CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022529Orig1s000

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BELVIQ safely and effectively. See full prescribing information for BELVIQ.

BELVIQ (lorcaserin hydrochloride) tablets, for oral use
Initial U.S. Approval: 2012

INDICATIONS AND USAGE

BELVIQ is a serotonin 2C receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese) (1) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition, (e.g., hypertension, dyslipidemia, type 2 diabetes) (1)

Limitations of Use:

- The safety and efficacy of coadministration with other products for weight loss have not been established (1)
- The effect of BELVIQ on cardiovascular morbidity and mortality has not been established (1)

DOSAGE AND ADMINISTRATION

- One tablet of 10 mg twice daily (2)
- Discontinue if 5% weight loss is not achieved by week 12 (2)

DOSAGE FORMS AND STRENGTHS

10 mg film-coated tablets (3)

CONTRAINDICATIONS

Pregnancy (4)

WARNINGS AND PRECAUTIONS

- Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions: The safety of coadministration with other serotonergic or antidopaminergic agents has not been established. Manage with immediate BELVIQ discontinuation and provide supportive treatment. (5.1)
- Valvular heart disease: If signs or symptoms develop consider BELVIQ discontinuation and evaluate the patient for possible valvulopathy. (5.2)
- Cognitive Impairment: May cause disturbances in attention or memory. Caution with use of hazardous machinery when starting BELVIQ treatment (5.3)
- Psychiatric Disorders, including euphoria and dissociation: Do not exceed recommended dose of 10 mg twice daily (5.4)
- Monitor for depression or suicidal thoughts. Discontinue if symptoms develop. (5.4)
- Use of Antidiabetic Medications: weight loss may cause hypoglycemia. Monitor blood glucose. BELVIQ has not been studied in patients taking insulin. (5.5)
- Priapism: Patients should seek emergency treatment if an erection lasts >4 hours. Use BELVIQ with caution in patients predisposed to priapism. (5.6)

ADVERSE REACTIONS

Most common adverse reactions (greater than 5%) in non-diabetic patients are headache, dizziness, fatigue, nausea, dry mouth, and constipation, and in diabetic patients are hypoglycemia, headache, back pain, cough, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 or FDA at 1-800-FDA-1088 or at *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Serotonergic drugs (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), triptans, bupropion, dextromethorphan, St. John's Wort): use with extreme caution due to the risk of serotonin syndrome. (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue drug or nursing. (8.3)
- Pediatric Use: Safety and effectiveness not established and use not recommended. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions
5.2 Valvular Heart Disease
5.3 Cognitive Impairment
5.4 Psychiatric Disorders
5.5 Potential Risk of Hypoglycemia in Patients with Type 2 Diabetes Mellitus on Anti-diabetic Therapy
5.6 Priapism
5.7 Heart Rate Decreases
5.8 Hematological Changes
5.9 Prolactin Elevation
5.10 Pulmonary Hypertension
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
7.1 Use with Other Agents that Affect Serotonin Pathways
7.2 Cytochrome P450 (2D6) substrates
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
9 DRUG ABUSE AND DEPENDENCE
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BELVIQ is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes)

[*see Dosage and Administration (2)*]

Limitations of Use:

- The safety and efficacy of coadministration of BELVIQ with other products intended for weight loss including prescription drugs (e.g., phentermine), over-the-counter drugs, and herbal preparations have not been established
- The effect of BELVIQ on cardiovascular morbidity and mortality has not been established

2 DOSAGE AND ADMINISTRATION

The recommended dose of BELVIQ is 10 mg administered orally twice daily. Do not exceed recommended dose [*see Warnings and Precautions (5.4) and Patient Counseling Information (17)*].

BELVIQ can be taken with or without food.

Response to therapy should be evaluated by week 12. If a patient has not lost at least 5% of baseline body weight, discontinue BELVIQ, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment [*see Clinical Studies (14)*].

BMI is calculated by dividing weight (in kg) by height (in meters) squared.

A BMI chart for height in inches and weight in pounds is provided below:

Table 1. BMI Conversion Chart

Weight	(lb)	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215	220	225
	(kg)	56. 8	59. 1	61. 4	63. 6	65. 9	68. 2	70. 5	72. 7	75. 0	77. 3	79. 5	81. 8	84. 1	86. 4	88. 6	90. 9	93. 2	95. 5	97. 7	100. 0	102. 3
Height																						
(in)	(cm)																					
58	147. 3	26	27	28	29	30	31	32	34	35	36	37	38	39	40	41	42	43	44	45	46	47
59	149. 9	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	43	44	45	46
60	152. 4	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
61	154. 9	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
62	157. 5	23	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	38	39	40	41
63	160. 0	22	23	24	25	26	27	28	28	29	30	31	32	33	34	35	36	36	37	38	39	40
64	162. 6	22	22	23	24	25	26	27	28	28	29	30	31	32	33	34	34	35	36	37	38	39
65	165. 1	21	22	23	23	24	25	26	27	28	28	29	30	31	32	33	33	34	35	36	37	38
66	167. 6	20	21	22	23	23	24	25	26	27	27	28	29	30	31	32	32	33	34	35	36	36
67	170. 2	20	20	21	22	23	24	24	25	26	27	27	28	29	30	31	31	32	33	34	35	35
68	172. 7	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	34	34
69	175. 3	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	33
70	177. 8	18	19	19	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	32	32
71	180. 3	17	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	31
72	182. 9	17	18	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31
73	185. 4	17	17	18	19	19	20	20	21	22	22	23	24	24	25	26	26	27	28	28	29	30
74	188. 0	16	17	17	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28	29
75	190. 5	16	16	17	18	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28
76	193. 0	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	24	25	26	26	27	27

3 DOSAGE FORMS AND STRENGTHS

BELVIQ is provided as blue, film-coated, 10 mg tablets. The tablets are round, biconvex, debossed with “A” on one side and “10” on the other side.

4 CONTRAINDICATIONS

- Pregnancy [*see Use in Specific Populations (8.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions

BELVIQ is a serotonergic drug. The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported during use of serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), bupropion, triptans, dietary supplements such as St. John’s Wort and tryptophan, drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs]), dextromethorphan, lithium, tramadol, antipsychotics or other dopamine antagonists, particularly when used in combination [*see Drug Interactions (7.1)*].

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g.,

hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., 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 fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The safety of BELVIQ when coadministered with other serotonergic or antidopaminergic agents, including antipsychotics, or drugs that impair metabolism of serotonin, including MAOIs, has not been systematically evaluated and has not been established.

If concomitant administration of BELVIQ with an agent that affects the serotonergic neurotransmitter system is clinically warranted, extreme caution and careful observation of the patient is advised, particularly during treatment initiation and dose increases. Treatment with BELVIQ and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated [*see Adverse Reactions (6.1) and Drug Interactions (7.1)*].

5.2 Valvular Heart Disease

Regurgitant cardiac valvular disease, primarily affecting the mitral and/or aortic valves, has been reported in patients who took serotonergic drugs with 5-HT_{2B} receptor agonist activity. The etiology of the regurgitant valvular disease is thought to be activation of 5-HT_{2B} receptors on cardiac interstitial cells. At therapeutic concentrations, BELVIQ is selective for 5-HT_{2C} receptors as compared to 5-HT_{2B} receptors. In clinical trials of 1-year duration, 2.4% of patients receiving BELVIQ and 2.0% of patients receiving placebo developed echocardiographic criteria for valvular regurgitation at one year (mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation): none of these patients was symptomatic [*see Adverse Reactions (6.1) see Clinical Pharmacology (12.1)*].

BELVIQ has not been studied in patients with congestive heart failure or hemodynamically-significant valvular heart disease. Preliminary data suggest that $5HT_{2B}$ receptors may be overexpressed in congestive heart failure, Therefore, BELVIQ should be used with caution in patients with congestive heart failure.

BELVIQ should not be used in combination with serotonergic and dopaminergic drugs that are potent 5-HT_{2B} receptor agonists and are known to increase the risk for cardiac valvulopathy (e.g., cabergoline).

Patients who develop signs or symptoms of valvular heart disease, including dyspnea, dependent edema, congestive heart failure, or a new cardiac murmur while being treated with BELVIQ should be evaluated and discontinuation of BELVIQ should be considered.

5.3 Cognitive Impairment

In clinical trials of at least one year in duration, impairments in attention and memory were reported adverse reactions associated with 1.9% of patients treated with BELVIQ and 0.5% of patients treated with placebo, and led to discontinuation in 0.3% and 0.1% of these patients, respectively. Other reported adverse reactions associated with BELVIQ in clinical trials included confusion, somnolence, and fatigue [*see Adverse Reactions (6.1)*].

Since BELVIQ has the potential to impair cognitive function, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that BELVIQ therapy does not affect them adversely [*see Patient Counseling Information (17)*].

