

*APPLICATION NUMBER:*  
**21-173**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

Olanzapine Pamoate Monohydrate

NDA No.: 22-173

**ITEM 13: PATENT INFORMATION**

The following patents cover the above referenced product, claiming the drug substance, the drug product, and/or a method of use. This product is the subject of an application submitted under Section 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA).

<b>Patent Number</b>	<b>Expiration Date</b>
U. S. 5,229,382	April 23, 2011
U.S. 6,169,084	September 30, 2018

The above patents are owned by Eli Lilly and Company or it wholly owned subsidiary Lilly Industry Limited, or exclusively licensed by Eli Lilly and Company. Attached is an FDA Form 3542a for each patent.

**ITEM 14: CLAIMED EXCLUSIVITY**

Eli Lilly and Company (Lilly) claims a three-year period of exclusivity for Zyprexa® Adhera™ as provided in 21 C.F.R. § 314.108(b)(4) and 21 U.S.C. §§ 355(c)(3)(E)(iii) and 355(j)(5)(F)(iii). Zyprexa® Adhera™ contains an active moiety that has been approved in another application under 21 U.S.C. § 355(b). The present application contains reports of new clinical investigations (other than bioavailability studies) that were conducted or sponsored by Lilly, and that are essential to the approval of the application, as follows:

1. “New Clinical Investigation”: To the best of Lilly’s knowledge and belief, each of the clinical investigations included in this application meets the definition of a “new clinical investigation” set forth in 21 C.F.R. § 314.108(a);
2. “Essential to Approval”:  
Lilly has thoroughly searched the scientific literature for all published studies and publicly available reports of clinical investigations relevant to the approval being requested in this application. No such studies or publicly available reports were identified. Therefore the clinical investigations contained in this application are essential to approval as defined in 21 C.F.R. § 314.108(a).
3. “Conducted or Sponsored By Lilly”:  
Lilly was the sponsor named in the Form FDA-1571 for an investigational new drug application, IND No. 60,701 under which the new clinical investigation(s) that are essential to the approval of its application were conducted.

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use**

NDA NUMBER

22-173

NAME OF APPLICANT / NDA HOLDER

Eli Lilly and Company

**The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.**

TRADE NAME (OR PROPOSED TRADE NAME)

Zyprexa® Adhera™

ACTIVE INGREDIENT(S)

Olanzapine pamoate monohydrate

STRENGTH(S)

210mg base equivalent, 300mg base equivalent, 405mg base equivalent

DOSAGE FORM

injectable

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number  
5,229,382

b. Issue Date of Patent  
July 20, 1993

c. Expiration Date of Patent  
April 23, 2011

d. Name of Patent Owner  
Lilly Industries Limited  
(now known as Eli Lilly and Company Limited)

Address (of Patent Owner)  
Kingsclere Road

City/State  
Basingstoke Hampshire RG21-6XA

ZIP Code  
United Kingdom

FAX Number (if available)  
44-1256-315170

Telephone Number  
44-1256-315000

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)  
P.O. Box 6288

City/State  
Indianapolis, Indiana

ZIP Code  
46206-6288

FAX Number (if available)  
317-276-3861

Telephone Number  
317-276-2958

E-Mail Address (if available)  
patents@lilly.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?  Yes  No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?  Yes  No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**3. Drug Product (Composition/Formulation)**

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2	Patent Claim Number (as listed in the patent) 4	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Zyprexa® Adhera™ is indicated for treatment of Schizophrenia.	
4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2	Patent Claim Number (as listed in the patent) 5	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Zyprexa® Adhera™ is indicated for treatment of Schizophrenia.	

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 7	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Zyprexa® Adhera™ is indicated for treatment of Schizophrenia.
<b>5. No Relevant Patents</b>	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. <input type="checkbox"/> Yes	

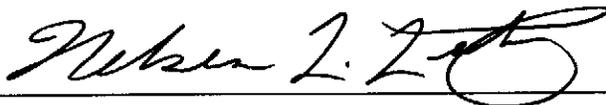
**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)**

Date Signed



April 12, 2007

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name  
Nelsen L. Lentz

Address  
P.O. Box 6288

City/State  
Indianapolis, Indiana

ZIP Code  
46206-6288

Telephone Number  
317-276-1207

FAX Number (if available)  
317-277-6534

E-Mail Address (if available)  
lentz\_nelsen\_l@lilly.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/dahtm/dahtm.html>.

