Mail Stop 6010

January 12, 2007

Gary D. Tollefson, M.D., Ph.D.
President and Chief Executive Officer
Orexigen Therapeutics, Inc.
12841 High Bluff Drive, Suite 160
San Diego, CA 92130

Re: Orexigen Therapeutics, Inc.
Registration Statement on Form S-1
Filed December 19, 2006
File No. 333-139496

Dear Dr. Tollefson:

We have reviewed your filing and have the following comments. Where indicated, we think you should revise your document in response to these comments. If you disagree, we will consider your explanation as to why our comment is inapplicable or a revision is unnecessary. Please be as detailed as necessary in your explanation. In some of our comments, we may ask you to provide us with information so we may better understand your disclosure. After reviewing this information, we may raise additional comments.

Please understand that the purpose of our review process is to assist you in your compliance with the applicable disclosure requirements and to enhance the overall disclosure in your filing. We look forward to working with you in these respects. We welcome any questions you may have about our comments or any other aspect of our review. Feel free to call us at the telephone numbers listed at the end of this letter.

FORM S-1
General

1. We note that you intend to seek confidential treatment for certain of your exhibits. In that regard, please be advised that comments related to your request for confidential treatment will be delivered under separate cover. We will not be in a position to consider a request for acceleration of effectiveness of this registration statement until we resolve all issues concerning the confidential treatment request.

2. Please provide us proofs of all graphic, visual, or photographic information you will provide in the printed prospectus prior to its use, for example in a preliminary

prospectus. Please note we may have comments regarding these materials.

3. Please note that when you file a pre-effective amendment containing pricing-related information, we may have additional comments. As you are likely aware, you must file this amendment prior to circulating the prospectus.

4. Please note that when you file a pre-effective amendment that includes your price range, it must be bona fide. We interpret this to mean your range may not exceed $2 if you price below $20 and 10% if you price above $20.

5. Please note that where we provide examples to illustrate what we mean by our comments, they are examples and not complete lists. If our comments are applicable to portions of the filing that we have not cited as examples, please make the appropriate changes in accordance with our comments.

Prospectus Summary

6. We note that first paragraphs of your Summary, MD&A and Business sections are identical. Please revise your disclosure to eliminate this unnecessary repetition.

7. You state that you are focused on developing and commercializing pharmaceutical products. We note that you have no products and that your focus to date has developing your product candidates. Also, disclosure in your MD&A section indicates that while you have expended funds to develop product candidates and conduct FDA testing, you have not expended funds for marketing, pre-marketing, sales or other commercial activity. Please revise your disclosure in this sentence and throughout the prospectus to reflect that your company is developing product candidates that may or may not ever become products or be commercialized.

8. You go on to state that your product candidates combine approved drugs with post-marketing safety records. Throughout the prospectus where you make these statements and in more detail the risk factor on page 10 entitled, “Our product candidates may cause undesirable side effects…,” please disclose that the safety of the combined consumption of these drugs that are your product candidates has not received regulatory approval and is not yet known.

9. Throughout this section and the rest of your document, including your Business and MD&A sections, you reference several industry sources and various statistics and other figures, including statements relating to the market in which you expect your products to compete. In some places, you do not provide the source of your information. In that regard, please revise your document to indicate the sources of information you have relied on making these statements.

10. We note that much of the statistical information relating to your potential market relates to the estimated worldwide market and the market in the United States. On page 14 your disclosure suggests that you will be directing each of your lead product candidates to specific segments of the obesity marketplace. In that regard, please revise to highlight the estimate for the market(s) where you expect to market your product candidates to the extent possible.

11. We note that a key constituent of Contrave and Excalia is bupropion, which is used in the treatment of depression and to assist smoking cessation. We further note that many, if not all, of your clinical trials have been conducted using non-smoking patients exclusively. Please disclose why you have limited the patient pool to non-smokers. Any perceived risks or precautions you are taking as to non-smokers should be disclosed in the Business and Risk Factors sections, and any possible limitations on your market opportunity for these product candidates should be articulated where you discuss the potential market size.

12. We note your disclosure of the results of your clinical trials throughout this section and the rest of your document. Please revise your discussions to include appropriate caveats indicating that the results do not provide enough evidence regarding efficacy or safety to support an application with the FDA, that additional tests will be conducted and that subsequent results often do not corroborate earlier results. Also, where you discuss the results of your clinical trials, you should note any adverse events or side-effects that were observed.

