Medical Management of Obesity in the Psychiatric Practice

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Excessive weight gain is a concern for most people, particularly patients who have psychiatric disorders. Many factors acting together contribute to obesity—including behavioral, environmental, psychological, genetic, and physiologic influences. Certain medications, such as antipsychotics and some antidepressants, can cause weight gain. Many clinicians consider excess body fat to be a cosmetic issue. However, obesity itself is a medical disease, comprising physical, biochemical, and psychological problems, and it must be managed along with one’s other diseases, including psychiatric disorders.1

Obesity Overview

For diagnosis, obesity is traditionally classified by body mass index (BMI) (Table 1). BMI is a simple tool that is useful for tracking a patient’s progress. However, a full assessment includes not only the extent of obesity but also the condition of the patient overall.2

Obesity can have many medical comorbidities. These include biomechanical complications such as stress on weight-bearing joints, as well as tissue compression (eg, sleep apnea and gastrointestinal reflux) and rashes. Additionally, excess adipose tissue can become dysfunctional and result in deranged endocrine and immune responses. This can lead to dyslipidemia, hypertension, diabetes, and other metabolic diseases.3

Across the US, the incidence of obesity among adults in the last 20 years has increased from about 22% to 35%.4 Among psychiatric patients in particular (eg, schizophrenia and depression), there is an even higher rate of obesity. One study found that 50% of female and 41% of male patients with severe mental illness were obese, compared to 27% of women and 20% of men in the matched comparison groups with no mental illness.5

Obesity in the Psychiatric Practice

There have been many connections observed between psychiatric disorders and obesity (Figure 1), and although causality is difficult to determine, the associations are striking. For example, epidemiologic studies have consistently found an association of binge eating disorder (BED) with obesity.6 In clinical samples, up to 74% of patients with recent BED are overweight or obese,7 and conversely, 30% of people seeking treatment for obesity have binge eating behavior.8 Simon et al demonstrated significant positive associations between obesity and a range of mood and anxiety disorders.9 One meta-analysis conducted by Luppino et al found bidirectional correlations between obesity and depression, such that obese persons have a 55% increased risk for onset of depression over time, and depressed adults have a 58% increased risk of becoming obese.10 Pagoto et al found a significant link between obesity and post-traumatic stress disorder (PTSD). Among patients with PTSD within one year prior to analysis, 32.6% were obese, compared to 24.1% of those with no PTSD.

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal Weight</td>
<td>18.5–24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0–29.9</td>
</tr>
<tr>
<td>Obesity (Class 1)</td>
<td>30.0–34.9</td>
</tr>
<tr>
<td>Obesity (Class 2)</td>
<td>35.0–39.9</td>
</tr>
<tr>
<td>Extreme Obesity (Class 3)</td>
<td>≥40</td>
</tr>
</tbody>
</table>

Table 1: Obesity Classifications

The content and funding for this supplement was provided by Eisai Inc. and was not reviewed by Psychiatric Times.
Abdominal obesity, along with high fasting glucose and triglycerides, low high-density lipoprotein (HDL) cholesterol, and hypertension, characterizes metabolic syndrome. Development of the syndrome increases the risk of cardiovascular disease, type 2 diabetes, and all-cause mortality. Puusniemi et al examined the chance of developing metabolic syndrome over 5–7 years of follow-up based on baseline level of psychological distress, assessed by the General Health Questionnaire (GHQ-12). They found that patients with high psychological distress at baseline were more than twice as likely to develop metabolic syndrome as those with low psychological distress. Subanalyses suggested that differences in health behaviors and demographic characteristics do not alone explain this connection, and the researchers hypothesize that inflammation caused by psychological distress could be mediating the development of metabolic syndrome. Not only are psychiatric disorders associated with obesity, but psychiatric medications may also cause weight gain. Many tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are associated with weight gain as a side effect. Some selective serotonin reuptake inhibitors (SSRIs) are associated with early minimal weight loss only to be followed by long-term weight gain; bupropion may be one of the only antidepressants routinely associated with modest weight loss. Furthermore, second-generation (atypical) antipsychotics may not only cause weight gain, but also appear in some cases to have an independent effect on glucose and lipid metabolism, putting patients who are using these medications at significant risk for developing obesity and metabolic syndrome.

