The prevalence of obesity in the United States has increased to epidemic proportions over the past several decades. National Health and Nutrition Examination Survey (NHANES) data from 2009 - 2010 indicate that 35.7%, or more than one-third, of US adults are obese. The rising rate of obesity is not limited just to the US, as worldwide obesity has doubled since 1980. In fact, global estimates from the World Health Organization (WHO) suggest that in 2008, more than 1.4 billion adults were overweight, and of these, approximately 500 million were obese.

Obesity, defined as a body mass index (BMI) ≥ 30kg/m², is associated with significant morbidity and mortality. Obesity can lead to the development of a number of medical conditions, including type 2 diabetes, dyslipidemia, cardiovascular disease, hypertension, osteoarthritis, sleep apnea, and some cancers. Being overweight or obese results in an estimated 2.8 million or more adult deaths worldwide each year. In addition to the increased risk of adverse health effects, obesity also results in a significant financial burden. In the US, obesity-related medical costs were estimated at $147 billion in 2008 and medical costs in 2006 were $1,429 higher for an obese patient compared to a patient of normal weight.

The currently recommended initial weight loss target is a 10% reduction in body weight over a period of six months. However, even a weight loss of ≥5% may be associated with an improvement in lipid levels, glucose control, and blood pressure control, with potential reductions in cardiovascular disease. Obesity is considered a chronic disease, and successful treatment requires a lifelong effort. However, despite the chronic nature and associated costs of the disease, there are limited long-term pharmacological options available. Until recently, orlistat was the only FDA-approved agent for long-term treatment of obesity.

On June 27, 2012, the FDA approved lorcaserin hydrochloride for chronic weight management, when used in conjunction with a reduced-calorie diet and increased physical activity. Lorcaserin is the first drug to be approved by the FDA for the treatment of obesity in 13 years, since orlistat was approved in 1999. Lorcaserin is approved for use in adults with BMI ≥30kg/m² or a BMI ≥27kg/m² with at least one weight-related comorbid condition, such as hypertension, type

**Editor’s Summary: Lorcaserin (Belviq®)**

**Description & Indication**
- Selective serotonin 2C (5-HT₂C) receptor agonist
- Approved for the treatment of weight-loss in combination with lifestyle and dietary modifications

**Dosing**
- 10 mg orally twice daily
- No dose-adjustments specified for renal or hepatic impairment, but use with caution in CrCL 30-50 mL/min; not studied in severe renal or hepatic impairment

**Efficacy**
- ~3 kg placebo-subtracted weight loss over 1 year with lorcaserin + lifestyle modifications; approximately 50% of users achieve ≥ 5% weight loss from baseline (vs. ~20% for placebo)
- Modest improvements in secondary surrogate markers

**Safety**
- Generally well-tolerated; headache and nasopharyngitis were the most commonly-reported adverse effects in clinical trials; no long-term (>2 yr) CV safety data
2 diabetes, or dyslipidemia.\textsuperscript{9,10} Lorcaserin is available as a 10 mg tablet, marketed under the brand name Belviq® manufactured by Arena Pharmaceuticals, and distributed by Eisai Inc.\textsuperscript{9} The purpose of this article is to discuss the pharmacology, relevant clinical studies, safety and tolerability of lorcaserin.

**PHARMACOLOGY & PHARMACOKINETICS**

**Mechanism of Action**

Lorcaserin is a selective serotonin 2C (5-HT\textsubscript{2C}) receptor agonist.\textsuperscript{10} Agents that promote serotonin release, inhibit serotonin reuptake, or interact with serotonin receptors can lead to weight loss by promoting pre- and post-meal satiety and reducing meal size and caloric intake.\textsuperscript{11} Previous weight loss agents with serotonin properties include sibutramine (a serotonin/norepinephrine inhibitor) and fenfluramine/dexfenfluramine (enhanced serotonin release and receptor agonist).\textsuperscript{11}

Although the exact mechanism of action of lorcaserin has not yet been fully elucidated, lorcaserin appears to decrease food consumption and promote satiety by mimicking the effects of serotonin at the 5-HT\textsubscript{2C} receptors located in the hypothalamus.\textsuperscript{2,10,11} Serotonin acts at 5-HT\textsubscript{2C} receptors on pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus, which causes the release of \(\alpha\)-melanocyte stimulating hormone (\(\alpha\)-MSH). \(\alpha\)-MSH subsequently activates melanocortin-4 receptors (MC\textsubscript{4}R), known modulators of appetite, on neurons in the hypothalamic paraventricular nucleus. These neurons communicate with the dorsal vagal complex in the brainstem to relay these signals to the periphery to control food intake and energy balance.\textsuperscript{11}

**Pharmacokinetics**

The clinical pharmacokinetic (PK) properties of lorcaserin are highlighted in Table 1. Population PK modeling indicate that a patient’s gender, race, and BMI do not affect lorcaserin exposure.\textsuperscript{11} Of note, lorcaserin is approximately 70\% bound to plasma proteins and undergoes extensive metabolism in the liver by multiple enzymatic pathways. The major circulating metabolite is lorcaserin sulfamate, which is not active at serotonin receptors. The major metabolite in the urine is N-carbamoyl glucuronide lorcaserin.\textsuperscript{10,11}

**DRUG INTERACTIONS**

Lorcaserin is a cytochrome P450 (CYP) 2D6 inhibitor and therefore, should be used with caution when administered with CYP 2D6 substrates. Co-administration of lorcaserin with medications that are CYP 2D6 substrates can result in increased exposure of these medications.\textsuperscript{10} Table 2 lists some common CYP 2D6 substrates.\textsuperscript{10,12}