5.4 Psychiatric Disorders

Events of euphoria, hallucination, and dissociation were seen with BELVIQ at supratherapeutic doses in short-term studies [*see Adverse Reactions (6.1), Drug Abuse and Dependence (9.2), and Overdosage (10)*]. In clinical trials of at least 1-year in duration, 6 patients (0.2%) treated with BELVIQ developed euphoria, as compared with 1 patient (<0.1%) treated with placebo. Doses of BELVIQ should not exceed 10 mg twice a day.

Some drugs that target the central nervous system have been associated with depression or suicidal ideation. Patients treated with BELVIQ should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue BELVIQ in patients who experience suicidal thoughts or behaviors [*see Adverse Reactions (6.1)*].

5.5 Potential Risk of Hypoglycemia in Patients with Type 2 Diabetes Mellitus on Anti-diabetic Therapy

Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (e.g., sulfonylureas); hypoglycemia was observed in clinical trials with BELVIQ. BELVIQ has not been studied in combination with insulin. Measurement of blood glucose levels prior to starting BELVIQ and during BELVIQ treatment is recommended in patients with type 2 diabetes. Decreases in medication doses for anti-diabetic medications which are non-glucose-dependent should be considered to mitigate the risk of hypoglycemia. If a patient develops hypoglycemia after starting BELVIQ, appropriate changes should be made to the anti-diabetic drug regimen [*see Adverse Reactions (6.1)*].

5.6 Priapism

Priapism (painful erections greater than 6 hours in duration) is a potential effect of 5-HT_{2C} receptor agonism.

If not treated promptly, priapism can result in irreversible damage to the erectile tissue. Men who have an erection lasting greater than 4 hours, whether painful or not, should immediately discontinue the drug and seek emergency medical attention.

BELVIQ should be used with caution in men who have conditions that might predispose them to 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). There is limited experience with the combination of BELVIQ and medication indicated for erectile dysfunction (e.g., phosphodiesterase type 5 inhibitors). Therefore, the combination of BELVIQ and these medications should be used with caution.

5.7 Heart Rate Decreases

In clinical trials of at least 1-year in duration, the mean change in heart rate (HR) was -1.2 beats per minute (bpm) in BELVIQ and -0.4 bpm in placebo-treated patients without diabetes and -2.0 beats per minute (bpm) in BELVIQ- and -0.4 bpm in placebo-treated patients with type 2 diabetes. The incidence of HR less than 50 bpm was 5.3% in BELVIQ and 3.2% in placebo-treated patients without diabetes and 3.6% in BELVIQ and 2.0% in placebo-treated patients with type 2 diabetes. In the combined population, adverse reactions of bradycardia occurred in 0.3% of BELVIQ and 0.1% of placebo-treated patients. Use with caution in patients with bradycardia or a history of heart block greater than first degree.

5.8 Hematological Changes

In clinical trials of at least one year in duration, adverse reactions of decreases in white blood cell count (including leukopenia, lymphopenia, neutropenia, and decreased white cell count) were reported in 0.4% of patients treated with BELVIQ as compared to 0.2% of patients treated with placebo. Adverse reactions of decreases in red blood cell count (including anemia and decreases in hemoglobin and hematocrit) were reported by 1.3% of patients treated with BELVIQ as compared to 1.2% treated with placebo [*see Adverse Reactions (6.1)*]. Consider periodic monitoring of complete blood count during treatment with BELVIQ.

5.9 Prolactin Elevation

Lorcaserin moderately elevates prolactin levels. In a subset of placebo-controlled clinical trials of at least one year in duration, elevations of prolactin greater than the upper limit of normal, two times the upper limit of normal, and five times the upper limit of normal, measured both before and 2 hours after dosing, occurred in 6.7%, 1.7%, and 0.1% of BELVIQ-treated patients and 4.8%, 0.8%, and 0.0% of placebo-treated patients, respectively [*see Adverse Reactions (6.1)*]. Prolactin should be measured when symptoms and signs of prolactin excess are suspected (e.g., galactorrhea, gynecomastia). There was one patient treated with BELVIQ who developed a prolactinoma during the trial. The relationship of BELVIQ to the prolactinoma in this patient is unknown.

5.10 Pulmonary Hypertension

Certain centrally-acting weight loss agents that act on the serotonin system have been associated with pulmonary hypertension, a rare but lethal disease. Because of the low incidence of this disease, the clinical trial experience with BELVIQ is inadequate to determine if BELVIQ increases the risk for pulmonary hypertension.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in labeling:

- Serotonin Syndrome or NMS-like Reactions [*see Warnings and Precautions (5.1)*]
- Valvular Heart Disease [*see Warnings and Precautions (5.2)*]
- Cognitive Impairment [*see Warnings and Precautions (5.3)*]
- Psychiatric Disorders [*see Warnings and Precautions (5.4)*]
- Hypoglycemia [*see Warnings and Precautions (5.5)*]
- Heart Rate Decreases [*see Warnings and Precautions (5.7)*]
- Hematological Changes [*see Warnings and Precautions (5.8)*]
- Prolactin Elevation [*see Warnings and Precautions (5.9)*]

6.1 Clinical Trials Experience

In the BELVIQ placebo-controlled clinical database of trials of at least one year in duration, of 6888 patients (3451 BELVIQ vs. 3437 placebo; age range 18-66 years, 79.3% women, 66.6% Caucasians, 19.2% Blacks, 11.8% Hispanics, 2.4% other, 7.4% type 2 diabetics), a total of 1969 patients were exposed to BELVIQ 10 mg twice daily for 1 year and 426 patients were exposed for 2 years.

In clinical trials of at least one year in duration, 8.6% of patients treated with BELVIQ prematurely discontinued treatment due to adverse reactions, compared with 6.7% of placebo-treated patients. The most

common adverse reactions leading to discontinuation more often among BELVIQ treated patients than placebo were headache (1.3% vs. 0.8%), depression (0.9% vs. 0.5%) and dizziness (0.7% vs. 0.2%).

Most Common Adverse Reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions for non-diabetic patients (greater than 5% and more commonly than placebo) treated with BELVIQ compared to placebo were headache, dizziness, fatigue, nausea, dry mouth, and constipation. The most common adverse reactions for diabetic patients were hypoglycemia, headache, back pain, cough, and fatigue. Adverse reactions that were reported by greater than or equal to 2% of patients and were more frequently reported by patients taking BELVIQ compared to placebo are summarized in Table 2 (non-diabetic subjects) and Table 3 (subjects with type 2 diabetes mellitus).

Table 2. Adverse Reactions Reported by Greater Than or Equal to 2% of BELVIQ Patients and More Commonly than with Placebo in Patients without Diabetes Mellitus

	Number of patients (%)	
Adverse Reaction	**BELVIQ 10 mg BID N=3195**	**Placebo N=3185**
Gastrointestinal Disorders		
Nausea	264 (8.3)	170 (5.3)
Diarrhea	207 (6.5)	179 (5.6)
Constipation	186 (5.8)	125 (3.9)
Dry mouth	169 (5.3)	74 (2.3)
Vomiting	122 (3.8)	83 (2.6)
General Disorders And Administration Site Conditions		
Fatigue	229 (7.2)	114 (3.6)
Infections And Infestations		
Upper respiratory tract infection	439 (13.7)	391 (12.3)
Nasopharyngitis	414 (13.0)	381 (12.0)
Urinary tract infection	207 (6.5)	171 (5.4)
Musculoskeletal And Connective Tissue Disorders		
Back pain	201 (6.3)	178 (5.6)
Musculoskeletal pain	65 (2.0)	43 (1.4)
Nervous System Disorders		
Headache	537 (16.8)	321 (10.1)
Dizziness	270 (8.5)	122 (3.8)
Respiratory, Thoracic And Mediastinal Disorders		
Cough	136 (4.3)	109 (3.4)
Oropharyngeal pain	111 (3.5)	80 (2.5)
Sinus congestion	93 (2.9)	78 (2.4)
Skin And Subcutaneous Tissue Disorders		
Rash	67 (2.1)	58 (1.8)

Table 3. Adverse Reactions Reported by Greater Than or Equal to 2% of BELVIQ Patients and More Commonly than with Placebo in Patients with Type 2 Diabetes Mellitus

	Number of patients (%)	
Adverse Reaction	**BELVIQ 10 mg BID N=256**	**Placebo N=252**
Gastrointestinal Disorders		
Nausea	24 (9.4)	20 (7.9)
Toothache	7 (2.7)	0
General Disorders And Administration Site Conditions		
Fatigue	19 (7.4)	10 (4.0)
Peripheral edema	12 (4.7)	6 (2.4)
Immune System Disorders		
Seasonal allergy	8 (3.1)	2 (0.8)
Infections And Infestations		
Nasopharyngitis	29 (11.3)	25 (9.9)
Urinary tract infection	23 (9.0)	15 (6.0)
Gastroenteritis	8 (3.1)	5 (2.0)
Metabolism And Nutrition Disorders		
Hypoglycemia	75 (29.3)	53 (21.0)
Worsening of diabetes mellitus	7 (2.7)	2 (0.8)
Decreased appetite	6 (2.3)	1 (0.4)
Musculoskeletal And Connective Tissue Disorders		
Back pain	30 (11.7)	20 (7.9)
Muscle spasms	12 (4.7)	9 (3.6)
Nervous System Disorders		
Headache	37 (14.5)	18 (7.1)
Dizziness	18 (7.0)	16 (6.3)
Psychiatric Disorders		
Anxiety	9 (3.5)	8 (3.2)
Insomnia	9 (3.5)	6 (2.4)
Stress	7 (2.7)	3 (1.2)
Depression	6 (2.3)	5 (2.0)
Respiratory, Thoracic And Mediastinal Disorders		
Cough	21 (8.2)	11 (4.4)
Vascular Disorders		
Hypertension	13 (5.1)	8 (3.2)