**First Section**

Complete all items in this section.

**1. General Section**

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

**2. Drug Substance (Active Ingredient)**

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

**4. Method of Use**

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**  
*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use*

NDA NUMBER

22-173

NAME OF APPLICANT / NDA HOLDER

Eli Lilly and Company

**The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.**

TRADE NAME (OR PROPOSED TRADE NAME)

Zyprexa® Adhera®

ACTIVE INGREDIENT(S)

Olanzapine pamoate monohydrate

STRENGTH(S)

210mg base equivalent, 300mg base equivalent, 405mg base equivalent

DOSAGE FORM

injectable

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number  
6,169,084

b. Issue Date of Patent  
January 2, 2001

c. Expiration Date of Patent  
September 30, 2018

d. Name of Patent Owner  
Eli Lilly and Company

Address (of Patent Owner)  
P.O. Box 6288

City/State  
Indianapolis, Indiana

ZIP Code  
46206-6288

FAX Number (if available)  
317-276-3861

Telephone Number  
317-276-2958

E-Mail Address (if available)  
patents@lilly.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)  
P.O. Box 6288

City/State  
Indianapolis, Indiana

ZIP Code  
46206-6288

FAX Number (if available)  
317-276-3861

Telephone Number  
317-276-2958

E-Mail Address (if available)  
patents@lilly.com

General Patent Counsel, Eli Lilly and Company

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes  No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes  No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

**2. Drug Substance (Active Ingredient)**

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No
- 2.6 Does the patent claim only an intermediate?  Yes  No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No
- 3.2 Does the patent claim only an intermediate?  Yes  No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No  
7
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)  
Zyprexa® Adhera™ indicated for treatment of Schizophrenia.

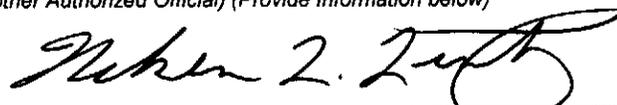
**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

<b>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</b> 	<b>Date Signed</b> <i>April 12, 2007</i>
---	---

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<b>Name</b> Nelsen L. Lentz	
<b>Address</b> P.O. Box 6288	<b>City/State</b> Indianapolis, Indiana
<b>ZIP Code</b> 46206-6288	<b>Telephone Number</b> 317-276-1207
<b>FAX Number (if available)</b> 317-277-6534	<b>E-Mail Address (if available)</b> lentz_nelsen_l@lilly.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
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- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/dahtm/fdahim.html>.

**First Section**

Complete all items in this section.

**1. General Section**

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

**2. Drug Substance (Active Ingredient)**

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

**4. Method of Use**

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

## EXCLUSIVITY SUMMARY

NDA # 22-173

SUPPL # n/a

HFD # 130

Trade Name Zyprexa Relprevv For Extended Release Injectable Suspension

Generic Name olanzapine

Applicant Name Eli Lilly

Approval Date, If Known 9/11/09

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505 (b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).



summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

HGJZ  
HGKA  
HGKB

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

no to all investigations

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

no to all investigations

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

HGJZ  
HGKA  
HGKB

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # 60,701            YES             ! NO   
! Explain:

Investigation #2  
IND # 60701            YES             ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

all investigations carried out under IND 60,701

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Keith Kiedrow

Title: Regulatory Project Manager

Date: 9/11/09

Name of Office/Division Director signing form: Thomas Laughren

Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22173	ORIG-1	ELI LILLY CO	ZYPREXA/ADHERA

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/s/

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KEITH J KIEDROW  
09/14/2009

THOMAS P LAUGHREN  
09/14/2009

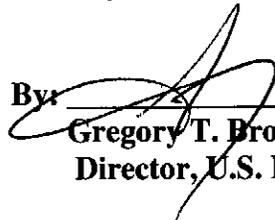
**Debarment Certification**

**NDA No: 22-173**

**Drug Name: Zyprexa Adhera (olanzapine pamoate) Injection, Powder, for Suspension for Intramuscular use**

**Pursuant to provision of 21 U.S.C. 335a(k)(1), Eli Lilly and company, through Gregory T. Brophy, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b)[21 U.S.C. 335a(a) or (b) of the Generic Drug enforcement Act of 1992, in connection with the above referenced application.**