Since lorcaserin is a serotonergic drug, caution is recommended when using it with other medications that may affect the serotonergic neurotransmitter systems due to the theoretical potential for serotonin syndrome.\textsuperscript{10} Table 2 lists serotonergic agents that may interact with lorcaserin.\textsuperscript{10}

**CLINICAL TRIALS**

The efficacy and safety of lorcaserin was evaluated in three phase III, randomized, double-blind, placebo-controlled trials, BLOOM, BLOSSOM, and BLOOM-DM, with more than 7,000 patients enrolled overall. The studies ranged in duration from 52-104 weeks.\textsuperscript{13-15} BLOOM and BLOSSOM included adult patients who were either obese (BMI 30-45 kg/m\textsuperscript{2}) regardless of weight-related comorbidities, or overweight (BMI 27-29.9 kg/m\textsuperscript{2}) with at least one weight-related comorbid condition, such as hypertension, dyslipidemia, cardiovascular disease, impaired glucose intolerance, or sleep apnea. BLOOM-DM was designed to specifically evaluate the use of lorcaserin in patients with type 2 diabetes and as such, included adult type 2 diabetic pa-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical pharmacokinetic properties of lorcaserin.\textsuperscript{8,10,11}</th>
</tr>
</thead>
</table>
| **Absorption** | **C\textsubscript{max}: 46.0 ng/mL**  
\textsuperscript{Tmax: 1.5 – 2 hours}  
**Effect of food: High-fat, high calorie meal delays \textsuperscript{Tmax} by 1 hour** |
| **Distribution** | **Vd: 252 L**  
**Protein binding: \textasciitilde 70\%** |
| **Metabolism** | **Extensively metabolized in the liver by multiple enzymatic pathways.**  
**The principal metabolites are not active at serotonin receptors** |
| **Elimination** | **t\textsubscript{1/2}: \textasciitilde 11 hours**  
**Metabolites are mainly excreted in the urine (92.3\%) and to a lesser extent in the feces (2.2\%).** |

\(C\textsubscript{max} = \text{maximum concentration}; T\textsubscript{max} = \text{Time to maximum concentration}; Vd = \text{volume of distribution}; t\textsubscript{1/2} = \text{half-life}
patients with a BMI 27-45 kg/m², who were taking metformin, a sulfonylurea, or both.13-15

BLOOM evaluated lorcaserin 10mg BID versus placebo, whereas BLOSSOM and BLOOM-DM evaluated different dose ranges of lorcaserin 10mg, specifically once daily and twice daily, versus placebo. In addition to the study medications, all patients received nutritional and physical exercise counseling at each study visit, which included instructions to exercise moderately for 30 minutes each day and to reduce their daily caloric intake by 600 kcal below their individual estimated energy requirements.13-15

All three trials had the same co-primary endpoints: (1) the proportion of patients with a reduction in the baseline body weight of ≥5%; (2) the change in weight between baseline and the end of year 1; and (3) the proportion of patients with a reduction in the baseline body weight of ≥10%. Study design, inclusion criteria, treatment arms, primary endpoints, and results are summarized in Table 3 and Table 4.13-15

BLOOM

The Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trial was a two-year trial assessing the efficacy and safety of lorcaserin for weight loss and weight loss maintenance, when used in conjunction with lifestyle modification.13

In year one of the BLOOM study, patients were randomly assigned in a 1:1 fashion to receive lorcaserin 10 mg or placebo twice daily, in addition to standardized nutritional and exercise counseling. Patients remaining in the trial at the end of year one were eligible to continue in the study for a second year. In year two, patients who previously received placebo, continued with placebo therapy, and those who received lorcaserin in year one were once again randomly assigned in a 2:1 fashion to continue with lorcaserin 10 mg twice daily or to switch to placebo. A total of 3,182 patients were fully enrolled in year one. The baseline characteristics between each treatment group appeared to be well-matched. Of note, the mean age of patients in the trial was 44 years, the mean BMI was 36 kg/m², and 83% were female. The primary efficacy analysis used an intention-to-treat population with the last observation carried forward for missing values. Dropout rates for year one were high, with the rate of completion being 55.4% in the lorcaserin group and 45.1% in the placebo group. At the end of year one, significantly more patients lost ≥5% of their baseline body weight in the lorcaserin group (47.5%) compared with placebo (20.3%) (p<0.001). In addition, more patients lost ≥10% of their baseline body weight with lorcaserin (22.6%) compared to placebo (7.7%) (p<0.001). With respect to weight change from baseline, patients lost significantly more weight in the lorcaserin group (average of 5.8 kg) compared to placebo (average of 2.2 kg) (p<0.001).

A total of 1553 patients from year one continued in the trial to year two. The second year of the BLOOM study was designed to evaluate the use of lorcaserin for weight loss maintenance. The primary endpoint for year two of the study was the proportion of patients who had a reduction in the baseline body weight of 5% or more at the end of year one and who maintained the reduction during year two. Of the patients who achieved a ≥5% weight loss in year one, significantly more patients maintained the weight loss with lorcaserin (67.9%) compared to those who were re-assigned to placebo (50.3%) (p<0.001).

Significant improvements in several key secondary outcomes were seen with lorcaserin when compared with placebo, including mean reductions in waist circumference and BMI, improvements in systolic and diastolic blood pressure, improvements in total and LDL-cholesterol, improvements in triglycerides, and improvements in fasting glucose, insulin resistance, and A1c levels.