While many psychiatrists monitor patients for weight gain and its associated health concerns, given the demonstrated risk of patients with psychiatric disorders for obesity, diabetes, and dyslipidemia, all psychiatricians should carefully monitor their patients for these conditions. In 2004, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity (now the Obesity Society) published a consensus statement on the connection between the use of antipsychotic drugs and obesity and diabetes. They advised close monitoring of weight and metabolic parameters, and stated that “patients’ psychiatric illness should not discourage clinicians from addressing the metabolic complications for which these patients are at increased risk.” Despite these statements, however, adherence to their recommendations to screen patients remains low.

**Treatment Options for Obesity**

For effective weight management, the treatment options should be tailored to each patient’s individual needs. These approaches include lifestyle modifications, behavioral therapy, pharmacotherapy, and bariatric surgery. The initial consideration for each treatment should be made based on the patient’s BMI (Table 2).

The basis of any treatment for obesity includes improved nutrition and increased physical activity, along with behavioral therapy. Behavioral therapy should include frequent encounters with a medical professional. Psychiatrists are uniquely positioned to provide behavioral therapy and ongoing support to their patients. Cognitive behavioral therapy can be effective to help patients lose weight initially; however, many physiological factors continue to challenge long-term weight maintenance. To overcome physiological factors, many guidelines recommend adding pharmacotherapy, such as lorcaserin, as an adjunct to lifestyle modification for chronic weight management.

Lorcaserin is a selective 5-HT<sub>2C</sub> receptor agonist that is believed to promote satiety via the proopiomelanocortin neurons in the hypothalamus. The exact mechanism of action is not known. Lorcaserin at the recommended daily dose selectively interacts with 5-HT<sub>2C</sub> receptors as compared to 5-HT<sub>1A</sub> and 5-HT<sub>2B</sub> receptors, 5-HT<sub>2C</sub> receptor subtypes, the 5-HT<sub>2B</sub> receptor transporter, and 5-HT<sub>2B</sub> receptors in the hypothalamus, but does not increase serotonin levels.

Lorcaserin is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m<sup>2</sup> or greater. Obese (BMI ≥ 35 kg/m<sup>2</sup>) or obese with comorbidities (Table 2).

### Warnings and Precautions

**Lorcaserin is a serotoninergic drug.** The development of potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)–like reactions have been reported during use of serotoninergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors, 5-HT<sub>2C</sub> receptor antagonists. Lorcaserin is a selective 5-HT<sub>2C</sub> receptor agonist that is believed to promote satiety via the proopiomelanocortin neurons in the hypothalamus. The exact mechanism of action is not known. Lorcaserin at the recommended daily dose selectively interacts with 5-HT<sub>2C</sub> receptors as compared to 5-HT<sub>1A</sub> and 5-HT<sub>2B</sub> receptors, 5-HT<sub>2C</sub> receptor subtypes, the 5-HT<sub>2B</sub> receptor transporter, and 5-HT<sub>2B</sub> receptors in the hypothalamus, but does not increase serotonin levels.

**Contraindications**

- Lorcaserin should not be taken during pregnancy or by women who are planning to become pregnant.

**Pharmacotherapy**

<table>
<thead>
<tr>
<th>BMI Category (kg/m&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>Diet, Physical Activity, and Behavioral Therapy</th>
<th>Pharmacotherapy</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight 25.0–26.9</td>
<td>Recommended with comorbidities</td>
<td>Recommended with comorbidities</td>
<td></td>
</tr>
<tr>
<td>27.0–29.9</td>
<td>Recommended</td>
<td>Recommended with comorbidities</td>
<td></td>
</tr>
<tr>
<td>30.0–34.9</td>
<td>Recommended</td>
<td>Recommended with comorbidities</td>
<td></td>
</tr>
<tr>
<td>Obese 35.0–39.9</td>
<td>Recommended</td>
<td>Recommended with comorbidities</td>
<td></td>
</tr>
<tr>
<td>40+</td>
<td>Recommended</td>
<td>Recommended with comorbidities</td>
<td></td>
</tr>
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</table>

**Table 2: National Guidelines for Treating Obesity**

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Clinical Trial Data With Lorcaserin

The safety and efficacy of lorcaserin for chronic weight management was studied in three long-term, Phase 3, randomized, double-blind, placebo-controlled trials. The primary efficacy parameter in all three trials was weight loss at one year, assessed by percent of patients achieving ≥5% and ≥10% weight loss and mean weight change. Secondary efficacy parameters included measurements of vital signs (blood pressure, heart rate), lipid parameters (HDL cholesterol, low-density lipoprotein [LDL] cholesterol, total cholesterol, triglycerides), and glycemic control (fasting glucose, fasting insulin, and, in patients with diabetes, hemoglobin A1c [HbA1c]).