Other Adverse Reactions

Serotonin-associated Adverse Reactions

SSRIs, SNRIs, bupropion, tricyclic antidepressants, and MAOIs were excluded from the BELVIQ trials. Triptans and dextromethorphan were permitted: 2% and 15%, respectively, of patients without diabetes and 1% and 12%, respectively, of patients with type 2 diabetes experienced concomitant use at some point during the trials. Two patients treated with BELVIQ in the clinical program experienced a constellation of symptoms and signs consistent with serotonergic excess, including one patient on concomitant dextromethorphan who reported an event of serotonin syndrome. Some symptoms of possible serotonergic etiology that are included in the criteria for serotonin syndrome were reported by patients treated with BELVIQ and placebo during clinical trials of at least 1 year in duration. In both groups, chills were the most frequent of these events (1.0% vs. 0.2%, respectively), followed by tremor (0.3% vs. 0.2%), confusional state (0.2% vs. less than 0.1%), disorientation (0.1% vs. 0.1%) and hyperhidrosis (0.1% vs. 0.2%). Because serotonin syndrome has a very low incidence, an

association between BELVIQ and serotonin syndrome cannot be excluded on the basis of clinical trial results [*see Warnings and Precautions (*5.*1)*].

Hypoglycemia in Patients with Type 2 Diabetes

In a clinical trial of patients with type 2 diabetes mellitus, hypoglycemia requiring the assistance of another person occurred in 4 (1.6%) of BELVIQ-treated patients and in 1 (0.4%) placebo-treated patient. Of these 4 BELVIQ-treated patients, all were concomitantly using a sulfonylurea (with or without metformin). BELVIQ has not been studied in patients taking insulin. Hypoglycemia defined as blood sugar less than or equal to 65 mg/dL and with symptoms occurred in 19 (7.4%) BELVIQ-treated patients and 16 (6.3%) placebo-treated patients.

Cognitive Impairment

In clinical trials of at least 1-year duration, adverse reactions related to cognitive impairment (e.g., difficulty with concentration/attention, difficulty with memory, and confusion) occurred in 2.3% of patients taking BELVIQ and 0.7% of patients taking placebo.

Psychiatric Disorders

Psychiatric disorders leading to hospitalization or drug withdrawal occurred more frequently in patients treated with BELVIQ (2.2%) as compared to placebo (1.1%) in non-diabetic patients.

Euphoria. In short-term studies with healthy individuals, the incidence of euphoric mood following supratherapeutic doses of BELVIQ (40 and 60 mg) was increased as compared to placebo [*see Drug Abuse and Dependence (9.2)*]. In clinical trials of at least 1-year duration in obese patients, euphoria was observed in 0.17% of patients taking BELVIQ and 0.03% taking placebo.

Depression and Suicidality. In trials of at least one year in duration, reports of depression/mood problems occurred in 2.6% BELVIQ-treated vs. 2.4% placebo-treated and suicidal ideation occurred in 0.6% BELVIQ-treated vs. 0.4% placebo-treated patients. 1.3% of BELVIQ patients vs. 0.6% of placebo patients discontinued drug due to depression-, mood-, or suicidal ideation-related events.

Laboratory Abnormalities

Lymphocyte and Neutrophil Counts. In clinical trials of at least 1-year duration, lymphocyte counts were below the lower limit of normal in 12.2% of patients taking BELVIQ and 9.0% taking placebo, and neutrophil counts were low in 5.6% and 4.3%, respectively.

Hemoglobin. In clinical trials of at least 1-year duration, 10.4% of patients taking BELVIQ and 9.3% taking placebo had hemoglobin below the lower limit of normal at some point during the trials.

Prolactin. In clinical trials, elevations of prolactin greater than the upper limit of normal, two times the upper limit of normal, and five times the upper limit of normal, occurred in 6.7%, 1.7%, and 0.1% of BELVIQ-treated patients and 4.8%, 0.8%, and 0.0% of placebo-treated patients, respectively.

Eye disorders.

More patients on BELVIQ reported an eye disorder than patients on placebo in clinical trials of patients without diabetes (4.5% vs. 3.0%) and with type 2 diabetes (6.3% vs. 1.6%). In the population without diabetes, events of blurred vision, dry eye, and visual impairment occurred in BELVIQ-treated patients at an incidence greater than that of placebo. In the population with type 2 diabetes, visual disorders, conjunctival infections, irritations, and inflammations, ocular sensation disorders, and cataract conditions occurred in BELVIQ-treated patients at an incidence greater than placebo.

Echocardiographic Safety Assessments

The possible occurrence of regurgitant cardiac valve disease was prospectively evaluated in 7794 patients in three clinical trials of at least one year in duration, 3451 of whom took BELVIQ 10 mg twice daily. The primary echocardiographic safety parameter was the proportion of patients who developed echocardiographic criteria of mild or greater aortic insufficiency and/or moderate or greater mitral insufficiency from baseline to 1 year. At 1 year, 2.4% of patients who received BELVIQ and 2.0% of patients who received placebo developed valvular regurgitation. The relative risk for valvulopathy with BELVIQ is summarized in Table 4. BELVIQ was not studied in patients with congestive heart failure or hemodynamically-significant valvular heart disease [*see Warnings and Precautions (5.2)*].

Table 4. Incidence of FDA-Defined Valvulopathy at Week 52 by Treatment Group[1]

	Study 1		**Study 2**		**Study 3**	
	BELVIQ N=1278	**Placebo N=1191**	**BELVIQ N=1208**	**Placebo N=1153**	**BELVIQ N=210**	**Placebo N=209**
FDA-defined Valvulopathy, n (%)	34 (2.7)	28 (2.4)	24 (2.0)	23 (2.0)	6 (2.9)	1 (0.5)
Relative Risk (95% CI)	1.13 (0.69, 1.85)		1.00 (0.57, 1.75)		5.97 (0.73, 49.17)	
Pooled RR (95% CI)	**1.16 (0.81, 1.67)**					

[1] Patients without valvulopathy at baseline who received study medication and had a post-baseline echocardiogram; ITT-intention-to-treat; LOCF-last observation carried forward

7 DRUG INTERACTIONS

7.1 Use with Other Agents that Affect Serotonin Pathways

Based on the mechanism of action of BELVIQ and the theoretical potential for serotonin syndrome, use with extreme caution in combination with other drugs that may affect the serotonergic neurotransmitter systems, including, but not limited to, triptans, monoamine oxidase inhibitors (MAOIs, including linezolid, an antibiotic which is a reversible non-selective MAOI), selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), dextromethorphan, tricyclic antidepressants (TCAs), bupropion, lithium, tramadol, tryptophan, and St. John's Wort [*see Warnings and Precautions (5.1)*].

7.2 Cytochrome P450 (2D6) substrates

Use caution when administering BELVIQ together with drugs that are CYP 2D6 substrates, as BELVIQ can increase exposure of these drugs [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X.

Risk Summary

BELVIQ is contraindicated during pregnancy, because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. Maternal exposure to lorcaserin in late pregnancy in rats resulted in lower body weight in offspring which persisted to adulthood. If this drug is used during pregnancy, or if the patient

becomes pregnant while taking this drug, the patient should be apprised of the potential hazard of maternal weight loss to the fetus.

Clinical Considerations
A minimum weight gain, and no weight loss, is currently recommended for all pregnant women, including those who are already overweight or obese, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.

Animal Data
Reproduction studies were performed in pregnant rats and rabbits that were administered lorcaserin during the period of embryofetal organogenesis. Plasma exposures up to 44 and 19 times human exposure in rats and rabbits, respectively, did not reveal evidence of teratogenicity or embryolethality with lorcaserin hydrochloride.

In a pre- and postnatal development study, maternal rats were dosed from gestation through post-natal day 21 at 5, 15, and 50mg/kg lorcaserin; pups were indirectly exposed *in utero* and throughout lactation. The highest dose (~44 times human exposure) resulted in stillborns and lower pup viability. All doses lowered pup body weight similarly at birth which persisted to adulthood; however, no developmental abnormalities were observed and reproductive performance was not affected at any dose.

8.3 Nursing Mothers

It is not known whether BELVIQ is excreted in human milk. Because many drugs are excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of BELVIQ in pediatric patients below the age of 18 have not been established and the use of BELVIQ is not recommended in pediatric patients.