BLOSSOM

The Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM) trial was a one year study assessing the efficacy and safety of differing strengths of lorcaserin in promoting weight loss in obese patients and at-risk overweight patients, when combined with a nutritional and physical exercise program.14 Patients were randomly assigned in a 2:1:2 fashion to receive either lorcaserin 10 mg twice daily,
Table 3 | Comparison of lorcaserin phase III clinical trials.13-15

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Inclusion Criteria</th>
<th>Treatment Groups</th>
<th>Primary Endpoints</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLOOM13</td>
<td>Phase III</td>
<td>Ages 18-65</td>
<td>Lorcaserin 10mg BID (n=1538)</td>
<td>Year 1: Proportion of patients achieving ≥5% reduction in baseline body weight at the end of year 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Randomized</td>
<td>BMI 30-45 kg/m² or BMI 27-45 kg/m² with at least 1 co-existing condition (HTN, dyslipidemia, CVD, IGT, or sleep apnea)</td>
<td>Placebo (n=1587)</td>
<td>Change in weight</td>
<td>Year 1: Significantly more patients lost ≥5% of their baseline body weight with lorcaserin (47.5%) when compared to placebo (20.3%) (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Placebo-controlled</td>
<td>Able to participate in moderate intensity exercise</td>
<td>Year 2: Lorcaserin 10mg BID in years 1 &amp; 2 (n=573)</td>
<td>Proportion of patients achieving ≥10% reduction in baseline body weight</td>
<td>Year 2: Weight loss was maintained in more patients who received lorcaserin (67.9%) during the second year of the trial compared to placebo (50.3%) (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Double-blind</td>
<td></td>
<td>Lorcaserin 10mg BID in year 1, placebo in year 2 (n=283)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multicenter</td>
<td></td>
<td>Placebo in year 1 &amp; 2 (n=697)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: 2 years</td>
<td></td>
<td>All treatment groups underwent diet and exercise counseling</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 3,182</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLOSSOM14</td>
<td>Phase III</td>
<td>Ages 18-65</td>
<td>Lorcaserin 10mg BID (n=1602)</td>
<td>Year 1: Proportion of patients achieving ≥5% reduction in baseline body weight at the end of year 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Randomized</td>
<td>BMI 30-45kg/m² or BMI 27-29.9kg/m² with at least 1 co-existing condition (HTN, dyslipidemia, CVD, IGT, or sleep apnea)</td>
<td>Placebo (n=1601)</td>
<td>Change in weight</td>
<td>Year 2: Proportion of patients achieving ≥10% reduction in baseline body weight</td>
</tr>
<tr>
<td></td>
<td>Placebo-controlled</td>
<td>Able to participate in moderate intensity exercise</td>
<td>All treatment groups underwent diet and exercise counseling</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Double-blind</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multicenter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: 1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 4,008</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLOOM-DM15</td>
<td>Phase III</td>
<td>Ages 18-65</td>
<td>Lorcaserin 10mg BID (n=256)</td>
<td>Year 1: Proportion of patients achieving ≥5% reduction in baseline body weight at the end of year 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Randomized</td>
<td>BMI 27-45 kg/m²</td>
<td>Lorcaserin 10mg QD + placebo QD (n=95)</td>
<td>Change in weight</td>
<td>Year 2: Proportion of patients achieving ≥10% reduction in baseline body weight</td>
</tr>
<tr>
<td></td>
<td>Placebo-controlled</td>
<td>Type II DM</td>
<td>Placebo BID (n=252)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Double-blind</td>
<td>Baseline treatment with metformin, SFU, or both</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multicenter</td>
<td>A1c 7-10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: 1 year</td>
<td>Able to participate in moderate intensity exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 604</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI = body mass index; HTN = hypertension; CVD = cardiovascular disease; IGT = impaired glucose tolerance; SFU = sulfonylurea; A1c = glycated hemoglobin
Results of primary and key secondary endpoints for lorcaserin phase III clinical trials.

