficacy findings

Cochrane Review[3]

An updated systematic review by the Cochrane Metabolic and Endocrine Disorders Group published in 2004 evaluated 5 sibutramine trials; only double-blind placebo controlled weight loss or weight maintenance trials were eligible for inclusion.

Weight Loss Trials

Three sibutramine weight loss trials met inclusion criteria which included: 1) only adults who were overweight or obese were enrolled, 2) placebo-controlled, 3) performed an intention-to-treat analysis, and 4) had at least a 1-year follow-up period. Exclusion criteria included: 1) obesity of endocrine in origin, 2) diabetes mellitus; 3) treatment with a medication which may alter body weight, 4) uncontrolled hypertension. Following a 2 to 10 week single-blind, placebo-controlled run-in phase, only subjects who were compliant with their diet or who were 75% compliant with placebo were randomized to placebo or sibutramine in maintenance dose of 10, 15, or 20 mg daily.

Demographics

- N=929
- Mean BMI = 33.4 kg/m^2
- Mean weight = 96 kg
- Mean age = 47 years
- Percent women = 80%
- Percent Caucasian = 75%

Table 2. Outcomes from weight loss trials included in the Cochrane Review

Outcome	Difference: Sibutramine to Placebo (95% CI)	Test of hetero-geneity, p-value
Weight lost	4.3 kg more (3.6 – 4.9 kg)	0.57
Percent weight lost	4.6% greater (3.8 – 5.4%)	0.29
$\geq$5% weight loss	34% more (28 – 40 %)	0.79
$\geq$10% weight loss	15% more (4 – 27%)	0.0008, I^2=86%
Change in BMI	1.5 kg/m^2 greater (1.2 – 1.8 kg/m^2)	0.79
Waist circumference	4 to 5 cm greater	<0.05
Waist:Hip	0.1 reduction	>0.05

HDL	1.3 – 3.5 mg/dL increase	<0.05
Triglycerides	15.9 – 20.4 mg/dL decrease	<0.05
Total cholesterol and LDL	No difference	-
Fasting blood glucose (FBG)	1.4 and 1.6 mg/dL decrease	-

I^2 = amount of variation explained by heterogeneity; values ≥65% indicates substantial heterogeneity.

Weight Maintenance Trials[3-5]

Two European studies (A and B) were included with a combined enrollment of 627 patients. The mean BMI was 37 kg/m^2, weight 103 kg, age 49 years, and 83% were women. Exclusion criteria were the same as the weight loss trials plus persons with "significant medical illnesses" were ineligible.

Study A consisted of a 6 month run-in with sibutramine 10 mg per day along with a 600 kcal per day diet deficit, lifestyle modifications and dietary consultation. Ninety-four percent of participants (499) achieved a 5% weight loss and a <2 kg weight regain during months 4 to 6, 82% were randomized to sibutramine 10 mg daily or placebo for 2 years. If weight gain occurred, the sibutramine dose was increased to 20 mg daily. The study's outcome measure was the percent of participants maintaining an 80% weight loss. At the end of 2 years, 56% of patients completed the trial, with 41% of patients taking sibutramine achieving the study's outcome compared to 14% taking placebo ($p<0.001$). The mean weight loss achieved by patients taking sibutramine was 4 kg greater than those taking placebo. Waist circumference decreased by a mean of 3.7 cm more with sibutramine (95% CI: 2.0-5.4) and waist:hip ratio was reduced by 1.3 with sibutramine (95% CI: 0.2 – 2.4). High density lipids increased by 0.13 mmol/L with sibutramine ($p<0.05$).

Study B included 205 patients taking a low calorie diet of 220 to 800 kcal per day deficit diet for 4 weeks. One hundred sixty patients lost ≥6 kg and were randomized to one year of treatment with sibutramine 10 mg daily or placebo as well as dietary consultation and exercise encouragement. After 1 year, patients randomized to sibutramine lost 6.2 kg (95% CI: 4.1 – 8.2 kg) more than those taking placebo.