Primary safety analysis included proportion of patients who developed new FDA-defined valvulopathy (mild or greater aortic valve regurgitation and/or moderate or greater mitral valve regurgitation) by Week 52.

Patients received lorcaserin 10 mg BID or matching placebo BID. Additionally, all patients in the three trials received lifestyle modification counseling (the Healthy Lifestyle Program). Patients received one-on-one instruction with the first dose of study medication and then every four weeks throughout the trials. Patients were advised to participate in moderate physical activity 30 minutes each day and to maintain a 600 kcal deficit based on individual estimates for daily energy requirements using World Health Organization criteria.

BLOOM and BLOSSOM

The BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management) and BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity Management) trials included adults (age 18–65 years) with a BMI of 30–45 kg/m², or a BMI of 27–29.9 kg/m² with at least one weight-related comorbid condition (hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea). Because the two trials were similarly designed, the data are pooled.

Among patients in the modified intent-to-treat population (mITT; all patients who received study medication and had a post-baseline measurement) using last-observation-carried-forward (LOCF) method, patients taking lorcaserin were more than twice as likely to lose ≥5% of their weight and more than 2.5 times more likely to lose ≥10% of their body weight than those taking placebo. Results were also calculated for completers, all patients who completed a full year of study participation (Figure 2). At Week 52, the mean weight loss was 5.8% with lorcaserin versus 2.5% with placebo in the mITT population (P<0.001); for completers, it was 8.0% with lorcaserin versus 3.7% with placebo. Response to therapy should be evaluated by Week 12. If a patient has not lost at least 5% of body weight, discontinue BELVIQ, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

Cardiometabolic parameters were also measured in the BLOOM and BLOSSOM trials (Table 3). Patients taking lorcaserin demonstrated greater improvement in systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, triglycerides, and fasting insulin compared to patients taking placebo. Other parameters, including blood pressure and heart rate, showed improvements consistent with what would be expected with weight loss in both groups.

LIMITATION OF USE

• The effect of lorcaserin on cardiovascular morbidity and mortality has not been established.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

• Patients should not take lorcaserin in combination with drugs that have been associated with valvular heart disease (eg, cabergoline). In clinical trials, 2.4% of patients taking lorcaserin and 2.0% of patients taking placebo developed valvular regurgitation: none of these patients were symptomatic. Lorcaserin should be used with caution in patients with congestive heart failure (CHF). Patients who develop signs and symptoms of valvular heart disease, including dyspnea, dependent edema, CHF, or a new cardiac murmur, should be evaluated and discontinuation of lorcaserin should be considered.

• Impairment in attention, memory, somnolence, confusion, and fatigue, have been reported in patients taking lorcaserin. Patients should not drive a car or operate heavy machinery until they know how lorcaserin affects them.

• The recommended dose of 10 mg twice daily should not be exceeded, as higher doses may cause the following: nausea, dry mouth, constipation, and dizziness. Patients may experience dizziness, lightheadedness, or syncope. If patients experience symptoms that are severe, persistent, or troublesome, immediately discontinue lorcaserin.

• Patients with a history of depression or bipolar disorder may be at increased risk for suicidal thoughts or behavior. Monitor patients closely during treatment and for any changes in mood, suicidal ideation, or behavior, and seek immediate medical evaluation if suicidal thoughts or behavior occur.

• Patients should be advised to report any new or worsening symptoms of depression or anxiety, suicidal thoughts or behaviors, to health care professionals immediately.

• Patients who develop suicidal thoughts or behaviors should be advised to stop taking lorcaserin and consult their health care provider immediately.

• Patients should be advised to avoid concurrent use of BELVIQ and warfarin, as there is a potential for drug interactions resulting in bleeding or an increased risk of thromboembolic events.

• Patients should not begin taking BELVIQ if they are pregnant or breast feeding.

