Orexigen Therapeutics Provides Statement on Termination of the Light Study and Updates on Contrave Collaboration with Takeda Pharmaceuticals

SAN DIEGO, May 12, 2015 /PRNewswire/ - Orexigen Therapeutics, Inc. (Nasdaq: OREX) today issued the following statement regarding the termination of the Light Study a cardiovascular (CV) outcomes trial that compared the obesity drug Contrave® (naltrexone HCl and bupropion HCl extended-release tablets) to placebo, in addition to diet and exercise counselling, in 8,909 overweight and obese patients with certain CV risk factors, and an update on its Contrave collaboration with Takeda Pharmaceuticals Company.

This morning we and Takeda announced termination of the Light Study. We agreed with our partner, and together discussed our preferences with the U.S. Food and Drug Administration (FDA), that it was best to conclude the study in an orderly fashion, search for and gather all CV events and other safety data, have the CV events properly adjudicated, carefully analyze the final data and have these data presented and published in a scientific forum.

Since continuation of the Light Study was not a postmarketing requirement (PMR), and the majority of patients are no longer on blinded study drug, Orexigen had long advocated shutting down the study in December 2014, corresponding with the time of the 50% interim analysis, and focusing resources on new studies to further evaluate the therapeutic profile of Contrave.

We are pleased that the Light Study is now being terminated and want to thank the patients and all of those involved in the study. This trial has yielded important information about the safety profile for Contrave.

We have been informed that Takeda is on track to initiate a PMR cardiovascular outcomes trial (CVOT) later this year and recently achieved the first planned milestone with FDA acceptance of the study protocol in April.

Today some of the 50% interim analysis of the Light Study was disclosed by a third party. Because most of our management team remains blinded to the 50% data, we are unable to comment.

There have been a lot of challenges surrounding the use of interim data from ongoing studies for regulatory purposes. There are competing tensions for data confidentiality to preserve study integrity, transparency laws, and guidelines from regulatory bodies. With respect to the Light Study, Orexigen filed patent applications based on the unexpected result of the 25% interim analysis of LIGHT Study data. The first of those applications was granted and issued in March, and the full clinical study report that was submitted to FDA in the patent application was disclosed by the USPTO.

A few articles on this topic have been published in the media today that include misleading statements about our company. Contrary to allegations cited today by a journalist, Orexigen has never misled patients. At the time of the patent issuance in March, we stated plainly and clearly that the effect of Contrave on CV morbidity and

mortality has not been established and that a larger number of MACE are required to precisely determine the effect of Contrave on CV outcomes.

Also contrary to the same story published today, Orexigen has not misled investors. Over the last 7 weeks, we have been working with the FDA, the Executive Steering Committee (ESC), the Data Monitoring Committee and Takeda to determine how, when and with what context the Light Study should be terminated. Takeda and Orexigen agreed that the appropriate manner to wind down the study was to collect the final information from the study and then to present and publish the study results. There was pressure from the ESC to release the 50% interim data. We maintained we would not be in a position to release data without access to the full data set, which we have not had and still do not have.

On another topic, we would also like to provide an update on Takeda. As you may recall we announced a non-binding term sheet at the time of approval as Takeda attempted to renegotiate the collaboration agreement. These discussions led to a previously disclosed non-binding term sheet. Since then, we have had the time to conduct our own diligence and the merits of Takeda's claims, and have continued to negotiate the terms of an amended collaboration agreement. Today, Takeda initiated a formal dispute process claiming material breach. Takeda is seeking, among other things, Orexigen to pay the entire cost of the new cardiovascular outcomes trial.

As a result of this claim, Takeda and Orexigen will now enter into a dispute resolution process, which may include arbitration, unless our differences can be resolved otherwise. The protocol for dispute resolution is set out in the collaboration agreement.

We are currently evaluating the assertions made by Takeda and believe they are without merit. Further we intend to vigorously defend all of our rights and remedies, and assert any counterclaims that we have against Takeda.

As you know, cardiovascular safety has been a major issue in the obesity pharmacotherapy field. We look forward to the completion of the final analysis and publication once the Light Study is closed out and believe it can contribute important information about the overall safety profile of Contrave.

Important Safety Information for CONTRAVE
(naltrexone HCl and bupropion HCl) 8 mg/90 mg extended-release tablets

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC REACTIONS

Suicidality and Antidepressant Drugs
CONTRAVE is not approved for use in the treatment of major depressive disorder or other psychiatric disorders. CONTRAVE contains bupropion, the same active ingredient as some other antidepressant medications (including, but not limited to, WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, and APLENZIN). Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects over age 24; there was a reduction in risk with antidepressant use in subjects aged 65 and older. In patients of all ages who are started on CONTRAVE,

monitor closely for worsening, and for the emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. CONTRAVE is not approved for use in pediatric patients.