Adverse Effects[3]

Four of the five trials reported numerical data on adverse effects.

- Systolic blood pressure (SBP) was increased 1.9 mm Hg with sibutramine (95% CI: 0.2 – 3.6 mm Hg; test for heterogeneity, $p=0.06$)
- Diastolic blood pressure (DBP) was increased 1 to 4 mm Hg with sibutramine ($p<0.05$ in all studies, data not pooled due to heterogeneity)
- Heart rate (HR) was increased 4 to 6 beats per minute (bpm) with sibutramine in all studies ($p<0.05$)
- Insomnia, nausea, dry mouth, and constipation were more frequently reported with sibutramine (7% to 20%) than placebo.

The conclusion of the Cochrane systematic review was that sibutramine was moderately effective in promoting weight loss, but that the studies were limited by attrition and that reported weight loss was from the beginning of the run-in phase rather than the point of randomization. The authors stated that additional studies are needed that are longer in duration and that measure sibutramine's effect on cardiovascular morbidity, diabetes, and mortality.

Meta-Analysis by Arterburn et al. 2004[6]

Arterburn et al conducted a systematic review with the goal of assessing the quality of published and unpublished data for sibutramine as a weight loss agent and to quantify its benefits and harms using a meta-analysis. To be eligible trials must have met the following criteria: 1) be a randomized controlled trial, 2) use 10 to 20 mg per day of sibutramine, 3) have a placebo control, 4) enroll participants ≥18 years of age with a BMI ≥25 kg/m^2, 5) assess weight loss, and be of 8-weeks duration or longer.

Twenty-nine trials met criteria and were included in the review. The mean age of participants ranged from 34 to 54 years. Women accounted for the majority of study participants ranging from 47% to 100%. Patients with controlled hypertension were eligible for inclusion in most trials, with some trials exclusively enrolled patients with hypertension, type 2 diabetes mellitus, hyperlipidemia, or obstructive

sleep apnea. Patients with cardiovascular disease were generally excluded. Other interventions included were diet (83% of trials), exercise (21%), and behavior modification (21%).

Table 3. Pooled results of sibutramine controlled trials by trial duration.

Duration (weeks)	Number of Trials (pooled n)	Mean difference in weight loss (kg) sibutramine-placebo (95% CI)	Test for heterogeneity (-value)
8 to 12	7 (546)	-2.78 (-3.29 to -2.26)	0.55
16 to 24	12 (1179	-5.06 (-6.16 to -3.96)	<0.001
	4	-3.43* (-4.50 to -2.36)	0.22
	5	-6.03^ (-7.36 to -4.70)	0.05
	3	-6.04# (-8.79 to -3.28)	0.02
44 to 54	5 (2188)	-4.45 (-5.29 to -3.62)	0.14

*Contains trials that used last observation carried forward and greater than 70% follow-up.
^Contains trials where only those who completed the trial were analyzed
#Contains trials with follow-up rates of less than 70%.

The weight loss achieved was similar in patients with diabetes mellitus, hypertension, hyperlipidemia, and healthy-obese adults. There was no evidence of a dose effect when the pooled summary mean difference in weight loss by dose and treatment duration was plotted. For all treatment durations, weight loss differed by <1 kg between 10 mg and 20 mg doses of sibutramine. The percentage of patients taking sibutramine 10 mg or 15 mg for 1 year who were more likely to obtain a 5% or 10% weight loss was 19% to 34% and 12% to 31%, respectively.

Effect on Blood Pressure, Heart Rate and Metabolic Outcome Parameters: Mean difference between sibutramine and placebo.