**Eli Lilly and Company**

By:  \_\_\_\_\_  
**Gregory T. Brophy, Ph.D.**  
**Director, U.S. Regulatory Affairs**

Date: 4/16/07  
\_\_\_\_\_ **April 16, 2007**

## Request for Waiver of Pediatric Studies

Eli Lilly and Company has not conducted, and does not intend to conduct studies of Zyprexa Adhera (olanzapine pamoate for depot administration) for schizophrenia in the pediatric population. As described in the Final Pediatric Rule (21 CFR 314.55 (a)), the following is a formal request for waiver of pediatric studies for the use of Zyprexa Adhera in the pediatric population. The waiver request follows the format outlined in Attachment A of the September 2005 draft Guidance for Industry entitled, "How to Comply with the Pediatric Research Equity Act."

**Product Name:** Zyprexa Adhera  
**NDA Number:** 22-173  
**Sponsor:** Eli Lilly and Company  
**Indication:** Schizophrenia

- 1) This waiver request covers ages birth to 17 years old.
- 2) The main justification for our request for waiver of pediatric assessment requirements is that Zyprexa Adhera is unlikely to be used in a substantial number of pediatric patients, for several reasons, including that it does not represent a meaningful therapeutic benefit over existing therapies for the pediatric population (21 CFR 314.55[2c]). Briefly, schizophrenia is less common overall in children and adolescents than in adults; compliance issues that make depot formulations attractive are less common in pediatric populations than in adult populations; and generally accepted clinical practice guidelines for treatment of schizophrenia in children and adolescents recommend only limited use of depot antipsychotics. Eli Lilly has conducted studies in schizophrenia in children and adolescents with oral olanzapine and these studies are currently under review by the FDA. If oral olanzapine is approved for use in this population it will offer an appropriate therapy by the oral route.
- 3) Further details that support this reasoning are provided below.
  - The average age of onset for schizophrenia is 18 years for men and 25 years for women. Thus, schizophrenia is much less common in children and adolescents than in adults, affecting only about 1 in 40,000 children under 18, with about 1 in 10,000 children developing the disease before the age of 12 (Burd and Kerbeshian 1987, Young and Findling 2004).
  - Depot formulations of antipsychotics are generally used in the treatment of patients with schizophrenia who are noncompliant with daily oral medications. Compliance tends to be less problematic in pediatric populations since children and adolescents are typically in the care of a parent or other adult caregiver that does not have the illness and can administer medication to the patient. Thus, while the adherence-improving feature of depot

formulations makes them an improvement over existing formulations for adult patients, adherence is less of an issue for pediatric patients and as such, depot formulations do not represent a meaningful improvement over existing therapies in this population.

- In the most recent guideline for the treatment of children and adolescents with schizophrenia from the American Academy of Child and Adolescent Psychiatry (AACAP 2001), depot antipsychotic medication is explicitly not recommended for patients with onset of schizophrenia before age 13, and is to be considered for older adolescents only in the presence of a documented history of chronic psychotic symptoms and poor medication compliance. These recommendations are based on two major considerations: First, psychotic episodes experienced by children and adolescents are not always evidence of schizophrenia, but could instead represent brief periods of psychosis related to other illnesses that will not require lifelong maintenance treatment with antipsychotics. Depot formulations are intended for use in patients who require lifelong maintenance treatment, and therefore would not be appropriate for pediatric patients until it can be ascertained that patients do not fall into the latter group. Second, a patient in the care of a responsible adult caregiver is unlikely to have adherence problems. Again, because depot formulations are generally reserved for patients who have already demonstrated difficulty with adherence to oral regimens, they again are highly unlikely to be used in younger patients, although the practice guidelines allow for this possibility in adolescents in whom chronic symptoms have been documented and who have demonstrated poor adherence.

IMS data demonstrates that these guidelines are generally being followed: In a review of prescriptions written for all of the existing depot formulations of antipsychotics in 2006 (Risperdal Consta, Haldol decanoate, haloperidol decanoate, Prolixin decanoate, and fluphenazine decanoate), (b) (4) were written for people between the ages of 19 and 59, with (b) (4) written for adolescents between the ages of 12 and 18, and none for patients 11 and younger.