8.5 Geriatric Use

In the BELVIQ clinical trials, a total of 135 (2.5%) of the patients were 65 years of age and older. Clinical studies of BELVIQ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Since elderly patients have a higher incidence of renal impairment, use of BELVIQ in the elderly should be made on the basis of renal function [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*]. Elderly patients with normal renal function should require no dose adjustment.

8.6 Renal Impairment

No dose adjustment of BELVIQ is required in patients with mild renal impairment. Use BELVIQ with caution in patients with moderate renal impairment. Use of BELVIQ in patients with severe renal impairment or end stage renal disease is not recommended [*see Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

Dose adjustment is not required for patients with mild hepatic impairment (Child-Pugh score 5-6) to moderate hepatic impairment (Child-Pugh score 7-9). The effect of severe hepatic impairment on lorcaserin was not

evaluated. Use lorcaserin with caution in patients with severe hepatic impairment [*see Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.2 Abuse

In a human abuse potential study in recreational drug abusers, supratherapeutic oral doses of lorcaserin (40 and 60 mg) produced up to two- to six-fold increases on measures of “High”, “Good Drug Effects”, “Hallucinations” and “Sedation” compared to placebo. These responses were similar to those produced by oral administration of the positive control drugs, zolpidem (15 and 30 mg) and ketamine (100 mg). In this study, the incidence of the adverse reaction of euphoria following lorcaserin administration (40 and 60 mg; 19%) is similar to the incidence following zolpidem administration (13-16%), but less than the incidence following ketamine administration (50%). The duration of euphoria following lorcaserin administration persisted longer (> 9 hours) than that following zolpidem (1.5 hours) or ketamine (2.5 hours) administration.

Overall, in short-term studies with healthy individuals, the rate of euphoria following oral administration of lorcaserin was 16% following 40 mg (n = 11 of 70) and 19% following 60 mg (n = 6 of 31). However, in clinical studies with obese patients with durations of 4 weeks to 2 years, the incidence of euphoria and hallucinations following oral doses of lorcaserin up to 40 mg was low (< 1.0%).

9.3 Dependence

There are no data from well-conducted animal or human studies that evaluate whether lorcaserin can induce physical dependence, as evidenced by a withdrawal syndrome. However, the ability of lorcaserin to produce hallucinations, euphoria, and positive subjective responses at supratherapeutic doses suggests that lorcaserin may produce psychic dependence.

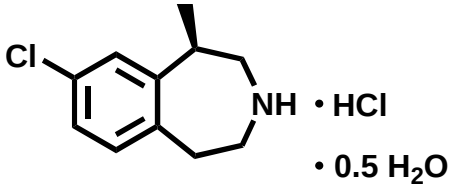
10 OVERDOSAGE

No experience with overdose of BELVIQ is available. In clinical studies that used doses that were higher than the recommended dose, the most frequent adverse reactions associated with BELVIQ were headache, nausea, abdominal discomfort, and dizziness. Single 40- and 60-mg doses of BELVIQ caused euphoria, altered mood, and hallucination in some subjects. Treatment of overdose should consist of BELVIQ discontinuation and general supportive measures in the management of overdosage. BELVIQ is not eliminated to a therapeutically significant degree by hemodialysis.

11 DESCRIPTION

BELVIQ (lorcaserin hydrochloride) is a serotonin 2C receptor agonist for oral administration used for chronic weight management. Its chemical name is (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride hemihydrate. The empirical formula is $C_{11}H_{15}Cl_2N{\cdot}0.5H_2O$, and the molecular weight of the hemihydrate form is 241.16 g/mol.

The structural formula is:



Lorcaserin hydrochloride hemihydrate is a white to off-white powder with solubility in water greater than 400 mg/mL. Each BELVIQ tablet contains 10.4 mg of crystalline lorcaserin hydrochloride hemihydrate, equivalent to 10.0 mg anhydrous lorcaserin hydrochloride, and the following inactive ingredients: silicified microcrystalline cellulose; hydroxypropyl cellulose NF; croscarmellose sodium NF; colloidal silicon dioxide NF, polyvinyl alcohol USP, polyethylene glycol NF, titanium dioxide USP, talc USP, FD&C Blue #2 aluminum lake, and magnesium stearate NF.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lorcaserin is believed to decrease food consumption and promote satiety by selectively activating 5-HT_{2C} receptors on anorexigenic pro-opiomelanocortin neurons located in the hypothalamus. The exact mechanism of action is not known.

Lorcaserin at the recommended daily dose selectivity interacts with 5-HT_{2C} receptors as compared to 5-HT_{2A} and 5-HT_{2B} receptors (see Table 5), other 5-HT receptor subtypes, the 5-HT receptor transporter, and 5-HT reuptake sites.

Table 5. Lorcaserin Potency (EC50) and Binding Affinity (Ki) to Human 5-$HT2_A$, 5-$HT2_B$, and 5-$HT2_C$ Receptor Subtypes

Serotonin Receptor Subtype	EC_{50}, nM	Ki, nM
$5HT_{2C}$	39	13
$5HT_{2B}$	2380	147
$5HT_{2A}$	553	92

12.2 Pharmacodynamics

Cardiac Electrophysiology. The effect of multiple oral doses of lorcaserin 15 mg and 40 mg once daily on QTc interval was evaluated in a randomized, placebo- and active- (moxifloxacin 400 mg) controlled four-treatment arm parallel thorough QT study in 244 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 ms, the threshold for regulatory concern.

12.3 Pharmacokinetics

Absorption

Lorcaserin is absorbed from the gastrointestinal tract with peak plasma concentration occurring 1.5 - 2 hours after oral dosing. The absolute bioavailability of lorcaserin has not been determined. Lorcaserin has a plasma half life of ~11 hours; steady state is reached within 3 days after twice daily dosing, and accumulation is estimated to be approximately 70%.

Effect of Food. Twelve adult volunteers (6 men and 6 women) were given a single 10 mg oral dose of BELVIQ in a fasted state and after administration of a high fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800–1000 calories) meal. The C_{max} increased approximately 9% and exposure (AUC) increased approximately 5% under fed conditions. T_{max} was delayed approximately 1 hour in the fed state. BELVIQ can be administered with or without food.

Distribution

Lorcaserin distributes to the cerebrospinal fluid and central nervous system in humans. Lorcaserin hydrochloride is moderately bound (~70%) to human plasma proteins.

Metabolism

Lorcaserin is extensively metabolized in the liver by multiple enzymatic pathways. After oral administration of BELVIQ, the major circulating metabolite is lorcaserin sulfamate (M1), with a plasma C_{max} that exceeds lorcaserin C_{max} by 1- to 5-fold. *N*-carbamoyl glucuronide lorcaserin (M5) is the major metabolite in urine; M1 is a minor metabolite in urine, representing approximately 3% of dose. Other minor metabolites excreted in urine were identified as glucuronide or sulfate conjugates of oxidative metabolites. The principal metabolites exert no pharmacological activity at serotonin receptors.

Elimination

Lorcaserin is extensively metabolized by the liver and the metabolites are excreted in the urine. In a human mass balance study in which healthy subjects ingested radiolabeled lorcaserin, 94.5% of radiolabeled material was recovered, with 92.3% and 2.2% recovered from urine and feces, respectively.

Specific Populations

Renal Impairment. The disposition of lorcaserin was studied in patients with varying degrees of renal function. Creatinine clearance (CLcr) was calculated by Cockgroft-Gault equation based on ideal body weight (IBW). Impaired renal function decreased C_{max} of lorcaserin, with no change in AUC.

Exposure of lorcaserin sulfamate metabolite (M1) was increased in patients with impaired renal function by approximately 1.7-fold in mild (CLcr = 50-80 mL/min), 2.3-fold in moderate (CLcr = 30-50 mL/min) and 10.5-fold in severe renal impairment (CLcr = <30 mL/min) compared to normal subjects (CLcr >80 mL/min).

Exposure of the N-carbamoyl-glucuronide metabolite (M5) was increased in patients with impaired renal function by approximately 1.5-fold in mild (CLcr = 50-80 mL/min), 2.5-fold in moderate (CLcr = 30-50 mL/min) and 5.1-fold in severe renal impairment (CLcr = <30 mL/min) compared to normal subjects (CLcr >80 mL/min).

The terminal half-life of M1 is prolonged by 26%, 96%, and 508% in mild, moderate, and severe renal impairment, respectively. The terminal half-life of M5 is prolonged by 0%, 26%, and 22% in mild, moderate,

and severe renal impairment, respectively. The metabolites M1 and M5 accumulate in patients with severely impaired renal function.

Approximately 18% of metabolite M5 in the body was cleared from the body during a standard 4-hour hemodialysis procedure. Lorcaserin and M1 were not cleared by hemodialysis. Lorcaserin is not recommended for patients with severe renal impairment (CLcr <30 mL/min) or patients with end stage renal disease [*see Use in Specific Populations (8.6)*].

Estimate Ideal Body Weight (IBW) in (kg)

Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.
Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.