Neuropsychiatric Reactions in Patients Taking Bupropion for Smoking Cessation
Serious neuropsychiatric reactions have occurred in patients taking bupropion for smoking cessation. The majority of these reactions occurred during bupropion treatment, but some occurred in the context of discontinuing treatment. In many cases, a causal relationship to bupropion treatment is not certain, because depressed mood may be a symptom of nicotine withdrawal. However, some of the cases occurred in patients taking bupropion who continued to smoke. Although CONTRAVE is not approved for smoking cessation, observe all patients for neuropsychiatric reactions. Instruct the patient to contact a healthcare provider if such reactions occur.

Contraindications
CONTRAVE is contraindicated in: uncontrolled hypertension; seizure disorder or a history of seizures; use of other bupropion-containing products; bulimia or anorexia nervosa, which increase the risk for seizure; chronic opioid or opiate agonist (eg, methadone) or partial agonists (eg, buprenorphine) use, or acute opiate withdrawal; patients undergoing an abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs; use during/within 14 days following treatment with monoamine oxidase inhibitors (MAOIs)—there is an increased risk of hypertensive reactions when CONTRAVE is used concomitantly with MAOIs and use with reversible MAOIs such as linezolid or intravenous methylene blue is also contraindicated; known allergy to any component of CONTRAVE anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported; pregnancy.

WARNINGS AND PRECAUTIONS

Suicidal Behavior and Ideation
All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. This warning applies to CONTRAVE because one of its components, bupropion, is a member of an antidepressant class.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of anxiety, agitation, irritability, unusual changes in behavior, and other symptoms, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by

families and caregivers. Prescriptions for CONTRAVE should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment
CONTRAVE is not approved for smoking cessation treatment, but serious neuropsychiatric symptoms have been reported in patients taking bupropion for smoking cessation. These have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Observe patients for the occurrence of neuropsychiatric reactions. Instruct patients to contact a healthcare professional if such reactions occur.

Seizures
CONTRAVE can cause seizures. The risk of seizure is dose-related. Discontinue treatment and do not restart CONTRAVE in patients who experience a seizure. Caution should be used when prescribing CONTRAVE to patients with predisposing factors that may increase the risk of seizure, including: history of head trauma or prior seizure, severe stroke, arteriovenous malformation, central nervous system tumor or infection, or metabolic disorders (eg, hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia); excessive use of alcohol or sedatives, addiction to cocaine or stimulants, or withdrawal from sedatives; patients with diabetes treated with insulin and/or oral diabetic medications (sulfonylureas and meglitinides) that may cause hypoglycemia; concomitant administration of medications that may lower the seizure threshold, including other bupropion products, antipsychotics, tricyclic antidepressants, theophylline, systemic steroids.

Clinical experience with bupropion suggests that the risk of seizure may be minimized by adhering to the recommended dosing recommendations, in particular: the total daily dose of CONTRAVE does not exceed 360 mg of the bupropion component (ie, four tablets per day); the daily dose is administered in divided doses (twice daily); the dose is escalated gradually; no more than two tablets are taken at one time; coadministration of CONTRAVE with high-fat meals is avoided; if a dose is missed, a patient should wait until the next scheduled dose to resume the regular dosing schedule.

Patients Receiving Opioid Analgesics
Vulnerability to Opioid Overdose: CONTRAVE should not be administered to patients receiving chronic opioids, due to the naltrexone component, which is an opioid receptor antagonist. If chronic opiate therapy is required, CONTRAVE treatment should be stopped. In patients requiring intermittent opiate treatment, CONTRAVE therapy should be temporarily discontinued and lower doses of opioids may be needed. Patients should be alerted that they may be more sensitive to opioids, even at lower doses, after CONTRAVE treatment is discontinued. An attempt by a patient to overcome any naltrexone opioid blockade by administering large amounts of exogenous opioids is especially dangerous and may lead to a fatal overdose or life-threatening opioid intoxication (eg, respiratory arrest, circulatory collapse). Patients should be told of the serious consequences of trying to overcome the opioid blockade.

Precipitated Opioid Withdrawal: An opioid-free interval of a minimum of 7 to 10 days is recommended for patients previously dependent on short-acting opioids, and those patients transitioning from buprenorphine or methadone may need as long as two

weeks. Patients should be made aware of the risks associated with precipitated withdrawal and encouraged to give an accurate account of last opioid use.

Increase in Blood Pressure (BP) and Heart Rate (HR)
CONTRAVE can cause an increase in systolic BP, diastolic BP, and/or resting HR. These events were observed in both patients with and without evidence of preexisting hypertension. In clinical practice with other bupropion-containing products, hypertension, in some cases severe and requiring acute treatment, has been reported. Blood pressure and pulse should be measured prior to starting therapy with CONTRAVE and should be monitored at regular intervals consistent with usual clinical practice, particularly among patients with cardiac or cerebrovascular disease and/or with controlled hypertension prior to treatment.

Allergic Reactions
Anaphylactoid/anaphylactic reactions and symptoms suggestive of delayed hypersensitivity have been reported with bupropion, as well as rare spontaneous reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock. Instruct patients to discontinue CONTRAVE and consult a healthcare provider if they develop an allergic or anaphylactoid/anaphylactic reaction (eg, skin rash, pruritus, hives, chest pain, edema, or shortness of breath) during this treatment.