### Table 4 | Results of primary and key secondary endpoints for lorcaserin phase III clinical trials.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>BLOOM 10 mg BID</th>
<th>PCB</th>
<th>P-value</th>
<th>L 10 mg BID</th>
<th>L 10 mg QD</th>
<th>PCB</th>
<th>P-value</th>
<th>L 10 mg BID</th>
<th>L 10 mg QD</th>
<th>PCB</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥5% LBW (%)</td>
<td>47.5</td>
<td>20.3</td>
<td>&lt;0.001</td>
<td>47.2</td>
<td>40.2</td>
<td>25.0</td>
<td>&lt;0.001</td>
<td>37.5</td>
<td>44.7</td>
<td>16.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight change (kg)</td>
<td>-5.8±0.2</td>
<td>-2.2±0.1</td>
<td>&lt;0.001</td>
<td>-5.8</td>
<td>-4.7</td>
<td>-2.9</td>
<td>&lt;0.001</td>
<td>-4.7±0.4</td>
<td>-5.0±0.6</td>
<td>-1.6±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥10% LBW (%)</td>
<td>22.6</td>
<td>7.7</td>
<td>&lt;0.001</td>
<td>22.6</td>
<td>17.4</td>
<td>9.7</td>
<td>&lt;0.001</td>
<td>16.3</td>
<td>18.1</td>
<td>4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>-6.8±0.2</td>
<td>-3.9±0.2</td>
<td>&lt;0.001</td>
<td>-6.3</td>
<td>-5.8</td>
<td>-4.1</td>
<td>&lt;0.001</td>
<td>-5.5±0.5</td>
<td>-5.0±0.8</td>
<td>-3.3±0.5</td>
<td>0.001  0.053</td>
</tr>
<tr>
<td>BMI</td>
<td>-2.09±0.06</td>
<td>-0.78±0.05</td>
<td>&lt;0.001</td>
<td>-2.1</td>
<td>-1.7</td>
<td>-1.0</td>
<td>&lt;0.001</td>
<td>-1.6±0.1</td>
<td>-1.7±0.2</td>
<td>-0.6±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>1.4±0.3</td>
<td>0.8±0.3</td>
<td>0.04</td>
<td>1.3</td>
<td>-1.2</td>
<td>0.9</td>
<td>NS</td>
<td>-0.8±0.8</td>
<td>0.56±1.3</td>
<td>-0.9±0.9</td>
<td>0.891  0.288</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>-1.1±0.2</td>
<td>-0.6±0.2</td>
<td>0.01</td>
<td>-1.1</td>
<td>-1.4</td>
<td>0.3</td>
<td>NS</td>
<td>-1.1±0.6</td>
<td>0.29±0.9</td>
<td>-0.7±0.6</td>
<td>0.563  0.317</td>
</tr>
<tr>
<td>Total cholesterol(%)</td>
<td>0.9±0.3</td>
<td>0.57±0.34</td>
<td>0.001</td>
<td>0.7±0.34</td>
<td>0.8±0.34</td>
<td>0.3</td>
<td>NS</td>
<td>0.3±0.3</td>
<td>0.7±1.1</td>
<td>0.1±1.2</td>
<td>0.714  0.423</td>
</tr>
<tr>
<td>LDL-cholesterol (%)</td>
<td>2.87±0.56</td>
<td>4.03±0.58</td>
<td>0.049</td>
<td>5.1±0.6</td>
<td>4.2±1.1</td>
<td>1.1</td>
<td>NS</td>
<td>4.6±2.6</td>
<td>4.4±1.6</td>
<td>3.1±0.6</td>
<td>0.001  0.108</td>
</tr>
<tr>
<td>HDL-cholesterol (%)</td>
<td>0.05±0.33</td>
<td>-0.21±0.34</td>
<td>0.72</td>
<td>3.7±1.3</td>
<td>3.5±1.3</td>
<td>1.3</td>
<td>&lt;0.001</td>
<td>0.05±0.33</td>
<td>0.44±1.6</td>
<td>1.6±1.0</td>
<td>0.05  0.108</td>
</tr>
<tr>
<td>Triglycerides (%)</td>
<td>-0.15±0.13</td>
<td>-0.14±0.99</td>
<td>&lt;0.001</td>
<td>-4.3</td>
<td>-5.5</td>
<td>-0.9</td>
<td>0.02</td>
<td>&lt;0.01</td>
<td>-10.7±2.4</td>
<td>-5.5±3.8</td>
<td>0.054  0.866</td>
</tr>
<tr>
<td>FBG (mg/dL)</td>
<td>0.0±0.3</td>
<td>1.1±0.3</td>
<td>&lt;0.001</td>
<td>-0.7±0.34</td>
<td>-0.8±0.34</td>
<td>0.6</td>
<td>ND</td>
<td>-0.9±0.06</td>
<td>-1.0±0.9</td>
<td>-0.4±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>-0.04±0.01</td>
<td>0.03±0.01</td>
<td>&lt;0.001</td>
<td>-0.19</td>
<td>-0.17</td>
<td>-0.14</td>
<td>ND</td>
<td>-0.9±0.06</td>
<td>-1.0±0.9</td>
<td>-0.4±0.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LBW = low of body weight; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL = low density lipoprotein; HDL = high density lipoprotein; FBG = fasting blood glucose; A1c = glycated hemoglobin; L = lorcaserin; BID = twice daily; QD = once daily; PCB = placebo.

*P-value for lorcaserin BID group vs. placebo.
†P-value for lorcaserin QD group vs. placebo.

**Note:** The mean age of patients in the trial was 52.8 years, the mean BMI was 36 kg/m² in each treatment group, and 604 patients were enrolled. The baseline characteristics between all three treatment groups appeared to be well-matched. On average, the mean age of patients completing the trial was 52.8 years, the mean BMI was 36 kg/m², and 604 patients were enrolled. The baseline characteristics between all three treatment groups appeared to be well-matched.
m², 54.6% were female, and the mean A1c was 8.1%. The primary efficacy analysis used a modified intention-to-treat population, which included all patients who took at least one dose of the study medication and had at least one post-baseline weight measurement recorded. The overall study dropout rate was 36%.

At the end of one year, significantly more patients achieved a ≥5% weight loss with lorcaserin 10 mg BID (37.5%) and lorcaserin QD (44.7%) compared to placebo (16.1%) (p<0.001 for the comparison of both lorcaserin groups to placebo). In addition, significantly more patients achieved a ≥10% weight loss with lorcaserin 10 mg BID (16.3%) and lorcaserin QD (18.1%) compared to placebo (4.4%) (p<0.001 for the comparison of both lorcaserin groups to placebo). The percentage change in weight loss was also significantly greater with lorcaserin BID (4.5%) and lorcaserin QD (5.0%) compared to placebo (1.5%) (p<0.001 for the comparison of both lorcaserin groups to placebo).

Glycemic control was evaluated as a secondary outcome in the BLOOM-DM trial and included such parameters as A1c, fasting plasma glucose, fasting insulin, and insulin resistance as measured by the HOMA-IR. Of note, at the end of one year, both the A1c and the mean fasting plasma glucose decreased significantly more in both lorcaserin groups compared to placebo. In addition, insulin resistance was significantly improved in the lorcaserin BID group compared with placebo. Although the difference was not statistically significant, more patients in the lorcaserin BID group (17.2%) and lorcaserin 10mg QD group (23.4%) decreased their overall use of oral anti-diabetic medications when compared to placebo (11.7%) (p=0.087 for the comparison of lorcaserin to placebo) and less patients in the lorcaserin groups increased their total daily dose of anti-diabetic medications compared with placebo (13.5% in the lorcaserin BID group and 11.7% in the lorcaserin QD group versus 22.2% in the placebo group; p=0.011 for the comparison of lorcaserin to placebo).