Studies 8 to 12 weeks in duration

- SBP - 0.2 mm Hg
- DBP 1.6 mm Hg
- HR 1.3 bpm
- FBG -19.8 mg/dL
- HgA1c -0.4%

Studies 16 to 24 weeks in duration

- SBP -1.6 – 5.6 mm Hg
- DBP -0.8 – 1.7 mm Hg
- HR 0.75 – 5.9 mm Hg
- FBG -9.0 - -4.0 mg/dL
- HgA1c -0.1%
- Cholesterol
  - Total -1.9 – 1.8 mg/dL
  - LDL 0.6 – 2.6 mg/dL
  - HDL 1.3 – 5.5 mg/dL
- Triglycerides -16.8 - 0 mg/dL

Studies 44 to 55 weeks in duration

- SBP 4.6 mm Hg
- DBP 2.8 mm Hg
- HR 5.9 mm Hg
- FBG -3.6 g/dL
- HgA1c -0.3%
- Cholesterol
  - Total 0
  - LDL 0
  - HDL 1.8 mg/dL
- Triglycerides -3.6 mg/dL

The National Institute for Clinical Excellence (NICE) Systematic Review[7]

The NICE systematic review of the clinical effectiveness and cost effectiveness of sibutramine was initially completed in 2000, with the final cost effectiveness analysis completed after May 2001 when final price information became available. The methodology was similar to that of other systematic reviews and included many of the same studies. Not surprisingly the NICE findings and recommendations were similar to those of the preceding reviews which were completed at a later date. Consequently, only the following two tables are included in the document since they provide outcome data stratified by gender and race. The cost-effectiveness analysis appears later in the monograph.

Table 4. Placebo-subtracted mean change in bodyweight from baseline by duration, sibutramine dose and gender using LOCF (data provided to NICE by the manufacturer of sibutramine)

Duration/Sibutramine dose	Placebo –subtracted percentage change in body weight by gender			Interaction p-value*
	All (n)	Men (n)	Women (n)	
Week 12				
10 mg	-2.5 (2390)	-2.5 (487)	-2.5 (1903)	0.92
15 mg	-3.5 (2999)	-3.2 (710)	-3.6 (2289)	0.21
Week 24				
10 mg	-3.6 (1469)	-3.6 (277)	-3.6 (1192)	0.96
15 mg	-4.6 (2359)	-4.2 (575)	-4.8 (1784)	0.34
Week 52				
10 mg	-3.8 (1058)	-3.5 (201)	-3.8 (857)	0.91
15 mg	-4.92 (665)	-4.2 (210)	-5.3 (455)	0.22

*Treatment by gender sub-category interaction. Non-significant interactions indicate a consistency of treatment effect over gender categories. Analysis of variance with factors for sex, study treatment and sex-by-treatment interaction.

Table 5. Placebo-subtracted mean change in bodyweight from baseline by duration, sibutramine dose and race using LOCF (data provided to NICE by the manufacturer of sibutramine)

Duration/ Sibutramine dose	Placebo –subtracted percentage change in body weight by race					Interaction p-value*
	All (n)	Caucasian (n)	Black (n)	Oriental (n)	Other (n)	
Week 12						
10 mg	-2.5 (1821)	-2.5 (1734)	-2.0 (60)	-4.1 (8)	-2.0 (19)	065
15 mg	-3.4 (2819)	-3.5 (2667)	-4.6 (79)	-7.9 (2)	-3.6 (71)	0.67
Week 24						
10 mg	-3.6 (87)	-3.6 (805)	-2.8 (51)	-(2)	-3.3 (18)	0.82
15 mg	-4.2 (2179)	-4.3 (2104)	-2.3 (50)	-11 (2)	-1.6 (23)	0.20
Week 52						
10 mg	-3.8 (465)	-3.7 (457)	-11 (6)	-(2)	-(0)	0.16
15 mg	-4.9 (665)	-5.0 (655)	-4.1 (4)	-(1)	-3 (5)	0.25

*Treatment by race sub-category interaction. Non-significant interactions indicate a consistency of treatment effect over race categories. Analysis of variance with factors for race, study treatment and race-by-treatment interaction.