13. We note you disclose the results of your various clinical trial studies in this section. The disclosure in the summary should be limited to a discussion of the extent of testing, such as the drugs, indication(s) and current phase of testing. In that regard, please relocate the disclosure regarding the efficacy results from the summary to your Business section.

14. Where you discuss naltrexone for the first time on page 2, you should disclose the associated nausea side effects.

Risk Factors (In Summary section), page 4

15. Please revise to state that you have a history of losses, quantify the losses for each of the last three years and your accumulated deficit, state that you expect to continue to incur significant operating losses in future periods and state that none of your product candidates has been approved for sale by regulatory authorities.

"We are largely dependent on the success of our two product candidates . . . .," page 9

16. We note your disclosure that you are not permitted to market your product candidates in the United States until you receive approval of a new drug

application. If true, please provide similar disclosure with respect to your ability to market your product candidates in foreign countries as well.

"Our clinical trials may fail to demonstrate acceptable levels of safety . . . .," page 9

17. We note your disclosure that you may need to complete additional preclinical testing of your product candidates to evaluate "genotoxicity, reproductive toxicology carcinogenicity." Please revise your document to explain these terms.

"We expect intense competition in the obesity marketplace for Contrave . . . .," page 13

18. You indicate that Sanofi-Aventis received an "approvable letter from the FDA" relating to potential marketing in the United States regarding the drug Simonabant. Please explain what an approvable letter from the FDA is in this risk factor.

"We will need to increase the size of our organization, and we may . . . .," page 21

19. We note your disclosure that you have engaged the consulting firm PharmaDirections, Inc., who serves as your primary drug development consultant and manages subcontractors on your behalf as disclosed on page 77 of your document. To the extent you have entered into an agreement with this firm, please file the agreement and describe the terms of the agreement in an appropriate part of your Business section. You should also file the agreement as an exhibit. If you do not believe the agreement is material, please provide us with a detail analysis explaining why you are not substantially dependent on the agreement you have with PharmaDirections.

"We may not be able to manage our business effectively if we are unable . . . .," page 22

20. Please identify the members that you consider key personnel.

21. To the extent that you have experienced difficulties attracting and retaining key personnel, please revise to discuss these difficulties. Also, disclose whether any key personnel have plans to retire or leave your company in the near future.

"Our business involves the use of hazardous materials and we and our . . . .," page 24

22. Please indicate if you currently maintain insurance coverage related to your use of hazardous materials? If yes, please disclose the coverage amount. If no, please indicate if you intend to seek such coverage and approximately when you intend to do so. Also, here and in MD&A, please note and quantify to the extent possible expected increases in expense for coverage for hazardous waste or other forms of insurance coverage going forward, if any.

"Our business and operations would suffer in the even to system failures," page 24

23. To the extent you have experienced system failures in the past that have materially impacted you, please describe the incidence and its impacts on your business and operations.

"The issued patent rights that we have in-licensed covering Contrave and . . . .," page 25

24. You indicate that both pending Weber/Cowley patent applications were initially rejected by the US Patent and Trademark Offices. Please specify the reasons these applications were initially rejected.

"If we are sued for infringing intellectual property rights of third parties . . . .," page 27

25. Please disclose who has the obligations to take necessary actions to protect patents under your license and collaboration agreements. If you do not have the obligation to take action, do you have the right to take necessary actions if the other party does not?

"We have never paid dividends on our capital stock, and we do not . . . .," page 37

26. Please revise the heading of this risk factor to state that because you do not anticipate paying any dividends on the common stock, capital appreciation, if any, of your common stock will be the investor's sole source of gain. We note you have provided for this disclosure in the body of the risk factor.

Special Note Reagrding Forward Looking Statements, page 38

27. On page 39, please expand the last sentence of this section to state that the forward-looking statements are also excluded from Section 21E of the Exchange Act.

Use of Proceeds, page 40

28. Please disclose the approximate amount and timing of the proceeds you plan to use for each of your lead product candidates, Contrave and Excalia, including where in the drug development process you expect to be after the expenditure of these proceeds.