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Please see additional Important Safety Information presented throughout this paper.
BLOOM 2-Year Data

Modest weight loss can be beneficial for many patients, but only as long as it is maintained. Weight maintenance, however, is extremely difficult for many patients and lost weight is often regained over time. Relapse or success is often attributed to the patient’s ability to adhere to the behavioral modifications he/she adopted to initially lose weight, but there are several potential mechanisms driving this behavior. Psychological factors believed to be associated with successful weight maintenance include:22

- Achieving a predetermined goal weight
- Successful coping strategies and problem-solving skills to deal with stressful situations
- Self-confidence in ability to control weight and food intake
- Vigilance in maintaining improved nutrition and physical activity
- Assessing efforts versus benefits of weight loss and maintenance

These attitudes and techniques should be encouraged regularly when managing patients requiring chronic weight treatment.22 Additionally, there are physiological factors to consider that complicate long-term weight maintenance. Biological changes that occur with weight loss and that can promote weight regain include changes in adipose cellularity, changes in energy metabolism, and altered neuroendocrine function. One potential result of these changes in endocrine function is decreased satiety and increased hunger.28

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Using Lorcaserin in Patients With Psychiatric Disorders

Lorcaserin is not contraindicated in patients with psychiatric disorders or in concomitant use with antidepressants or antipsychotics.21 However, there are some special considerations when using lorcaserin in this patient population. In patients taking lorcaserin with other serotonergic agents (eg, SSRIs, SNRIs, TCAs, MAOIs, lithium, bupropion, triptans, desomorphine), extreme caution and careful observation is advised for the development of potentially life-threatening serotonin syndrome. Symptoms of serotonin syndrome may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia and incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuations in vital signs, and mental status changes.21 The onset of serotonin syndrome is usually rapid and often accompanies the initial use, overdose, or dosing change of a medication that causes serotonin excess. Treatment with lorcaserin and any concomitant serotonergic or antidepressant agents should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated.21

Patients using SSRIs, SNRIs, TCAs, and MAOIs were excluded from the clinical trials with lorcaserin, but triptans and desomorphine were permitted. 2% and 1% of patients without diabetes and overweight patients with diabetes, respectively, used triptans concurrently; 15% and 12% of patients without diabetes and overweight patients with diabetes, respectively, used desomorphine concurrently at some point during clinical trials. Two patients treated with lorcaserin experienced a constellation of symptoms consistent with serotonin excess, including one patient on concomitant desomorphine who reported an adverse event of serotonin syndrome.21

Some drugs that target the central nervous system have been associated with depression or suicidal ideation.21 Patients with a recent history of BED, major depression, anxiety, or other psychiatric disorders requiring prescription medication were excluded from clinical trials.21 Patients were assessed using the Beck Depression Inventory-II at baseline and throughout the trials, and patients were monitored for new psychiatric events.21 2.6% of patients taking lorcaserin and 2.4% of patients taking placebo experienced depression or mood problems, and suicidal ideation occurred in 0.6% of patients taking lorcaserin and 0.4% of patients taking placebo. 1.3% and 0.6% of patients on lorcaserin and placebo, respectively, discontinued treatment due to depression-, mood-, or suicidal ideation-related events. All patients taking lorcaserin should be monitored for the emergence or worsening of depression, suicidal ideation, and/or any unusual changes in mood or behavior, and lorcaserin should be discontinued if they occur.21

BLOOM-DM

Over 85% of patients with type 2 diabetes are overweight or obese. However, it is even more difficult for patients with type 2 diabetes to lose weight than those without diabetes. The BLOOM-DM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) trial was prospectively designed to study the safety and efficacy of lorcaserin for chronic weight management in patients with type 2 diabetes.26

Patients in BLOOM-DM were adults (age 18–65 years) with a BMI of 27–45 kg/m² and poorly controlled type 2 diabetes (HbA1c 7%–10%). All patients were being treated with metformin, a sulfonylurea, or both.26

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Please see additional Important Safety Information presented throughout this paper.
Among patients in the mITT population using LOCF method, patients taking lorcaserin were more than twice as likely to lose ≥5% of their weight and nearly four times more likely to lose ≥10% of their body weight than those taking placebo. Patients in both groups showed improvements in most of these parameters consistent with changes that typically accompany weight loss (Table 4). An important consideration for patients with diabetes is improvement in glycemic control along with weight loss. In BLOOM-DM, patients in the mITT population taking lorcaserin demonstrated a 0.9% decrease in HbA1c levels and a 27.4 mg/dL decrease in fasting plasma glucose levels, compared to 0.4% and 11.9 mg/dL reductions, respectively, in patients taking placebo (Figure 5). Additionally, vital signs, lipid measurements, and waist circumference were assessed. Patients who completed a full year of study participation (Figure 4). Results were also calculated for completer patients (Figure 4).
Safety Assessment