Agency for Healthcare Research and Quality (AHRQ) Evidence Report/Technology Assessment: Pharmacological and Surgical Treatment of Obesity[8]

This evidence report incorporated the systematic review and meta-analysis by Arterburn et al discussed above in its analysis of the role of sibutramine in the treatment of obesity. The report's authors also calculated that the randomized clinical trials contained sufficient number of patients exposed to sibutramine to evaluate adverse outcomes occurring at a rate of 8 per 10,000 or higher.

Absolute Weight Loss

In clinical trials of 12 months duration whose randomization criteria did not require a set amount of weight loss during the run-in period, mean absolute weight loss ranged from -6.4 to -6.4 kg with sibutramine and -1.6 to +0.5 kg for placebo. One weight maintenance trial (Study B) required patients to lose at least 6 kg in the 4-week run-in phase prior to randomization. After 12 months, patients taking sibutramine lost an absolute average of ~14 kg, while those taking placebo lost an absolute average of ~7.2 kg. The other weight maintenance trial (Study A) randomized patients to sibutramine or placebo after 6

months of sibutramine and a reduced calorie diet. At the end of the study, patients who took sibutramine the entire 24 months lost an absolute average of 10.2 kg (LOCF 8.9 kg) compared to 4.7 kg (LOCF 4.9 kg) for those randomized to placebo for the final 18 months of the trial.

Adverse Events (Safety Data)[2,3,6,9]

Deaths and Other Serious Adverse Events

A systematic review found no deaths were reported in 44 published clinical trials. No deaths have been reported due to the use of sibutramine. However, deaths have been reported in patients taking sibutramine in Italy resulting in a suspension of its prescribing. This suspension was lifted after a review by Europe's Committee for Proprietary Medicinal Products released a report in June of 2002 that sibutramine's benefit/risk ratio was favorable. Health Canada reviewed the 28 adverse reactions reported in Canada between December 2000 and February 2002, and another 53 reported between March 2002 and November 2002. It was concluded that the reactions reported were consistent with those known to occur with sibutramine including increased blood pressure, chest pain, stroke, and eye pain and hemorrhage. No deaths were reported. Health Canada concluded that sibutramine continued to meet the requirements for sale in Canada.

In the US, Public Citizen, a nation wide consumer organization, petitioned Secretary Tommy Thompson to have the FDA withdraw sibutramine from the market. Public Citizen based its petition on the concerns raised during the initial FDA approval, Italy's recent suspension of sibutramine's marketing, and its own review of 397 serious adverse reactions reported to the FDA between February 1991 and September 2001. Of the 397 patients, 152 were hospitalized, and 29 died; 19 from cardiovascular causes. Another 143 patients were reported to have an arrhythmia. The FDA rejected Public Citizen's petition on August 17, 2005 stating that "sibutramine's overall risk-benefit profile supports it remaining available as a prescription drug for the treatment of appropriately selected obese patients."

Primary pulmonary hypertension and valvular disorders attributed to other weight loss agents or their combinations have not been reported with sibutramine, presumably because its mechanism of action differs from these other agents. Sibutramine may result in dangerous elevations in blood pressure or heart rate, thus these parameters should be monitored and sibutramine should not be prescribed to patients with uncontrolled or poorly controlled hypertension or uncontrolled or poorly controlled hypertension. The systematic review's analysis of sibutramine's versus placebo's effect on change in blood pressure and heart rate reported in "high-quality" clinical trials found that the mean difference in change in systolic and diastolic blood pressure and heart rate increased with the duration of use. In trials lasting 44 to 54 weeks, the mean differences in change (sibutramine – placebo) in systolic and diastolic blood pressure were increases of 4.6 mm Hg and 2.6 mm Hg, respectively, while heart increased 5. 9 beats per minute. Two clinical trials with a combined enrollment of 394 subjects found no difference between sibutramine and placebo in the incidence of valvular disease based on echocardiogram findings. (See Contraindications).

Common Adverse Events

Table 6. Adverse events reported by ≥2% of patients treated with sibutramine and more often than patients taking placebo.