Hepatotoxicity
Cases of hepatitis, clinically significant liver dysfunction, and transient asymptomatic hepatic transaminase elevations have been observed with naltrexone exposure. Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis. CONTRAVE should be discontinued in the event of symptoms/signs of acute hepatitis.

Activation of Mania
Bupropion, a component of CONTRAVE, is a drug used for the treatment of depression. Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating CONTRAVE, screen patients for history of bipolar disorder and the presence of risk factors for bipolar disorder (eg, family history of bipolar disorder, suicide, or depression). CONTRAVE is not approved for use in treating bipolar depression.

Angle-Closure Glaucoma
The pupillary dilation that occurs following use of many antidepressant drugs, including bupropion, may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Hypoglycemia with Use of Antidiabetic Medications
Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (eg, sulfonylureas). Measurement of blood glucose levels prior to starting CONTRAVE and during CONTRAVE treatment is recommended in patients with type 2 diabetes. Decreases in medication doses for antidiabetic medications which are non-glucose-dependent should be considered to mitigate the risk of hypoglycemia.

Adverse Reactions Most common adverse reactions (≥5%) include: nausea (32.5%), constipation (19.2%), headache (17.6%), vomiting (10.7%), dizziness (9.9%), insomnia (9.2%), dry mouth (8.1%), and diarrhea (7.1%).

Drug Interactions
Increased risk of hypertensive reactions can occur when CONTRAVE is used concomitantly with MAOIs. Use caution and consider dose reduction of drugs metabolized by CYP2D6 when using with CONTRAVE. Avoid concomitant use with CYP2B6 inducers. Reduce CONTRAVE dose when taken with CYP2B6 inhibitors. Dose CONTRAVE with caution when used with drugs that lower seizure threshold. Use caution and monitor for CNS toxicity when using CONTRAVE concomitantly with dopaminergic drugs (levodopa and amantadine). CONTRAVE can cause false positive urine test results for amphetamines.

Indication
CONTRAVE is 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/m2 or greater (obese) or

· 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (eg, hypertension, type 2 diabetes mellitus, or dyslipidemia)

Limitations of Use
The effect of CONTRAVE on cardiovascular morbidity and mortality has not been established. The safety and effectiveness of CONTRAVE in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established.

Please see accompanying full Prescribing Information and Medication Guide for CONTRAVE.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

About Orexigen Therapeutics
Orexigen Therapeutics, Inc. is a biopharmaceutical company focused on the treatment of obesity. Orexigen developed Contrave® (naltrexone HCl and bupropion HCl extended-release), which is approved in the United States and is being commercialized there by the company's North American partner, Takeda Pharmaceuticals. In Europe, the drug has been approved under the brand name Mysimba™ (naltrexone HCl/bupropion HCl prolonged release). Orexigen's strategy for Contrave/Mysimba is to pursue marketing authorizations worldwide and pharmaceutical partnerships for global commercialization. Further information about the Company can be found at www.orexigen.com.

Forward-Looking Statements

Statements included in this press release that are not a description of historical facts are forward-looking statements. Words such as "believes," "anticipates," "plans," "expects," "indicates," "will," "should," "intends," "potential," "suggests," "assuming," "designed" and similar expressions are intended to identify forward-looking statements. These statements are based on the Company's current beliefs and expectations. These forward-looking statements include statements regarding: that Takeda is on track to initiate a PMR CV outcomes trial later this year; the completion of the Light Study final analysis and the publication of the final results, our plans to enter into an arbitrated dispute resolution process with Takeda and the outcome of that process, as well as any rights, remedies or assertions of counterclaims that we may make. Inclusion of forward□ looking statements should not be regarded as a representation by the Company that any of its plans will be achieved. Actual results may differ materially from those expressed or implied in this release due to the risk and uncertainties inherent in the business, including, without limitation: the dispute with Takeda could result in an arbitrator determining that Orexigen is in material breach of the collaboration agreement, require Orexigen to pay large sums of money or have other adverse effects on Orexigen; Orexigen's dependence on Takeda to carry out the new CV outcomes trial and the commercialization of Contrave; competition in the obesity market, particularly from existing therapies; the ability to obtain and maintain intellectual property protection for Contrave; additional analysis of the interim results of the Light study or the additional CV outcomes trial, including safety-related data, may produce negative or inconclusive results; the therapeutic and commercial value of Contrave; legal or regulatory proceedings against Orexigen, as well as potential reputational harm, as a result of [misleading] public claims about Orexigen; and other risks described in Orexigen's filings with the Securities and Exchange Commission. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof, and Orexigen undertakes no obligation to revise or update this news release to reflect events or circumstances after the date hereof. Further information regarding these and other risks is included under the heading "Risk Factors" in Orexigen's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission May 8, 2015 and its other reports, which are available from the SEC's website (www.sec.gov) and on Orexigen's website (www.orexigen.com) under the heading "Investor Relations." All forward-looking statements are qualified in their entirety by this cautionary statement. This caution is made under the safe harbor provisions of Section 21E of the Private Securities Litigation Reform Act of 1995.

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