While the BLOSSOM study showed that lorcaserin was associated with a dose-dependent weight loss, this was not seen in the BLOOM-DM study, where there was similar efficacy between both the once daily and twice daily lorcaserin doses.

Safety & Adverse Effects

Adverse Effects

In all three clinical trials, lorcaserin appeared to be well-tolerated. In the BLOOM study, 7.1% of lorcaserin-treated patients and 6.7% of placebo patients withdrew from the trial due to adverse events, with more lorcaserin withdrawals due to headache and dizziness. In the BLOSSOM study, withdrawals due to adverse events were more common in the lorcaserin BID group (7.2%) and QD group (6.2%) compared to placebo (4.6%). Withdrawal rates due to adverse events were not reported for the BLOOM-DM study. Overall, the most common adverse events in non-diabetic patients included upper respiratory tract infections, headache, nausea, dizziness, fatigue, constipation, and dry mouth. The most common adverse events in diabetic patients included hypoglycemia, headache, back pain, nasopharyngitis, cough, fatigue, and nausea.

Table 5 provides a summary of adverse events reported in BLOOM and BLOSSOM, whereas Table 6 provides a summary of adverse events reported in BLOOM-DM.

Contraindications

Lorcaserin has a FDA pregnancy category of X. The use of lorcaserin is contraindicated during pregnancy as the risk outweighs the benefit for the majority of patients. In animal reproductive studies, there was no evidence of teratogenicity or embryolethality with lorcaserin. However, when rats were exposed to lorcaserin late in pregnancy, their offspring had lower body weights which persisted into adulthood.

Warnings and Precautions

Warnings and precautions associated with lorcaserin include a risk of serotonin syndrome or neuroleptic malignant syndrome-like reactions (described under drug interactions), valvular heart disease, cognitive impairment, psychiatric disorders, hypoglycemia, priapism, heart rate decreases, hematological changes, prolactin elevation, and pulmonary hypertension. Table 7 describes warnings and precautions associated with lorcaserin.

Dosing & Administration

The recommended dose of lorcaserin is 10 mg taken orally twice daily, with or without food. All patients should be evaluated at week 12 for their response to lorcaserin therapy. Lorcaserin should be discontinued if the patient has not lost at least 5% of baseline bodyweight by week 12, as it is unlikely that continued treatment will result in the patient achieving and sustaining clinically meaningful weight loss.

In patients with mild renal impairment (CrCl 50-80 mL/min), no dose adjustments are required. Lorcaserin should be used with caution in patients with moderate to severe renal impairment.
ate renal impairment (CrCl 30-50 mL/min). The use of lorcaserin in patients with severe renal impairment (CrCl <30 mL/min) or end-stage renal disease is not recommended. In patients with mild (Child-Pugh score 5-6) or moderate (Child-Pugh score 7-9) hepatic impairment, no dose adjustments are required. Lorcaserin should be used with caution in patients with severe hepatic impairment, as the effect of severe hepatic impairment during lorcaserin therapy has not been evaluated.

### CLINICAL CONSIDERATIONS

Although lorcaserin met the FDA guidance to be considered effective for weight management and subsequently received FDA approval, vast weight loss differences between patients receiving lorcaserin and those receiving placebo were not seen in the phase III clinical trials. Furthermore, as all of the Phase III clinical trials compared lorcaserin to placebo, head-to-head trials comparing lorcaserin to other agents indicated for the long-term treatment of weight loss, such as orlistat or phentermine/topiramate, are lacking. Therefore, making comparisons between these agents is difficult.

Certain patient populations were not included in phase III clinical trials of lorcaserin, including patients younger than 18 years, patients older than 65 years, and patients with a BMI >45 kg/m². In addition, patients were excluded from the phase III clinical trials if they had valvulopathy, blood pressure >140/90 mm Hg, or depression. Therefore, the efficacy and safety of lorcaserin in these patient populations is not known.

Previous serotonergic weight loss drugs, such as fenfluramine and dexfenfluramine, were non-selective. These agents were subsequently removed from the market after reports of serious adverse events, including valvular heart disease and an increased risk of pulmonary hypertension, thought to be related to activation of the 5-HT₂B receptor, which is mostly found in the cardiovascular system. At recommended doses, lorcaserin is selective for the 5-HT₂C receptor. However, the FDA has required that an additional randomized, double-blind, placebo-controlled trial be conducted to evaluate the effect of long-term treatment with lorcaserin on the incidence of major adverse cardiovas-
<table>
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<th>Table 7</th>
<th>Warnings and precautions associated with lorcaserin.¹⁰</th>
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**Valvular Heart Disease**
- Previous serotonergic weight loss drugs with 5-HT₂B receptor activity were reported to cause regurgitant cardiac valvular disease. Lorcaserin is a selective 5-HT₂C receptor agonist at therapeutic concentrations, as compared to 5-HT₂B receptors. Clinical trials of lorcaserin showed that 2.4% of patients receiving lorcaserin and 2.0% of patients receiving placebo developed echocardiographic criteria for valvular regurgitation.
- Caution should be used when using lorcaserin in patients with congestive heart failure (CHF), as lorcaserin has not been studied in patients with CHF and it is thought that 5-HT2B receptors may be overexpressed in CHF.
- Lorcaserin should not be used concomitantly with other potent 5-HT2B receptor serotonergic and dopaminergic drugs known to increase the risk for cardiac valvulopathy, such as cabergoline.
- Any patient who develops signs and symptoms of valvular heart disease with taking lorcaserin should be evaluated and consideration given to discontinuing treatment.

**Cognitive Impairments**
- Attention and memory impairments were reported to occur in 1.9% of patients receiving lorcaserin and 0.5% of patients receiving placebo. In addition, confusion, somnolence, and fatigue were also associated with lorcaserin.
- Due to the potential to impair cognitive function, lorcaserin should be used with caution in patients operating hazardous machinery, including automobiles, until they are certain how they will react to lorcaserin.