Given these practice guidelines and the lesser severity of adherence issues in pediatric populations, Zyprexa Adhera is unlikely to be used in a substantial number of pediatric patients. Depot products in general are not considered to represent a meaningful therapeutic benefit above existing therapies for pediatric patients.

- 4) In summary, and pursuant to 21 CFR 314.55(2c), a full waiver is requested because schizophrenia is relatively uncommon in children and adolescents; the use of depot antipsychotics is generally not recommended for children and uncommon in adolescents; and the adherence issues that often spur the use of depot antipsychotics are less common for pediatric patients who live with responsible adult caregivers. Given this background, Zyprexa Adhera does not

represent a meaningful therapeutic benefit over existing oral therapies, and is not likely to be used in a substantial number of pediatric patients who do have schizophrenia.

**References:**

[AACAP] American Academy of Child and Adolescent Psychiatry. 2001. Practice Parameter for the assessment and treatment of children and adolescents with schizophrenia. *J Am Acad Child Adolesc Psychiatry* 40(S7):4S-23S.

Burd L, Kerbeshian J. 1987. A North Dakota prevalence study of schizophrenia presenting in childhood. *J Am Acad Child Adolesc Psych* 26:347-350.

Young CM, Findling RL. 2004. Pharmacologic treatment of adolescent and child schizophrenia. *Expert Rev. Neurotherapeutics* 4: 53-60.



NDA 020592/S-040/S-041  
NDA 022173

## INFORMATION REQUEST

Eli Lilly and Company  
Attention: Gregory T. Brophy, Ph.D.  
Director, U.S. Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to your supplemental new drug applications dated October 30, 2006, received October 31, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) tablets, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg.

We also refer to your new drug application (NDA 022173) dated and received on April 30, 2007, for Zyprexa Relprevv (olanzapine) For Extended Release Injectable Suspension 210 mg, 300 mg, and 405 mg.

FDA received a recent inquiry from a consumer who raised a general question of whether or not FDA has in its possession all the relevant safety data it needs to make final decisions about pending applications from several manufacturers whose products were involved in certain tort litigation. This consumer referred to pending tort litigation in New Jersey involving three atypical antipsychotic drugs, including Zyprexa. Allegedly a 3-judge panel was appointed to give an opinion on whether the documents involved should be made publically available, and this panel presumably recommended that the documents be released. The consumer has alleged that the documents have remained sealed, however, because of an objection by one of the manufacturers involved in this case. The consumer has raised the question of whether or not FDA has access to any such sealed documents and has had an opportunity to examine them. The consumer has urged FDA to request these documents from the companies involved.

Under 505(k) of the FFDCFA, NDA holders are required to establish and maintain such records, and make such reports, "of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug," as FDA may require, "to determine, or facilitate a determination, whether there is or may be ground for" revoking approval. Additionally, under 21 CFR 314.80 and 314.81, when appropriate, NDA

NDA 020592/S-040/S-041

NDA 022173

Page 2

holders must submit the following reports bearing on drug safety: (1) 15-day expedited reports; (2) periodic reports; (3) field alert reports; and (4) annual reports.

By this letter, we are asking you to ensure that you are in compliance with all applicable statutes and regulations, and we further request that you submit to the agency all data and information regarding any olanzapine products involved in the New Jersey case in question. If there were no documents or other information from your company that were involved in this litigation, we ask that you formally assert that by return letter. We would be happy to discuss these matters if you would find that helpful in preparing a response to this inquiry.

If you have any questions, call Kimberly Updegraff, M.S, Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.

Director

Division of Psychiatry Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20592	SUPPL-40	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/
NDA-20592	SUPPL-41	ELI LILLY AND CO	ZYPREXA(OLANZAPINE) ORAL TABS 2.5MG/5MG/
NDA-22173	ORIG-1	ELI LILLY CO	ZYPREXA/ADHERA

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/s/

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THOMAS P LAUGHREN  
11/24/2009

## **Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF NEW DRUGS  
DIVISION OF PSYCHIATRY PRODUCTS**

---

**NDA/BLA #s:** 22-173  
**Products:** Zyprexa Relprevv (olanzapine) for Extended Release Injectable Suspension  
**SPONSOR:** Eli Lilly and Company  
**FROM:** Thomas P. Laughren, MD  
**DATE:** 10/23/2009