Adverse Event	Sibutramine (n=2068) % Incidence	Placebo (n=884) % Incidence
Headache	30.3	18.6
Dry mouth	17.2	4.2
Anorexia	13.0	3.5
Constipation	11.5	6.0
Insomnia	10.7	4.5
Rhinitis	10.2	7.1
Pharyngitis	10.0	8.4
Increased appetite	8.7	2.7
Back pain	8.2	5.5
Flu syndrome	8.2	5.8
Dizziness	7.0	3.4
Accidental injury	5.9	4.1
Asthenia	5.9	5.3

Nausea	5.9	2.8
Arthralgia	5.9	5.0
Nervousness	5.2	2.9
Dyspepsia	5.0	2.6
Sinusitis	5.0	2.6
Abdominal pain	4.5	3.6
Anxiety	4.5	3.4
Depression	4.3	2.5
Cough increase	3.8	3.3
Rash	3.8	2.5
Dysmenorrhea	3.5	1.4
Tachycardia	2.6	0.6
Sweating	2.5	0.9
Vasodilation	2.4	0.9
Migraine	2.4	2.0
Urinary tract infection	2.3	2.0
Taste perversion	2.2	0.8
Hypertension/increased BP	2.1	0.9
Palpitation	2.0	0.8
Paresthesia	2.0	0.5

Other Adverse Events

In clinical trials, seizures were reported in 0.1% (3/2068; 2 of the three had risk factors for seizures) of patients randomized to sibutramine and 0/884 patients taking placebo. Bruising was reported in 0.7% and 0.2% of patients taking sibutramine and placebo, respectively. One case of acute interstitial nephritis has been reported in a patient taking sibutramine. Abnormal liver function tests have been reported sporadically with sibutramine. Cases of depression and suicidal ideation have been reported rarely, there does not appear to be a direct link between the use of sibutramine and these events. Sibutramine has been reported to impair memory and cognitive function. Hypersensitivity reactions including urticaria, mild skin eruptions, angioedema and anaphylaxis have been reported.

Tolerability

According to sibutramine's package insert, 9% of patients taking sibutramine (n=2068) in placebo-controlled trials with withdrew due to adverse events compared to 7% of those taking placebo (n=884).

Precautions/Contraindications[2]

Sibutramine is a schedule C-IV agent. It is recommended only for obese patients with a body mass index $\geq$30 kg/m^2 or $\geq$27 kg/m^2 in the presence of other risk factors such as hypertension, diabetes and/or dyslipidemia.

Precautions

Pregnancy Category C. The use of sibutramine by women during pregnancy is not recommended. It is not known if sibutramine is excreted into breast milk and thus not recommended for women who are breast feeding.

Use with caution in severe renal impairment of severe hepatic dysfunction, seizure disorder, hypertension, gallstones, narrow-angle glaucoma, nursing mothers, and elderly patients. Sibutramine has not been reported to cause primary pulmonary hypertension, but other anorexiants have, and it is possible that may share this potential risk, thus patients should be monitored.

Contraindications

Hypersensitivity to sibutramine or any component of the formulation during or within 2 weeks of a monoamine oxidase inhibitor, or centrally acting appetite suppressants; anorexia nervosa; uncontrolled or poorly controlled hypertension; congestive heart failure; coronary heart disease; conduction disorders; stroke; or concurrent use with agents affecting the serotonin system.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:
LA/SA for generic name Sibutramine: Imipramine, topiramate
LA/SA for trade name Meridia: Mexitil, meperidine

Drug Interactions[2]

Drug-Drug Interactions

The use of sibutramine with a monoamine oxidase inhibitor is contraindicated. The use of sibutramine in combination with other CNS agents that affect serotonin concentrations (e.g., SSRI antidepressants and the triptans) may increase the risk of serotonin syndrome and patients requiring these combinations should be monitored.

Sibutramine taken with other agents, such as pseudoephedrine, that may increase blood pressure and heart rate.