**Psychiatric Disorders**
- Supratherapeutic doses of lorcaserin in short-term studies were associated with events of euphoria, hallucinations, and dissociation. In clinical trials, 6 patients receiving lorcaserin (0.2%) and 1 patient (<0.1%) in the placebo group developed euphoria.
- Doses of lorcaserin should not exceed 10mg BID.
- Patients receiving lorcaserin should be monitored for emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Lorcaserin should be discontinued in patients experiencing suicidal thoughts or behaviors.

**Hypoglycemia**
- The risk of hypoglycemia may be increased in T2D patients who experience weight loss and are also using insulin and/or insulin secretagogues. Hypoglycemia was observed in clinical trials of diabetic patients receiving lorcaserin.
- In patients with T2D, blood glucose levels should be measured prior to initiating and during lorcaserin therapy. For patients who develop hypoglycemia while taking lorcaserin, changes may need to be made to their diabetic drug regimen.

**Priapism**
- Priapism is a potential effect of 5-HT₂C receptor agonism.
- Men experiencing an erection lasting greater than 4 hours, whether painful or not, should immediately discontinue the drug and seek emergency medical attention.
- Use lorcaserin with caution in men with conditions that might predispose them to experiencing priapism (e.g., sickle cell anemia, multiple myeloma, or leukemia), or in men with anatomical deformation of the penis (e.g., angulation, cavernosal fibrosis, or Peyronie’s disease).
- The combination of lorcaserin and medications used for erectile dysfunction (e.g., phosphodiesterase type 5 inhibitors) should be used with caution, as there is limited experience with the combination.

**Heart Rate Decreases**
- Lorcaserin decreased heart rate (HR) more than placebo in clinical trials. In addition, incidence of patients with HR less than 50bpm was higher in the lorcaserin group compared with placebo.
- In patients with bradycardia or a history of heart block greater than first degree, lorcaserin should be used with caution.

**Hematological Changes**
- Decreases in white blood cell counts and red blood cell counts were seen in clinical trials of lorcaserin.
- Periodic monitoring of CBC should be considered while receiving lorcaserin.

**Prolactin Elevation**
- Lorcaserin has been shown to moderately elevate prolactin levels.
- When signs and symptoms of prolactin excess are suspected (e.g., galactorrhea, gynecomastia), prolactin should be measured.

**Pulmonary Hypertension**
- Some previous serotonergic weight loss drugs were associated with the development of pulmonary hypertension. Due to the low incidence of pulmonary hypertension, it is not known whether lorcaserin may increase this risk.
cular events in obese and overweight patients with cardiovascular disease or multiple cardiovascular risk factors. It should also be noted that each of the trials had large drop-out rates, although historically, weight loss trials have been plagued with large drop-out rates.

Although lorcaserin has been approved by the FDA, it is not yet available on the market and the cost of lorcaserin is not known at this time. Supratherapeutic doses of lorcaserin were shown to produce responses similar to zolpidem and ketamine in a human abuse potential study in recreational drug abusers. Given this potential for abuse with lorcaserin, the Drug Enforcement Agency must make a ruling on the final scheduling designation of lorcaserin. Lorcaserin will not be available for sale in the US until the DEA makes its final decision.

**CONCLUSIONS**

Lorcaserin is a new weight loss agent with a novel mechanism of action. The results of three phase III clinical trials demonstrate that treatment with lorcaserin achieves statistically significant weight loss when compared to placebo, in both diabetic and non-diabetic patients. Furthermore, results from year two of the BLOOM trial showed that lorcaserin was effective in maintaining weight loss. In addition, lorcaserin appeared to be well tolerated in all three clinical trials. The recommended dose of lorcaserin is 10 mg taken orally twice daily, with or without food. Consideration should be given to discontinuing lorcaserin if the patient has not lost at least 5% of baseline bodyweight by week 12. Lorcaserin is a CYP 2D6 inhibitor and should be used with caution when administered with CYP 2D6 substrates, as increased exposure of these medications may occur. Caution is also recommended when using lorcaserin with other serotoninergic drugs as there may be a risk of serotonin syndrome. Other warnings and precautions to take into consideration with lorcaserin include valvular heart disease, cognitive impairments, psychiatric disorders, hypoglycemia, priapism, heart rate decreases, hematological changes, prolactin elevation, and pulmonary hypertension.

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Antibiotics cause diarrhea by reducing the concentration of fecal anaerobes that are normally present, thus altering the balance of normal flora. As a result, the metabolism of carbohydrates and the breakdown of bile acids are decreased, possibly causing osmotic diarrhea and reduced colonic secretory agents, respectively. Neither mechanism is clearly established as a cause of AAD; however, the efficacy of enemas in treating this problem suggests that changes in fecal flora are a contributing factor. In addition, the alteration of normal fecal flora leads to a loss of colonization resistance, predisposing the gut to colonization by potentially pathogenic microbes, such as *Clostridium difficile*.

Probiotics are live microorganisms present in various forms of food products, and in formulations used for specific therapeutic purposes. Probiotics are thought to be effective for preventing and treating AAD by restoring the normal flora and thereby rebuilding the GI tract’s resistance to colonization by pathogenic bacteria. Probiotics are thought to work by breaking down non-absorbable compounds into absorbable products, inhibiting pathogenic toxins, and by enhancing immunity. Effects of probiotics appear to vary by strain and depend on each strain’s resistance to gastric acid and bile, ability to colonize the GI mucosa, and susceptibility to antibiotics.