29. Please describe which "general corporate purposes" you plan to use the proceeds from this offering for. State an approximate dollar amount for each.

30. You indicate that you may use a portion of your net proceeds to in-license, acquire or invest in complementary businesses or products. Please clarify from which currently specified allocation(s) you will take funds for such possible use.

Management's Discussion and Analysis of Financial, page 47

Critical Accounting Policies and Estimates, page 49
Stock-Based Compensation, page 49

31. Please revise this discussion to provide the price at which the Series B redeemable convertible preferred stock was issued in April and May 2005 and approximately how much of the proceeds were from unrelated parties. In addition, please clarify how the rights, preferences and privileges of the preferred stock relative to the common stock impacted the fair value of the common stock. Please note that we may have additional questions regarding the valuation methodologies once the price range of the offering has been determined.

Results of Operations, page 51

32. Under each of the headings pertaining to research and development, please provide more specific disclosure regarding upon which programs or trials you made r&d expenditures.

Liquidity and Capital Resources, page 53

33. Please revise to disclose the dates you issued the shares and option to purchase shares to Duke, Oregon Health & Science and Dr. Lee Dante, respectively, pursuant to license agreements with each of those parties. With respect to the option granted to Dr. Dante, please also disclose exercise price and expiration date of the option.

Business, page 57
Overview, page 57

34. You indicate in the fifth full paragraph that you anticipate moving one or more of your preclinical programs into clinical trials during 2007. Please identify and describe the preclinical programs you are referring to in this sentence.

Future Contrave Clinical Development Plans, page 68

35. We note your disclosure that in a recent correspondence with the FDA that the agency did not object to your conclusion that the results of your "Phase IIb clinical trial demonstrated that the combination of naltrexone and bupropion is more effective than the individual components." Please revise to clarify that the agency's non-objection to your conclusion does not necessarily mean that the agency supports your conclusion.

Oregon Health & Science University License Agreement, page 75

36. In Note 3 to the financial statements, there is disclosure that you were required to make 50% of the expenses incurred in the maintenance and prosecution of the licenses pursuant to the licensing agreement you have with Oregon Health & Science University. Please revise your disclosure on page 75 to clarify what, if any, expenses you paid in connection with the maintenance and prosecution of the licenses you obtained from Oregon Health & Science as well as what your obligations are regarding future expenses related to the maintenance and prosecution of licenses obtained from the Oregon Health & Science University.

Lee Dante License Agreement, page 76

37. Please disclose the exercise price of the option granted to Dr. Lee as well as the expiration date of the option.

Executive Officers, page 86
Board of Directors, pate 88

38. Please revise the discussion to provide the applicable dates and places of business for the last five years for Michael A. Cowley; Franklin P. Bymaster; and Eckard Weber.

Executive Compensation, page 92

39. Please note that your next amendment must comply with the new executive compensation rules and rules regarding related party transactions. Please see Release No. 33-8723A.

Summary Compensation Table, page 92

40. Please update your table to provide compensation information for the year ended December 31, 2006.

Principal Stockholders, page 103

41. Please provide the full name(s) of the natural persons having voting, dispositive or investment powers over the shares held by Morgenthaler Partners VII, LP.

Consulting Agreements, page 109

42. We note your disclosure regarding the consulting agreement you entered into with Mr. Crowley. You state that as consideration for his services you agreed not to exercise his right of repurchase with respect to 93,277 shares then owned by him. Please disclose the per share price that you would have repurchased the shares. Please also describe the material provisions of your right of repurchase.

Notes to Financial Statements, page F-7

43. Please consider disclosing the recently issued accounting standards that were adopted and describe the impact the adoption of these accounting standards had on your financial statements. Please refer to SAB 74 for guidance.

Note 1. Organization and Basis of Presentation, page F-7
Revenue Recognition, page F-9

44. Since your collaborative agreements contain multiple elements, please tell us and disclose your consideration of EITF 00-21. For non-refundable upfront fees, please clarify the circumstances when revenue would not be recognized over the period the related services are provided. See SAB Topic No. 104, Topic 13A.3(f). For the amounts received under collaborative research and development agreements, please clarify the circumstances when revenues are recognized as research costs are incurred over the period specified in the agreement as opposed to when services are performed. As it appears as though the first method uses an input measure (cost), please clarify for us why such a measure is appropriate given that output measures are typically more reliable for determining progress. In your explanation, describe the relationship between costs incurred and the performance of services.