The Cockroft-Gault calculation using the IBW:

female:

$$\text{GFR (mL/min)} = 0.85 \times \frac{(140\text{-age}) \times \text{ideal body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

male:

$$\text{GFR (mL/min)} = \frac{(140\text{-age}) \times \text{ideal body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

Hepatic Impairment. The disposition of lorcaserin was evaluated in patients with hepatic impairment and subjects with normal hepatic function. Lorcaserin C_{max} was 7.8% and 14.3% lower, in subjects with mild (Child-Pugh score 5-6) and moderate (Child-Pugh score 7-9) hepatic impairment, respectively, than that in subjects with normal hepatic function. The half-life of lorcaserin is prolonged by 59% to 19 hours in patients with moderate hepatic impairment. Lorcaserin exposure (AUC) is approximately 22% and 30% higher in patients with mild and moderate hepatic impairment, respectively. Dose adjustment is not required for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on lorcaserin was not evaluated [*see Use in Specific Populations (8.7)*].

Gender. No dosage adjustment based on gender is necessary. Gender did not meaningfully affect the pharmacokinetics of lorcaserin.

Geriatric. No dosage adjustment is required based on age alone. In a clinical trial of 12 healthy elderly (age greater than 65 years) subjects and 12 matched adult patients, lorcaserin exposure (AUC and C_{max}) was equivalent in the two groups. C_{max} was approximately 18% lower in the elderly group, and T_{max} was increased from 2 hours to 2.5 hours in the elderly group as compared to the non-elderly adult group.

Race. No dosage adjustment based on race is necessary. Race did not meaningfully affect the pharmacokinetics of lorcaserin.

Drug-Drug Interactions

Lorcaserin inhibits CYP 2D6-mediated metabolism. In a clinical trial in 21 CYP 2D6 extensive metabolizers, concomitant administration of lorcaserin (10 mg BID for 4 days) increased dextromethorphan peak concentrations (C_{max}) by approximately 76% and exposure (AUC) by approximately 2-fold [*see Drug Interactions (7.2)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenesis

Lorcaserin hydrochloride was not mutagenic in an *in vitro* bacterial mutation assay (Ames test), was not clastogenic in an *in vitro* chromosome aberration assay in Chinese hamster ovary cells, and was not genotoxic in an *in vivo* micronucleus assay in rat bone marrow.

Carcinogenesis

The carcinogenic potential of lorcaserin hydrochloride was assessed in two-year carcinogenicity studies in mice and rats. CD-1 mice received doses of 5, 25 and 50 mg/kg. There were no treatment-related increases in the incidence of any tumor in mice at doses that produced plasma exposure in males and females of 8 and 4-times the daily human clinical dose, respectively.

In the rat carcinogenicity study, male and female Sprague-Dawley rats received 10, 30, and 100 mg/kg lorcaserin hydrochloride. In females, mammary adenocarcinoma increased at 100 mg/kg, which was associated with plasma exposures that were 87-times the daily human clinical dose. The incidence of mammary fibroadenoma was increased in female rats at all doses with no safety margin to the clinical dose. The increases in adenocarcinomas and fibroadenomas may be associated with lorcaserin hydrochloride-induced changes in prolactin homeostasis in rats. The relevance of the increased incidence of mammary adenocarcinomas and fibroadenomas in rats to humans is unknown.

In male rats, treatment-related neoplastic changes were observed in the subcutis (fibroadenoma, Schwannoma), the skin (squamous cell carcinoma), mammary gland (adenocarcinoma and fibroadenoma), and the brain (astrocytoma) at greater than or equal to 30 mg/kg (plasma exposure 17-times human clinical dose). At higher exposure, liver adenoma and thyroid follicular cell adenoma were increased but were considered secondary to liver enzyme induction in rats and are not considered relevant to humans. Human brain exposure ($AUC_{24h,ss}$) to lorcaserin at the clinical dose is estimated to be 70-fold lower than brain exposure in rats at the dose at which no increased incidence of astrocytoma was observed. Excluding the liver and thyroid tumors, these neoplastic findings in male rats are of unknown relevance to humans.

Impairment of Fertility

Potential effects on fertility were assessed in Sprague-Dawley rats in which males were dosed with lorcaserin hydrochloride for 4 weeks prior to and through the mating period, and females were dosed for 2 weeks prior to mating and through gestation day 7. Lorcaserin hydrochloride had no effects on fertility in rats at exposures up to 29 times the human clinical dose.

14 CLINICAL STUDIES

The safety and efficacy of BELVIQ for chronic weight management in conjunction with reduced caloric intake and increased physical activity were evaluated in 3 randomized, double-blind, placebo-controlled trials with durations ranging from 52 to 104 weeks. Two trials in adults without type 2 diabetes mellitus (Study 1 and Study 2) and one study in adults with type 2 diabetes mellitus (Study 3) evaluated the effect of BELVIQ 10 mg twice daily. The primary efficacy parameter in these studies was weight loss at 1 year, which was assessed by percent of patients achieving greater than or equal to 5% weight loss, percent of patients achieving greater than or equal to 10% weight loss, and mean weight change. All patients received one-on-one instruction for a

reduced-calorie diet and exercise counseling that began with the first dose of study medication and continued every four weeks throughout the trial.

Study 1 was a 2-year study that enrolled 3182 patients who were obese (BMI 30-45 kg/m^2), or who were overweight (BMI 27-29.9 kg/m^2) and had at least one weight-related comorbid condition such as hypertension or dyslipidemia. In Year 2, placebo patients were continued on placebo and BELVIQ patients were re-randomized in a 2:1 ratio to continue BELVIQ or to switch to placebo. The mean age was 44 (range 18-65); 83.5% were women. Sixty-seven percent were Caucasian, 19% were African American and 12% were Hispanic. Mean baseline body weight was 100.0 kg and mean BMI was 36.2 kg/m^2.

Study 2 was a 1-year study that enrolled 4008 patients who were obese (BMI 30-45 kg/m^2) or were overweight (BMI 27-29.9 kg/m^2) with at least one comorbid condition such as hypertension or dyslipidemia. The mean age was 44 (range 18-65); 80% were women. Sixty-seven percent were Caucasian, 20% were African American and 11% were Hispanic. Mean baseline body weight was 100.2 kg and mean BMI was 35.9 kg/m^2.

Study 3 was a 1-year study that enrolled 604 adult patients with BMI greater than or equal to 27 kg/m^2 and inadequately controlled type 2 diabetes (HbA1c range 7-10%) being treated with metformin and/or a sulfonylurea. Mean age was 53 (range 21-65); 54% were women. Sixty-one percent were Caucasian, 21% African American and 14% were Hispanic. Mean BMI was 36 kg/m^2 and mean HbA1C was 8.1%.

A substantial percentage of randomized subjects withdrew from each study prior to week 52: 50% in Study 1, 45% in Study 2 and 36% in Study 3.

One-Year Weight Management in Patients without Diabetes Mellitus

Weight loss at 1 year in Studies 1 and 2 is presented in Table 6. The pooled data are reflective of the individual study results.

Statistically significantly greater weight loss was achieved with BELVIQ compared to placebo at week 52. The Year 1 placebo-adjusted weight loss achieved in patients treated with BELVIQ was 3.3 kg by ITT/LOCF analysis. The time course of weight loss with BELVIQ and placebo through week 52 is depicted in Figure 1.

Patients who did not lose at least 5% of baseline body weight by week 12 were unlikely to achieve at least 5% weight loss at week 52.

Table 6. Weight Loss at 1 Year in Studies 1 and 2 Combined

	BELVIQ 10 mg BID N=3098	Placebo N=3038
Weight (kg)		
Baseline mean (SD)	100.4 (15.7)	100.2 (15.9)
Change from baseline (adjusted mean[1]) (SE)	-5.8 (0.1)	-2.5 (0.1)
Difference from placebo (adjusted mean[1]) (95% CI)	-3.3** (-3.6, -2.9)	
Percent change from baseline (adjusted mean[1]) (SE)	-5.8 (0.1)	-2.5 (0.1)
Difference from placebo (adjusted mean[1]) (95% CI)	-3.3** (-3.6, -3.0)	
% of Patients losing greater than or equal to 5% body weight	47.1	22.6
Difference from placebo (95% CI)	24.5** (22.2, 26.8)	
% of Patients losing greater than or equal to 10% body weight	22.4	8.7
Difference from placebo (95% CI)	13.8** (12.0, 15.5)	