For a probiotic to be beneficial in preventing AAD, certain characteristics are desirable. In order to minimize risks and prevent AAD, a probiotic must be non-pathogenic and be able to destroy or replace pathogenic bacteria. Some probiotics work to inhibit pathogenic bacteria through competition of nutrients, adhering to the bacteria, enhancing immune function thereby preventing bacterial replication, or inhibiting bacterial growth. Importantly, probiotics should have a fairly rapid onset of action and be resilient to gastric acid, bile, and concurrent antibiotics. Two probiotic organisms that have been shown to display these common properties include *Saccharomyces boulardii* and lactobacilli.

Over the last twenty-five years, there has been increased interest in probiotic interventions for the treatment and prevention of AAD. Here we review the evidence supporting the use of probiotics for the prevention of ADD in the adult outpatient population.

**Efficacy for Preventing AAD**

Four meta-analyses and one recent randomized controlled trial have found probiotics to be beneficial for the prevention of AAD. These studies conflict with the findings from two randomized controlled trials that found probiotics were not efficacious in preventing AAD.

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**Probiotics for the Prevention of Antibiotic Associated Diarrhea in Adult Patients**

Amanda Romine-Nelson, PharmD Candidate
A meta-analysis on probiotic use for AAD included 25 randomized, placebo controlled trials. Sixteen of the RCTs evaluated adults while the other nine trials evaluated children. The trials included 2,656 inpatient and outpatient patients taking one or more of the following broad spectrum antibiotics: ampicillin, amoxicillin, and cephalosporin with or without clindamycin and a cephalosporin. The duration of antibiotic therapy was at least seven days. Exclusion criteria included initiation of an antibiotic greater than 48 hours after enrollment, ongoing diarrhea, and recent consumption of probiotics. The types of probiotics used varied from single strains (Saccharomyces boulardii, Lactobacillus rhamnosus GG, Bifidobacterium longum, Clostridium butyricum miyairir, Lactobacillus acidophilus, Enterococcus faecium SF68), to mixtures of any two of these probiotics. On average across the 25 trials, 18.5% of patients experienced AAD in the probiotic treatment groups compared to 36.6% of patients in the placebo groups.

This meta-analysis showed that participants assigned to probiotics had a 57% lower risk of developing AAD than placebo (RR 0.43; 95% CI 0.31-0.58; P<0.001).

A meta-analysis of 9 randomized, double blind, placebo controlled trials included 1214 patients. Two of the nine studies investigated the effects of antibiotics in children. The other seven trials evaluated inpatient and outpatient adults who were being treated with one or more of the following antibiotics: ampicillin, amoxicillin, clindamycin, and cephalosporins for at least seven days duration of therapy. Exclusion criteria included initiation of antibiotic greater than 48 hours prior to enrollment, ongoing diarrhea, recent consumption of probiotics, and inability to ingest capsules. Four trials used the probiotic organism Saccharomyces boulardii, four used lactobacilli, and one used a strain of enterococcus that produced lactic acid. Three of the nine trials used a combination of probiotic strains for a given bacteria species.

On average across the 9 trials, 15.9% of patients experienced AAD in the probiotic treatment group compared to 29.7% of patients in the placebo group. This meta-analysis showed that participants assigned to probiotics had significantly lower odds of developing AAD than participants in the control groups (OR 0.37; 95% CI 0.26-0.53; P<0.001). When considering the effect based on specific probiotic, the odds ratios were 0.39 (95% CI 0.25-0.62; P<0.001) for the probiotic organism Saccharomyces boulardii and 0.34 (95% CI 0.19-0.61; P<0.01) for Lactobacillus spp. In contrast, the Enterococcus SF68 spp was similar to placebo in preventing AAD (OR 0.25; 95% CI 0.05-1.43 P>0.05). Another meta-analysis of 7 randomized, placebo controlled trials of 881 patients also favored the use of the Saccharomyces boulardii and Lactobacillus spp probiotics for the prevention of AAD. Two of the seven studies included children while the other five were comprised of inpatient and outpatient adults. In these trials, patients were treated with one or more of the following antibiotics: clarithromycin, ampicillin, penicillin, clindamycin, a cephalosporin, and a beta-lactam. Three of these trials assessed the occurrence of AAD with Saccharomyces boulardii, whereas the other four evaluated the Lactobacillus spp. Overall, the meta-analysis found that probiotic supplementation was beneficial for preventing AAD. On average across the 7 trials, 7% of patients experienced AAD in the probiotic treatment group compared to 19.2% of patients in the placebo group. Participants assigned to probiotics had a significantly lower risk of developing AAD than placebo (RR 0.3966; 95% CI 0.27-0.57).

The most recent meta-analysis, evaluating probiotics for the prevention of AAD reviewed 63 randomized controlled double blind and unblended trials involving 11,811 participants. Subjects in the trials were in different patient settings, received a variety of probiotic strains, had diverse diagnoses, and received a variety of antibiotics. Participants assigned to probiotics had a 42 percent lower risk of developing AAD than participants in the control groups (RR 0.58; 95% CI 0.50-0.68), translating to a number needed to treat to prevent one case of antibiotic-associated diarrhea of 13.