Concomitant use of sibutramine with ketoconazole and erythromycin, inhibitors of the cytochrome P450 3A4 isozyme, resulted in moderate to small increases in M_1 and M_2 maximum plasma concentrations (Cmax) and area-under-the-curve (AUC). Concurrent us with cimetidine resulted in small increases in M_1 and M_2 Cmax and AUC values that are unlikely to be of clinical significance.

The concurrent use of sibutramine and alcohol is not recommended.

Sibutramine was not found to interfere with the suppression of ovulation by oral contraceptives and additional contraceptive alternatives are not needed for women while taking sibutramine.

The impact of highly protein bound drugs on sibutramine's active metabolites is unknown.

Acquisition Costs

Table 7. Cost per day and annual cost for sibutramine and orlistat

Drug	Dose	Cost/Day/patient ($)	Cost/Year/patient ($)
Sibutramine capsule	5 mg daily	1.84	*
Sibutramine capsule	10 mg daily	1.83	667.95
Sibutramine capsule	15 mg daily	2.36	861.40
Orlistat capsule	120 mg three times a day	2.40	876.00

*not applicable since 5 mg is only used in dose titration

Pharmacoeconomic Analysis[7,10]

A pharmacoeconomic appraisal of sibutramine for obesity was performed by NICE in the UK in 2001. Based on the manufacturer's price of £35 per 28 tablets of 10 mg and £39 per 28 tablets of 15 mg estimated the following:

Table 8. Pharmacoeconomic analysis from NICE

Parameter	Estimated cost per QALY gained (£)
Overall	10,500
Decreased cardiac morbidity and mortality	42,000
Diabetes	77,000
Cardiovascular and diabetes	26,000
Weight loss	19,000

A cost-effectiveness analysis performed by VISN 22 as part of its drug class review in August 2003 estimated the cost of 1 patient to lose 5% or 10% of body weight in a 1 and 2 year period. Costs were based on an average annual cost of sibutramine 10 mg and 15 mg per day, $701.37. At 1-year, the number-needed-to-treat (NNT) for 1 patient to lose 5% of their body weight with sibutramine was 3 at a cost of

$1835 - $2373. At 2-years, the NNT was 4 at a total cost of $5610. The NNT to achieve a 10% weight loss at 1 year with sibutramine was 3 and 5 at a cost of $1835 and $3955, respectively. At 2-years the NNT was 4 with a total cost of $5610.

Conclusions

The use of sibutramine in combination with a reduced calorie diet results in modest weight loss after 1 or 2 years. Also, the percentage of patients achieving a 5% or 10% loss of body weight was greater with sibutramine. The probability of sustaining this weight loss is increased with continued use of sibutramine. The longest clinical trial experience with sibutramine is 2 years and the manufacturer does not recommend use beyond 2 years. Sibutramine has also demonstrated statistically significant improvements in metabolic parameters such as lipids and glycemic control. The significance of these changes, including sibutramine-attributed weight loss, on clinical outcomes such as mortality, cardiovascular events, stroke, and reduced medication burden for chronic illnesses is unknown.

In clinical trials 9% of patients withdrew do to adverse events compared to 7% with placebo. Insomnia, nausea, dry mouth and constipation were the most frequently reported adverse events. Sibutramine can increase blood pressure and heart rate and should be avoided in patients with uncontrolled hypertension or serious concurrent cardiovascular disease. A patient's blood pressure and heart rate should be monitored throughout treatment with sibutramine.

Middle-aged, caucasian, women accounted for a large majority of participants in sibutramine clinical trials and do not accurately represent the current VA population. As such extrapolation of the clinical trial data should be done cautiously. There is insufficient information on the dose and safety of sibutramine in persons age 65 years and older, hence it should be used cautiously in this age group.

Formulary Decision

- Sibutramine will remain off of the VA National and VISN Formularies.
- Prescribers from a MOVE program (or a similar multidisciplinary weight loss program) may prescribe sibutramine to patients meeting its criteria-for-use and they must complete a non-formulary request.
- All patients prescribed sibutramine must be enrolled in the VA PBM/Strategic Health safety registry.

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