Note 3. Commitments and Contingencies, page F-13
Technology and License Agreements, page F-13

45. Please expand your disclosure to include the length of and termination provisions for all of the agreements. In addition, for the Cypress Bioscience agreement, please clarify that the upfront fee received is non-refundable and disclose the amount of future payments that you may be required to make to Duke upon Cypress's achievement of various regulatory milestones. Also revise your discussion related to contractual obligations on page 55 to include the total

amount that you may be required to pay to Duke under your agreement with Cypress.

46. Related to the Cypress agreement, disclose how much of the $57 million of potential milestones relate to sleep apnea and thus are unlikely to be received. In addition, disclose the period over which the upfront payment is being recognized over and how that period was determined. Clarify your obligations under the Cypress agreement, for example, indicate if you are performing research for Cypress under the agreement. Indicate why deferral of revenue is required.

Operating Lease, page F-14

47. Please expand your disclosure to include the withdrawal restrictions on the certificate of deposit that is included in restricted cash.

Note 7, Stock Options, page F-18

48. Upon completion of the pricing of this offering we may have comments on your accounting for stock compensation and related disclosure.

Item 15. Recent Sales of Unregistered Securities, page II-2

49. Please disclose the number of persons to whom you have issued stock options in sentence numbered "9." in this section.

Item 16. Exhibits and Financial Statement Schedules, page II-4

50. We note that some of your exhibits are not yet filed. Please note that once you have filed the remaining agreements as exhibits, we will need time to review the documents, and we may have comments on them.

* * *

As appropriate, please amend your registration statement in response to these comments. You may wish to provide us with marked copies of the amendment to expedite our review. Please furnish a cover letter with your amendment that keys your responses to our comments and provides any requested information. Detailed cover letters greatly facilitate our review. Please understand that we may have additional comments after reviewing your amendment and responses to our comments.

We urge all persons who are responsible for the accuracy and adequacy of the disclosure in the filing to be certain that the filing includes all information required under

the Securities Act of 1933 and that they have provided all information investors require for an informed investment decision. Since the company and its management are in possession of all facts relating to a company's disclosure, they are responsible for the accuracy and adequacy of the disclosures they have made.

Notwithstanding our comments, in the event the company requests acceleration of the effective date of the pending registration statement, it should furnish a letter, at the time of such request, acknowledging that:

- should the Commission or the staff, acting pursuant to delegated authority, declare the filing effective, it does not foreclose the Commission from taking any action with respect to the filing;

- the action of the Commission or the staff, acting pursuant to delegated authority, in declaring the filing effective, does not relieve the company from its full responsibility for the adequacy and accuracy of the disclosure in the filing; and

- the company may not assert staff comments and the declaration of effectiveness as a defense in any proceeding initiated by the Commission or any person under the federal securities laws of the United States.

In addition, please be advised that the Division of Enforcement has access to all information you provide to the staff of the Division of Corporation Finance in connection with our review of your filing or in response to our comments on your filing.

We will consider a written request for acceleration of the effective date of the registration statement as confirmation of the fact that those requesting acceleration are aware of their respective responsibilities under the Securities Act of 1933 and the Securities Exchange Act of 1934 as they relate to the proposed public offering of the securities specified in the above registration statement. We will act on the request and, pursuant to delegated authority, grant acceleration of the effective date.

We direct your attention to Rules 460 and 461 regarding requesting acceleration of a registration statement. Please allow adequate time after the filing of any amendment for further review before submitting a request for acceleration. Please provide this request at least two business days in advance of the requested effective date.

You may contact Vanessa Robertson at (202) 551-3649 or Lisa Vanjoske at (202) 551-3614 if you have questions regarding comments on the financial statements and related matters. Please contact Song Brandon at (202) 551-3621, Michael Reedich, Special Counsel at (202) 551-3612, or me at (202) 551-3715 with any other questions.

Sincerely,

Jeffrey Riedler
Assistant Director

cc: Charles K. Ruck, Esq.
Cheston J. Larson, Esq.
Latham & Watkins LLP
12636 High Bluff Drive, Suite 400
San Diego, CA 92130