A recent randomized double-blind placebo controlled trial evaluated the effect of a multispecies probiotic on the composition and metabolic activity of the intestinal microbiota and bowel habits in healthy volunteers taking amoxicillin. Forty-one healthy volunteers were given 500 mg amoxicillin twice daily for 7 days and were randomly assigned to either 5 gm of a multispecies probiotic containing 10 different probiotic strains, (Ecologic® AAD [109 cfu/gm]), or placebo twice daily for 14 days. Feces and questionnaires were collected on days 0, 7, 14, and 63. The feces was analyzed for the composition of the intestinal microbiota, and β-glucosidase activity, endotoxin concentration, Cladostocium difficile toxin A, short chain fatty acids (SCFAs), and pH. Bowel movements were scored according to the Bristol stool form. The study found no difference in the composition of the intestinal microbiota between the probiotic and the placebo groups, with the exception of a significant increase in fecal enteroccci in the probiotic group. The mean number of enterococci increased significantly from 0.6128 at day 0 to 0.7634 (day 7) and 0.839 (day 14) cfu/gm feces.
(P<0.05) during probiotic intake. Although not the primary endpoint, patient reported bowel movement frequency and stool consistency were significantly improved in the probiotic group compared to the placebo group. The probiotic group reported a 52% decrease in bowel movement frequency and increased stool consistency during and after the use of antibiotics compared to the 21% reported decrease in the placebo group (P<0.05).14

In contrast to the aforementioned trials that found probiotics to be beneficial in preventing AAD, another randomized, placebo controlled trial evaluated the efficacy of *Lactobacillus plantarum* 299v for the prevention of AAD in adults.15 A total of 163 inpatient and outpatient adults randomly received a drink containing 1010 CFU of *L. plantarum* 299v or an identical-tasting placebo drink within 48 hours of antibiotic initiation. Participants ingested the test drink daily during the time they were being treated with either clindamycin, ampicillin, a cephalosporin, or a quinolone antibiotic. Subjects continued to receive probiotic or placebo until a week after termination of their respective antibiotic treatment. The participants recorded the number and consistency of stools as well as gastrointestinal symptoms until up to 3 weeks after the last intake of test drink. The study found no difference in AAD between the treatment (6%) and placebo (7.5%) groups. However, treatment with *L. plantarum* 299v was associated with a decreased risk of developing at least one episode of loose or watery stools compared with placebo (OR 0.69; 95% CI 0.52-0.92; P=0.012).15

Similarly, another randomized, double blind placebo controlled trial found no benefit with the use of *Saccharomyces boulardii* to prevent AAD.16 This study, in ambulatory adults being treated with amoxicillin for 5 to 10 days, included eighty-six adults with acute infectious diseases, (excluding those arising in the gastrointestinal tract). Forty-one patients were randomly assigned to receive lyophilized *Saccharomyces boulardii* (500 mg/day) for 12 days, and 45 patients were assigned to placebo for the same period, regardless of antibiotic duration. The authors reported that a total of 10.4% of patients (9/86) reported acute diarrhea: 9.8% (4/41) in the treatment group and 11.1% (5/45) in the control group (P=0.10 for the comparison between groups).16

### SAFETY OF PROBIOTICS

Although probiotics are generally recognized as safe, fungemia, bacteremia and sepsis have been reported with the use of commercially available probiotics.26-29 Specifically, *S. boulardii* has been associated with fungemia in a case report.26 There are also reports of *Saccharomyces fungemia* occurring in immunocompromised patients receiving enteral *S. boulardii*, which suggests that this therapy should be avoided in such patients.27 Similarly, *Lactobacillus rhamnosus* and other lactobacilli have also been associated with bacteremia and sepsis, particularly in patients with severe underlying illness.28,29

### ADDITIONAL CLINICAL CONSIDERATIONS

Evidence suggests probiotics are beneficial in preventing AAD. Most trials of probiotics for AAD report diarrhea in around 15% to 20% of placebo-treated patients, with around 25% to 50% reduction in diarrhea with probiotic therapy compared with placebo.30 However, all studies to date have had significant limitations. All but one study to date considered multiple different antibiotics and probiotic regimens, limiting the ability to support the use of a specific probiotic regimen to prevent AAD. Although limited, there is evidence supporting the use of *Saccharomyces boulardii* and *Lactobacillus* probiotics, specifically for the prevention of AAD in adults and children. Further, the type of infection necessitating treatment also varied within the studies, which may limit the generalizability of the findings. One reason for the difference in findings between the studies may be that higher doses were used in the studies that found probiotics to be beneficial and lower doses were used in the studies that found probiotics to not be beneficial for preventing AAD. In general, it has been found that probiotics ranging from 100 billion CFU to 1.8 trillion CFU per day have greater efficacy in preventing AAD compared to lower doses.31,32 In addition, these studies show a lack of consistency in the study population and probiotic treatment regimen. Finally, there are limited studies available that evaluate the use of probiotics for the prevention of AAD in the adult outpatient population.

For patients who have previously had AAD, probiotics may be a reasonable treatment option in combination with subsequent courses of antibiotics, particularly those associated with a higher risk of AAD. Since probiotics appear to be more effective at higher doses,2,10,33 doses of at least 100 billion colony forming units should be used. Furthermore, consistent with literature to date, probiotics should be taken for the duration of antibiotic treatment and continued for one week thereafter.

The American Academy of Family Physicians states that probiotics are “safe and effective for preventing and treating antibiotic-associated diarrhea and..."
infectious diarrhea.” However, clinicians should consider patient-specific factors including previous response of a patient to antibiotic therapy and immune system status. Persons who are immunocompromised should avoid probiotics.

**CONCLUSION**

Currently, there is growing evidence to support using probiotics. However, given the limitations of the available evidence supporting the use of probiotics, as well as the relatively low incidence of AAD in otherwise healthy people, the use of probiotics for prevention of AAD should be limited to persons with past history of AAD. When used, probiotics should be given at higher doses, administered within 48 hours of antibiotic initiation and *S. boulardii* and *Lactococcus rhamnosus* GG (ATCC 53103) may be preferred, because there is more robust evidence supporting their efficacy. Further, probiotics should be avoided in persons who are immunocompromised. Finally, head-to-head studies comparing different probiotics and studies to identify groups of patients at greatest risk for AAD and who would most likely to benefit are needed to better understand the place in therapy for probiotics in the setting of AAD prevention.

**REFERENCES**