---

This memorandum amends the REMS memorandum for Zyprexa Relprevv for Extended Release Injectable Suspension signed December 13, 2008.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Zyprexa Relprevv (olanzapine) for Extended Release Injectable Suspension to ensure that the benefits of the drug outweigh the risks of a serious syndrome characterized by Central Nervous System depression associated with a spectrum of symptoms consistent with olanzapine overdose classified as "Post-injection Delirium/Sedation Syndrome" (PDSS) identified during the NDA review. As of May 31, 2008, a total of 29 PDSS events were identified in 28 patients during Zyprexa Relprevv (olanzapine) for Extended Release Injectable Suspension clinical trials (one patient experienced two events). Based on more than 40,000 Zyprexa Relprevv (olanzapine) for Extended Release Injectable Suspension injections given to 2,054 patients in clinical trials through May 31, 2008, PDSS events have occurred in approximately 0.07% of injections or 1.4% of patients.

We have also determined that a communication plan is necessary to ensure that the benefits of Zyprexa Relprevv for Extended Release Injectable Suspension outweigh its risks. The communication plan, a “Dear HealthCare Professional” (DHCP) letter, is an appropriate addition to the REMS elements because it will make healthcare providers aware of the risk of PDSS associated with the use of Zyprexa Relprevv for Extended Release Injectable Suspension. Addition of the communication plan will therefore enhance our efforts to mitigate the risk of PDSS associated with the use of Zyprexa Relprevv for Extended Release Injectable Suspension.

Furthermore, a Medication Guide is necessary for patients and caregivers to understand the risk of PDSS, in addition to the risks of hyperglycemia, hyperlipidemia, and weight gain associated with all dosage forms of olanzapine. In reaching this determination, we considered the following:

A. The number of patients with schizophrenia in the United States is estimated to be about 3 million. The number of patients diagnosed with schizophrenia requiring injectable therapy (e.g., those who are not compliant with oral treatment) is estimated to be less than 300,000.

B. Schizophrenia is a major psychiatric illness, which if left untreated, results in enormous personal, family, and social disability.

C. Use of Zyprexa Relprevv (olanzapine) for Extended Release Injectable Suspension to treat schizophrenia results in better control of symptoms, decreased hospitalizations, and return to more normal function.

D. The expected duration of therapy with Zyprexa Relprevv (olanzapine) for Extended Release Injectable Suspension is indefinite and may be lifelong, with patients receiving injections every two or four weeks depending on doses.

E. The most serious acute risk associated with the use of Zyprexa Relprevv (olanzapine) for Extended Release Injectable Suspension is PDSS. In addition, there are other risks associated with the use of olanzapine including increased mortality and increased risk of stroke in elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, hyperglycemia, hyperlipidemia, weight gain, tardive dyskinesia, orthostatic hypotension, seizures, impaired cognitive and motor function, and hyperprolactinemia.

F. Olanzapine is not a new molecular entity.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Zyprexa Relprevv (olanzapine) for Extended Release Injectable Suspension poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients’ safe and effective use of Zyprexa Relprevv (olanzapine) for Extended Release Injectable Suspension. FDA has determined that Zyprexa Relprevv

(olanzapine) for Extended Release Injectable Suspension is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Zyprexa Relprevv (olanzapine) for Extended Release Injectable Suspension. FDA has also determined that Zyprexa Relprevv (olanzapine) for Extended Release Injectable Suspension is a product for which patient labeling could help prevent serious adverse events.

The elements of the REMS will be a Medication Guide, a communication plan, and elements to assure safe use, including that Zyprexa Relprevv (olanzapine) for Extended Release Injectable Suspension will only be prescribed by prescribers who are specially certified (505-1(f)(3)(A)), is dispensed by pharmacies and health care settings (505-1(f)(3)(C)) who have been specially certified (505- 1(f)(3)(B)), is dispensed to patients with evidence or other documentation of safe-use conditions (505- 1(f)(3)(D)), and each patient using Zyprexa Relprevv for Extended Release Injectable Suspension will be subject to certain monitoring (505-1(f)(3)(E) and will be enrolled in a registry (505-1(f)(3)(F). The REMS will also include an implementation system and a timetable for submission of assessments of the REMS.