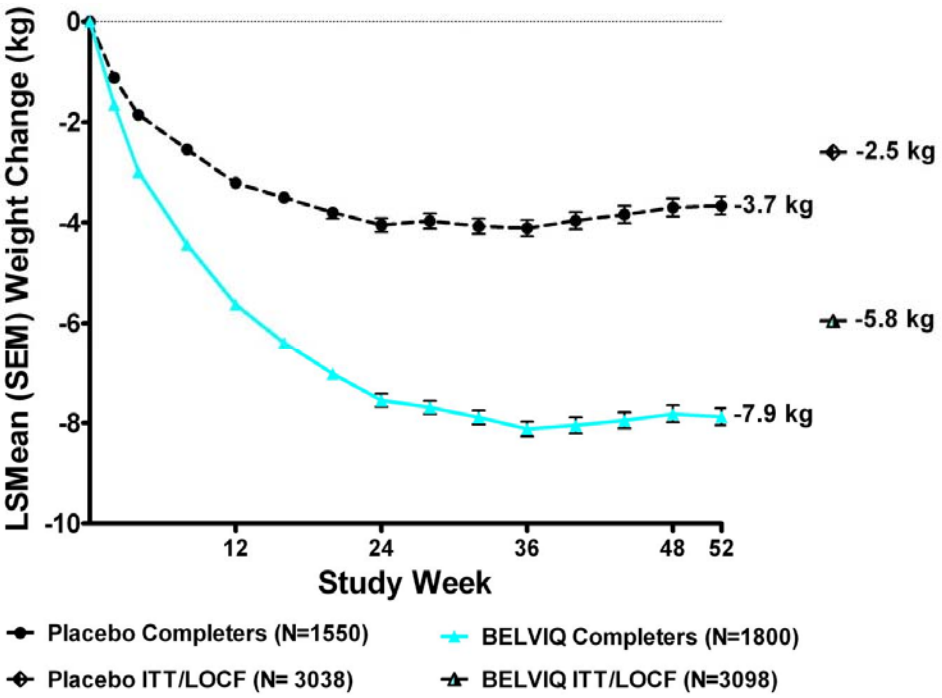
SD=Standard Deviation; SE=Standard Error; CI=Confidence Interval

Intent to Treat Population using last observation carried forward method; All patients who received study medication and had a post-baseline body weight. Forty-four percent (44%) of patients in Belviq and 51% in placebo dropped out before the 52-week endpoint.

[1]Least squares means adjusted for baseline value, treatment, study and treatment by study interaction.

**$p<0.001$ compared to placebo. Type 1 error was controlled across the three endpoints.

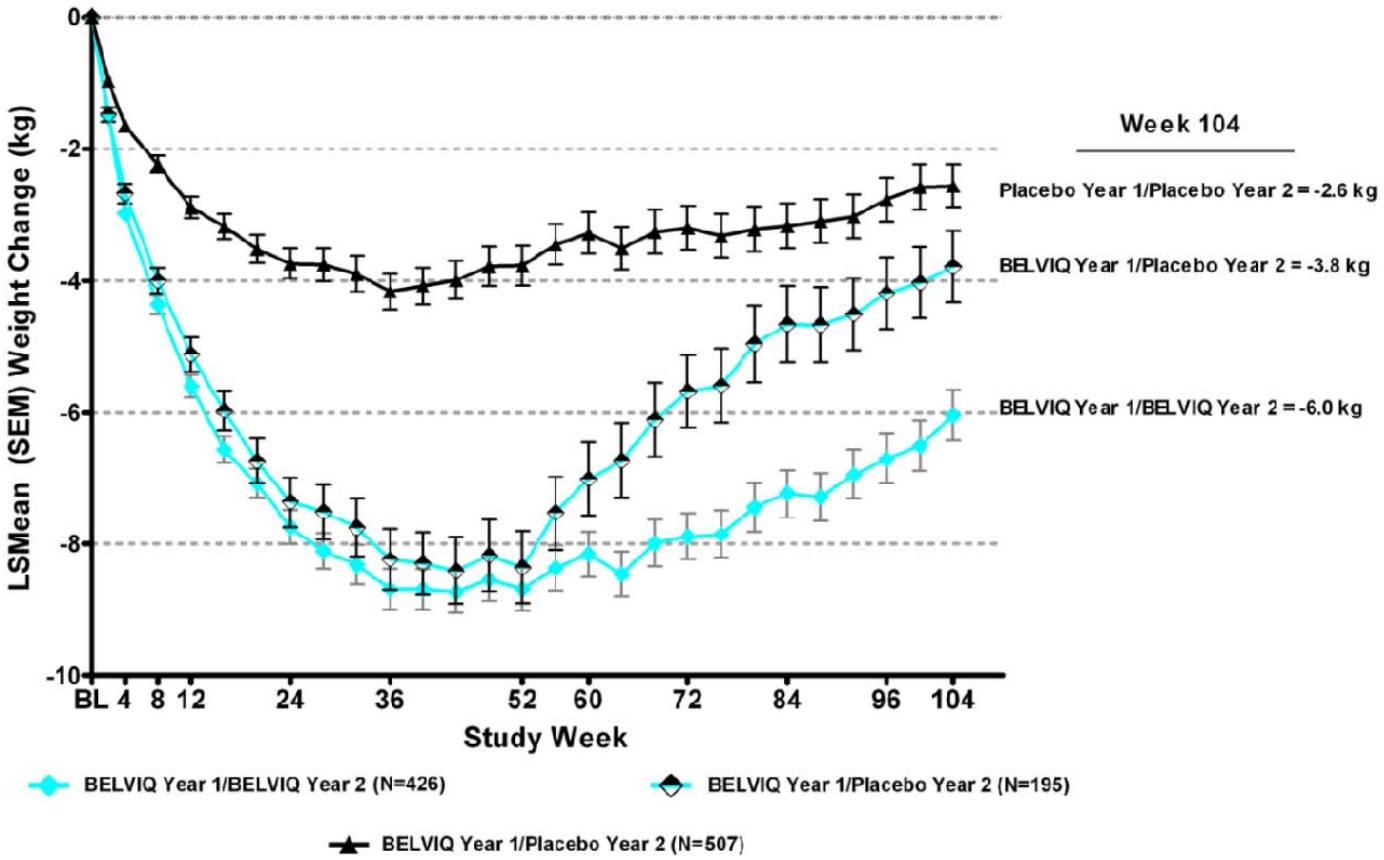
Figure 1. Longitudinal Weight Change (kg) in Completer Population: Studies 1 and 2



Two-Year Weight Management in Patients without Diabetes Mellitus

The safety and efficacy of BELVIQ for weight management during 2 years of treatment were evaluated in Study 1. Of the 3182 patients who were randomized in Year 1, 1553 (48.8%) were randomized in Year 2. Patients in all three Year 2 patient groups (BELVIQ Year 1/ BELVIQ Year 2, BELVIQ Year 1/placebo Year 2, and placebo Year 1/placebo Year 2) regained weight in Year 2 but remained below their Year 1 mean baseline weight (Figure 2).

Figure 2. Body Weight Changes during Study 1 in the Completers Population



Year 1 Randomized: BELVIQ N=1595, Placebo N=1587

Year 2 Randomized: BELVIQ Year 1/BELVIQ Year 2, N=573; BELVIQ Year 1/Placebo Year 2, N=283; Placebo Year 1/Placebo Year 2, N=697

Effect of BELVIQ on Cardiometabolic Parameters and Anthropometry

Changes in lipids, fasting glucose, fasting insulin, waist circumference, heart rate, and blood pressure with BELVIQ are shown in Table 7.

In a substudy of 154 patients conducted as part of Study 2, DEXA analysis showed a 9.9% reduction in fat mass from a baseline of 45.0 kg in patients treated with BELVIQ compared to a 4.6% reduction from a baseline of 44.5 kg in patients treated with placebo. The placebo-adjusted reduction in fat mass achieved on BELVIQ was -5.3%. Reductions in lean body mass were 1.9% and 0.3% from baseline values of 48.0 kg and 51.0 kg, respectively, for BELVIQ- and placebo-treated patients.

Table 7. Mean Changes in Cardiometabolic Parameters and Waist Circumference in Year 1 of Studies 1 and 2

	BELVIQ N=3096		Placebo N=3039		
	Baseline mg/dL	**% change from Baseline (LSMean[1])**	**Baseline mg/dL**	**% change from Baseline (LSMean)**	**BELVIQ minus Placebo (LSMean)**
Total Cholesterol	194.4	-0.9	194.8	0.4	-1.2*
LDL Cholesterol	114.3	1.6	114.1	2.9	-1.3*
HDL Cholesterol	53.2	1.8	53.5	0.6	1.2*
Triglycerides	135.4	-5.3	137.0	-0.5	-4.8*
	Baseline	**change from Baseline (LSMean)**	**Baseline**	**change from Baseline (LSMean)**	**BELVIQ minus Placebo (LSMean)**
Systolic blood pressure (mmHg)	121.4	-1.8	121.5	-1.0	-0.7*
Diastolic blood pressure (mmHg)	77.4	-1.6	77.7	-1.0	-0.6*
Heart Rate (bpm)	69.5	-1.2	69.5	-0.4	-0.8
Fasting glucose (mg/dL)	92.1	-0.2	92.4	0.6	-0.8
Fasting insulin[2] (µIU/mL)	15.9	-3.3	15.8	-1.3	-2.1*
Waist Circumference (cm)	109.3	-6.6	109.6	-4.0	-2.5

[1] Least squares means adjusted for baseline value, treatment, study and treatment by study interaction

[2] Measured in Study 1 only (n=1538)

* Statistically significant versus placebo based on the pre-specified gatekeeping method for controlling Type I error in key secondary endpoints.