Across all clinical trials of at least 1 year in duration, 6686 patients were evaluated, including 506 patients with type 2 diabetes. The overall discontinuation rate due to adverse reactions among patients taking lorcaserin (N=3451) was 8.6%, compared to 6.7% among those taking placebo (N=3437). The most common adverse reactions leading to discontinuation were more often among patients treated with lorcaserin than placebo: headache (1.3% versus 0.8%), depression (0.9% versus 0.5%), and dizziness (0.7% versus 0.2%).21 The overall most common adverse reactions among patients without diabetes and overweight patients with diabetes are shown in Tables 5 and 6. A key safety endpoint in all three trials was evaluation of valvular heart disease. Concentrations of lorcaserin is selective for the 5-HT2C receptor as compared to the 5-HT1A receptor. The incidence of FDA-defined valvulopathy (mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation) was assessed at Week 52; the incidence in patients taking lorcaserin was 2.4% and in patients taking placebo was 2.0%. None of these cases were symptomatic. The pooled relative risk of FDA-defined valvulopathy at Week 52 was 1.16 (95% Confidence Interval: 0.81–1.67) for lorcaserin versus placebo.21

### Table 5: Most Common Adverse Reactions in Patients Without Diabetes

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Lorcaserin (N=256)</th>
<th>Placebo (N=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16.8%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8.5%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7.2%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8.3%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>5.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Constipation</td>
<td>5.8%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

*Any patient with blood sugar ≤65 mg/dL with symptoms. Not all patients received the additional prevention intervention.

### Table 6: Most Common Adverse Reactions in Overweight Patients With Diabetes

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Lorcaserin (N=256)</th>
<th>Placebo (N=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>29.3%</td>
<td>21.0%</td>
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<tr>
<td>Symptomatic*</td>
<td>7.4%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Headache</td>
<td>14.5%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>11.7%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Cough</td>
<td>8.2%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7.4%</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

*Any patient with blood sugar ≤65 mg/dL with symptoms. Not all patients required the administration of any rescue therapy.

Summary

Obesity is correlated with many psychiatric disorders, including but not limited to BED, depression, anxiety, PTSD, and bipolar disorder.20,21 and should be managed along with these diseases. Initiation of a weight management treatment plan is essential for any overweight or obese patient, including those with psychiatric disorders. Lifestyle modification and behavioral therapy are components of chronic weight management, but lorcaserin may be an appropriate adjunctive therapy for patients who are obese or overweight with weight-related comorbid conditions.24 Lorcaserin has a novel mechanism of action that is believed to promote satiety, although the exact mechanism of action is not known. In clinical trials, all patients received lifestyle modification counseling, and compared to patients taking placebo, patients taking lorcaserin demonstrated greater weight loss at Year 1 and improved weight maintenance at Year 2.21 Patients taking lorcaserin also showed significant improvements in glycemic control at Year 1, with HbA1C reduction of 0.5% versus 0.4%, with placebo (P<0.001).25 The most common adverse reactions of lorcaserin versus placebo in patients without diabetes were headache, dizziness, fatigue, nausea, dry mouth, and constipation; in patients with diabetes they were hypoglycemia, headache, back pain, cough, and fatigue.21 As with many medications, special considerations should be taken when using lorcaserin in patients with psychiatric disorders.

### IMPORTANT SAFETY INFORMATION

**Warning and Precautions**

- Patients should not take lorcaserin in combination with drugs that have been associated with valvular heart disease (eg, cabergoline). In clinical trials, 2.4% of patients taking lorcaserin and 2.0% of patients taking placebo developed valvular regurgitation; none of these patients were symptomatic. Lorcaserin should be used with caution in patients with congestive heart failure (CHF). Patients who develop signs and symptoms of valvular heart disease, including dyspnea, dependent edema, CHF, or a new cardiac murmur, should be evaluated and discontinuation of lorcaserin should be considered.

**Nursing Mothers**

- Lorcaserin should not be taken by women who are nursing.

Lorcaserin is a federally controlled substance (CIV) because it may be abused or lead to dependence. Please see additional Important Safety Information presented throughout this paper.

For more information about BELVIQ®, please see accompanying full Prescribing Information.