One-Year Weight Management in Patients with Type 2 Diabetes Mellitus

Weight loss among patients with type 2 diabetes mellitus who were treated with BELVIQ was statistically significantly greater than that among patients treated with placebo (Table 8).

Table 8. Weight Loss at 1 Year in Study 3 (Type 2 Diabetes Mellitus)

	BELVIQ 10 mg BID N=251	Placebo N=248
Weight loss (kg)		
Baseline mean (SD)	103.5 (17.2)	102.3 (18.0)
Change from baseline (adjusted mean[1]) (SE)	-4.7 (0.4)	-1.6 (0.4)
Difference from placebo (adjusted mean[1])	-3.1**	
(95% CI)	(-4.0, -2.2)	
Percent change from baseline (adjusted mean[1]) (SE)	-4.5 (0.4)	-1.5 (0.4)
Difference from placebo (adjusted mean[1])	-3.1**	
(95% CI)	(-3.9, -2.2)	
% of Patients losing greater than or equal to 5% body weight	37.5	16.1
Difference from placebo	21.3**	
(95% CI)	(13.8, 28.9)	
% of Patients losing greater than or equal to 10% body weight	16.3	4.4
Difference from placebo	11.9**	
(95% CI)	(6.7, 17.1)	

SD=Standard Deviation; SE=Standard Error; CI=Confidence Interval

Intent to Treat Population using last observation carried forward method; All patients who received study medication and had a post-baseline body weight. Thirty-four percent (34%) of patients in Belviq and 38% in placebo dropped out before the 52-week endpoint.

[1]Least squares means adjusted for baseline value, baseline HbA1c stratum and prior antihyperglycemic medication stratum.

**p<0.001 compared to placebo. Type 1 error was controlled across the three endpoints.

Effect of BELVIQ on Cardiometabolic Parameters and Anthropometry in Patients with Type 2 Diabetes Mellitus

Patients in Study 3 were taking either metformin and/or a sulfonylurea at study start, and had inadequate glycemic control (HbA1c range 7-10%). Changes in HbA1c and fasting glucose with BELVIQ use are shown in Table 9.

Table 9. Mean Changes in Cardiometabolic Parameters and Waist Circumference in Patients with Type 2 Diabetes Mellitus

	BELVIQ N=256		Placebo N=252		BELVIQ minus Placebo (LSMean)
	Baseline	**Change from Baseline (LSMean[1])**	**Baseline**	**Change from Baseline (LSMean)**	
HbA1C (%)	8.1	-0.9	8.0	-0.4	-0.5*
Fasting glucose (mg/dL)	163.3	-27.4	160.0	-11.9	-15.5*
Systolic blood pressure (mmHg)	126.6	-0.8	126.5	-0.9	0.1
Diastolic blood pressure (mmHg)	77.9	-1.1	78.7	-0.7	-0.4
Heart Rate (bpm)	72.3	-2.0	72.7	-0.4	-1.6
	Baseline	**% Change from Baseline (LSMean)**	**Baseline**	**% Change from Baseline (LSMean)**	**BELVIQ minus Placebo (LSMean)**
Total Cholesterol (mg/dL)	173.5	-0.7	172.0	-0.1	-0.5
LDL Cholesterol (mg/dL)	95.0	4.2	94.6	5.0	-0.8
HDL Cholesterol (mg/dL)	45.3	5.2	45.7	1.6	3.6
Triglycerides (mg/dL)	172.1	-10.7	163.5	-4.8	-5.9
Waist Circumference (cm)	115.8	-5.5	113.5	-3.3	-2.2

Intent to Treat Population using last observation carried forward method; All patients who received study medication and had a post-baseline measurement.
* Statistically significant versus placebo based on the pre-specified gatekeeping method for controlling Type I error in key secondary endpoints.
[1]Least squares means adjusted for baseline value, baseline HbA1c stratum and prior antihyperglycemic medication stratum.

16 HOW SUPPLIED/STORAGE AND HANDLING

BELVIQ 10-mg tablets are supplied as blue-colored, round, biconvex, film-coated tablets debossed with “A” on one side and “10” on the other side and are available as follows:

- NDC 62856-529-10 Bottle of 100
- NDC 62856-529-51 Blister pack of 10

Store at 25°C (77°F): excursions permitted to 15–30°C (59–86°F) [see USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

- BELVIQ is indicated for chronic weight management only in conjunction with a reduced-calorie diet and increased physical activity.
- Patients should be instructed to discontinue use of BELVIQ if they have not achieved 5% weight loss by 12 weeks of treatment.
- Patients should be informed of the possibility of serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions with the combined use of BELVIQ with other serotonergic drugs, including selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), triptans, drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors

[MAOIs]), dietary supplements such as St. John's Wort and tryptophan, tramadol, or antipsychotics or other dopamine antagonists.

- Patients who develop signs or symptoms of valvular heart disease, including dyspnea or dependent edema should seek medical attention.
- Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that BELVIQ therapy does not affect them adversely.
- Patients should be instructed to seek medical attention in the event of emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
- Patients should be cautioned not to increase their dose of BELVIQ.
- Men who have an erection lasting greater than 4 hours, whether painful or not, should immediately discontinue the drug and seek emergency medical attention.
- Patients should be instructed to avoid pregnancy or breastfeeding while undergoing BELVIQ therapy and to talk to their prescribing physician should they get pregnant or decide to breastfeed.
- Patients should tell their healthcare provider about all the medications, nutritional supplements and vitamins (including any weight loss products) that they may take while taking BELVIQ.

BELVIQ® is a registered trademark of Arena Pharmaceuticals GmbH, Zofingen, Switzerland
Manufactured by Arena Pharmaceuticals GmbH, Untere Brühlstrasse 4, CH-4800, Zofingen, Switzerland
Distributed by Eisai Inc., Woodcliff Lake, NJ 07677

<COPYRIGHT>

PATIENT INFORMATION

BELVIQ® (BEL-VEEK)

(lorcaserin hydrochloride)

tablets

Read the Patient Information that comes with BELVIQ before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about BELVIQ, talk to your doctor or pharmacist.

What is BELVIQ?

BELVIQ is a prescription medicine that may help some obese adults or overweight adults who also have weight related medical problems lose weight and keep the weight off.

BELVIQ should be used with a reduced calorie diet and increased physical activity.

It is not known if BELVIQ is safe and effective when taken with other prescription, over-the-counter, or herbal weight loss products.

It is not known if BELVIQ changes your risk of heart problems or stroke or of death due to heart problems or stroke.

It is not known if BELVIQ is safe when taken with some other medicines that treat depression, migraines, mental problems, or the common cold (serotonergic or antidopaminergic agents).

It is not known if BELVIQ is safe and effective in children under 18 years old.

Who should not take BELVIQ?

Do not take BELVIQ if you:

- are pregnant or planning to become pregnant. BELVIQ may harm your unborn baby.

What should I tell my healthcare provider before taking BELVIQ?

Before you take BELVIQ, tell your doctor if you:

- **have or have had heart problems including:**
  - **congestive heart failure**
  - **heart valve problems**
  - **slow heart beat or heart block**
- have diabetes
- have a condition such as sickle cell anemia, multiple myeloma, or leukemia
- have a deformed penis, Peyronie's disease, or ever had an erection that lasted more than 4 hours
- have kidney problems

- have liver problems
- are pregnant or plan to become pregnant.
- are breast feeding or plan to breastfeed. It is not known if BELVIQ passes into your breastmilk. You and your doctor should decide if you will take BELVIQ or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

BELVIQ may affect the way other medicines work, and other medicines may affect how BELVIQ works.

Especially tell your doctor if you take medicines for depression, migraines or other medical conditions such as:

- triptans, used to treat migraine headache
- medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, selective serotonin uptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), or antipsychotics
- cabergoline
- linezolid, an antibiotic
- tramadol
- dextromethorphan, an over-the-counter medicine used to treat the common cold or cough
- over-the-counter supplements such as tryptophan or St. John's Wort
- medicines to treat erectile dysfunction

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.

Know all the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take BELVIQ?

- Take BELVIQ exactly as your doctor tells you to take it.
- Your doctor will tell you how much BELVIQ to take and when to take it.
  - Take 1 tablet 2 times each day.
  - **Do not** increase your dose of BELVIQ.
  - BELVIQ can be taken with or without food.
- Your doctor should start you on a diet and exercise program when you start taking BELVIQ. Stay on this program while you are taking BELVIQ.
- Your doctor should tell you to stop taking BELVIQ if you do not lose a certain amount of weight within the first 12 weeks of treatment.
- If you take too much BELVIQ or overdose, call your doctor or go to the nearest emergency room right away.

What should I avoid while taking BELVIQ?

- **Do not** drive a car or operate heavy machinery until you know how BELVIQ affects you. BELVIQ can slow your thinking.

What are the possible side effects of BELVIQ?

BELVIQ may cause serious side effects, including:

- **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions.**

  BELVIQ and certain medicines for depression, migraine, the common cold, or other medical problems may affect each other causing serious or life-threatening side effects. Call your doctor right away if you start to have any of the following symptoms while taking BELVIQ:

  - mental changes such as agitation, hallucinations, confusion, or other changes in mental status
  - coordination problems, uncontrolled muscle spasms, or muscle twitching (overactive reflexes)
  - restlessness
  - racing or fast heart beat, high or low blood pressure
  - sweating or fever
  - nausea, vomiting, or diarrhea
  - muscle rigidity (stiff muscles)

- **Valvular heart disease.** Some people taking medicines like BELVIQ have had problems with the valves in their heart. Call your doctor right away if you have any of the following symptoms while taking BELVIQ:
  - trouble breathing
  - swelling of the arms, legs, ankles, or feet
  - dizziness, fatigue, or weakness that will not go away
  - fast or irregular heartbeat

- **Changes in your attention or memory.**

- **Mental problems.** Taking BELVIQ in high doses may cause psychiatric problems such as:
  - hallucinations
  - feeling high or in a very good mood (euphoria)
  - feelings of standing next to yourself or out of your body (disassociation)

- **Depression or thoughts of suicide.** You should pay attention to any mental changes, especially sudden changes, in your mood, behaviors, thoughts, or feelings. Call your healthcare provider right away if you have any mental changes that are new, worse, or worry you.
- **Low blood sugar (hypoglycemia) in people with type 2 diabetes mellitus who also take medicines used to treat type 2 diabetes mellitus.** Weight loss can cause low blood sugar in people with type 2 diabetes mellitus who also take medicines used to treat type 2 diabetes mellitus (such as insulin or sulfonylureas). You should check your blood sugar before you start taking BELVIQ and while you take BELVIQ.

- **Painful erections (priapism).** The medicine in BELVIQ can cause painful erections that last more than 6 hours. If you have an erection lasting more than 4 hours whether it is painful or not, stop using BELVIQ and call your doctor or go to the nearest emergency room right away.

- **Slow heart beat.** BELVIQ may cause your heart to beat slower. Tell your doctor if you have a history of your heart beating slow or heart block.
- **Decreases in your blood cell count.** BELVIQ may cause your red and white blood cell count to decrease. Your doctor may do tests to check your blood cell count while you are taking BELVIQ.
- **Increase in prolactin.** The medicine in BELVIQ may increase the amount of a certain hormone your body makes called prolactin. Tell your doctor if your breasts begin to make milk or a milky discharge or if you are a male and your breasts begin to increase in size.

The most common side effects of BELVIQ include:

- headache
- dizziness
- fatigue
- nausea
- dry mouth
- constipation
- cough
- low blood sugar (hypoglycemia) in patients with diabetes
- back pain

Tell to your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of BELVIQ. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store BELVIQ?

Store BELVIQ at room temperature between 59°F to 86°F (15°C to 30°C).

Safely throw away medicine that is out of date or no longer need.

Keep BELVIQ and all medicines out of the reach of children.

General information about the safe and effective use of BELVIQ.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use BELVIQ for a condition for which it was not prescribed. Do not give BELVIQ to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about BELVIQ. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about BELVIQ that is written for health professionals.

For more information, go to www.BELVIQ.com Website or call 1-888-274-2378.

What are the ingredients in BELVIQ?

Active Ingredient: lorcaserin hydrochloride

Inactive Ingredients: silicified microcrystalline cellulose; hydroxypropyl cellulose NF; croscarmellose sodium NF; colloidal silicon dioxide NF; polyvinyl alcohol USP; polyethylene glycol NF; titanium dioxide USP; talc USP; FD&C Blue #2 aluminum lake; and magnesium stearate NF.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Rx Only

BELVIQ® is a registered trademark of Arena Pharmaceuticals GmbH, Zofingen, Switzerland
Manufactured by Arena Pharmaceuticals GmbH, Untere Brühlstrasse 4, CH-4800, Zofingen, Switzerland
Distributed by Eisai Inc., Woodcliff Lake, NJ 07677

2.5
25. mm
45. mm
Lot:
Exp:
Manufactured by: Arena Pharmaceuticals GmbH, Zofingen, Switzerland
Distributed by:
Eisai Inc., Woodcliff Lake, NJ 07677, USA
Made in Switzerland PN-409610 ver. 701762K
NDC 62856-529-10
℞ only
Contents:
100 Tablets
BELVIQ®
(lorcaserin HCl)
Tablets
10 mg
Each tablet contains 10 mg lorcaserin hydrochloride.
Store at 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Protect from heat and moisture.
See package insert for full prescribing information.
Dispense in a tight container as defined in USP, with a child-resistant closure (as required).
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.
www.belviq.com
N3
6 2 8 5 6 5 2 9 1 0 5
115 mm

BLISTER PACK SAMPLE BOX: 43x22x105mm

PRINTS 4 COLOR: BLACK, PMS 526, PMS 382, PMS 2935

BELVIQ®
(lorcaserin HCl)
Tablets
10 mg

NDC 62856-529-51
℞ only
Professional Sample
Not for Sale
Contents: 10 Tablets

Exp:
Lot:

43x22x105

Store at 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Protect from heat and moisture.
See package insert for full prescribing information.
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

RESERVE FOR PANEL NUMBER

BELVIQ®
(lorcaserin HCl)
Tablets

BELVIQ®
(lorcaserin HCl) Tablets
10 mg

NDC 62856-529-51
℞ only

Professional Sample
Not for Sale

Contents: 10 Tablets

Each tablet contains 10 mg lorcaserin hydrochloride.

Manufactured by:
Arena Pharmaceuticals GmbH, Zofingen, Switzerland

Distributed by:
Eisai Inc., Woodcliff Lake, NJ 07677, USA

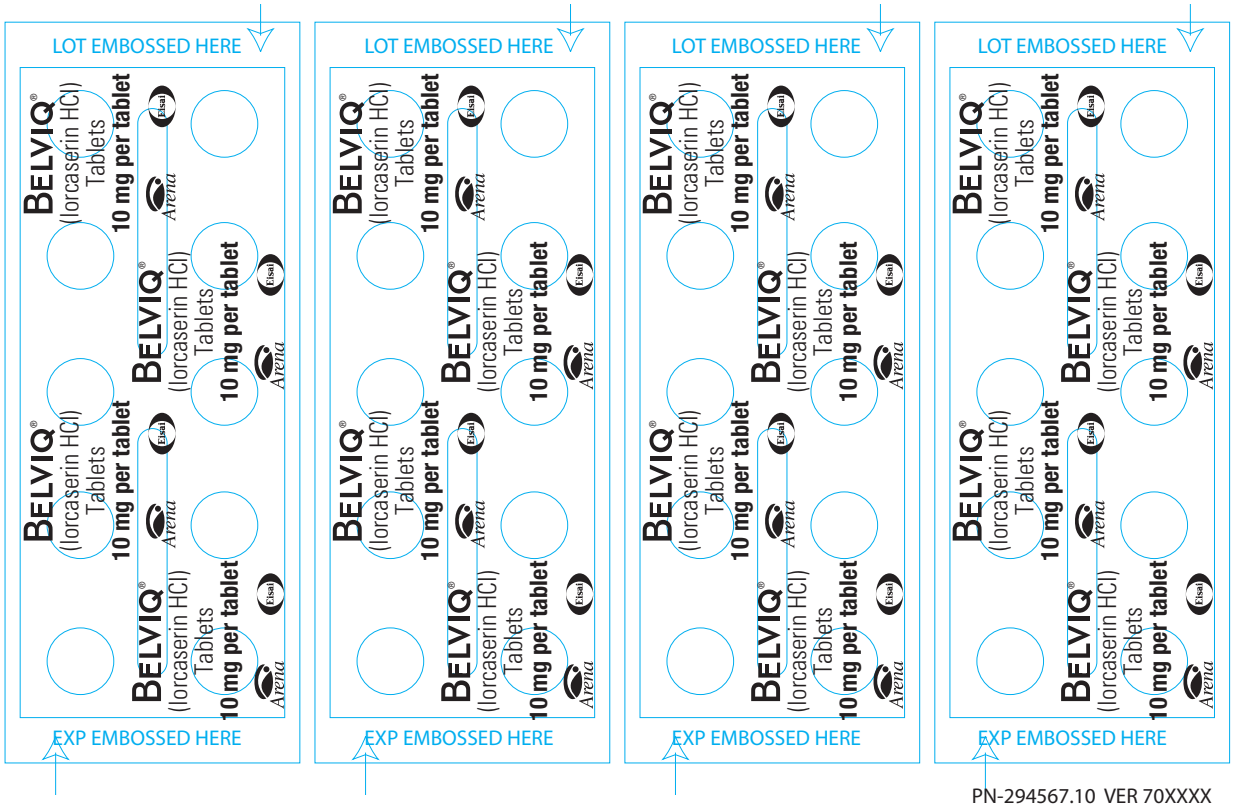
Made in Switzerland PN-409611 ver. 701776B

www.belviq.com

409611
701776B

Reference ID: 3151563

REV. 07JUNE2012



PN-294567.10 VER 70XXXX

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
06/27/2012