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Thomas P. Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of New Drugs

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22173	ORIG-1	ELI LILLY CO	ZYPREXA/ADHERA

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/s/

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KEITH J KIEDROW  
10/23/2009

THOMAS P LAUGHREN  
10/23/2009



NDA 22-173

Eli Lilly and Company  
Attention: Gregory T. Brophy, Ph.D.  
Director, U.S. Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to your new drug application, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa Relprevv (olanzapine) for Extended Release Injectable Suspension

Please also refer to your March 11, 2009 complete response submission to our December 15, 2008 complete response letter.

With the aid of the Division of Medication Error Prevention and Analysis of the Office of Surveillance and Epidemiology we have the following comments to share.

Container Label, Diluent Label and Carton Labeling

1. Although we acknowledge the change in font and stroke-width of the established name, the established name still does not have a prominence commensurate to that of the proprietary name. Revise the established name per 21 CFR 201.10(g)(2) which states: The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2. The revisions made to the "Relprevv" portion of the proprietary name are inadequate and still do not provide sufficient color contrast against the background color. Revise the color of the "Relprevv" portion of the name to a color that provides more contrast with the background color and increases the readability of the name. Additionally, the "Relprevv" portion of the name and the 300 mg strength share the same green color. The colors utilized for the proprietary name should not be used for product strength differentiation. When the same color is used for both the proprietary name and strength, the effectiveness of having non-overlapping distinct colors for strengths is diminished. To decrease the risk of product strength selection errors, we reiterate that you should revise the color schemes to ensure the font colors utilized for the proprietary name are not the same as any color used to differentiate the product strengths.

Diluent Label

1. Although the font size of “Diluent for” has been increased, the drug name Zyprexa Relprevv still appears prominent because it is in the same color and font as the vials with the actual medication. Decrease the size of the drug name and revise the appearance of the drug name “Zyprexa Relprevv” on the diluent label through the use of alternate colors, shading, boxing, or some other means so that it is not as prominent and is not identical to “Zyprexa Relprevv” that appears on the actual medication.

2

(b) (4)

If you have any questions, call Keith Kiedrow, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1924.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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THOMAS P LAUGHREN  
07/31/2009

**From:** Kiedrow, Keith  
**Sent:** Friday, July 24, 2009 1:43 PM  
**To:** 'Matt Kuntz'  
**Subject:** RE: NDA 22173, Zyprexa Relprevv  
Matt,

With the help of the DDMAC group, we have the following to share -

DDMAC objects to the name (b) (4) (b) (4) is promotional in tone and should not be used to brand their REMS program. According to the Merriam Webster dictionary (b) (4) can be translated to "something that occupies a front position." Therefore, the implication of this name may be that participation in this program results in the best care.

Let me know if you have any questions/concerns.

Regards,

Keith

*Keith J. Kiedrow, Pharm.D., RAC, LCDR USPHS  
Team Leader, Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1924  
Fax: (301) 796-9838  
Email: keith.kiedrow@fda.hhs.gov*

---

**From:** Matt Kuntz [mailto:KUNTZ\_MATT@LILLY.COM]  
**Sent:** Monday, July 20, 2009 9:13 PM  
**To:** Kiedrow, Keith  
**Subject:** RE: NDA 22173, Zyprexa Relprevv

Hi Keith,

We've discussed the OSE feedback at length. Given the objection to the use of (b) (4) as the name for the Zyprexa Relprevv ETASU system, we would like to propose branding the REMS program. Our proposed name is the Zyprexa Relprevv (b) (4) program.

We are conducting a legal clearance for trademark availability, and the name may change based on the findings. However, I would like to request FDA's review of the concept prior to submitting revised materials to ensure we are aligned with your expectations and making most efficient use of time on both sides.

I've attached an excerpt from the REMS document and a revised physician enrollment form to illustrate our proposal.

If this is not an acceptable approach, I would request that we convene a brief teleconference with OSE to resolve this issue as soon as possible.

Given the approaching action date, a response by July 24th would be greatly appreciated.

Many thanks,  
Matt

-----  
Matt Kuntz, RPh, MBA, RAC  
U.S. Regulatory Affairs  
Eli Lilly and Company  
Office 317.433.1766  
(b) (4)

-----  
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"Kiedrow, Keith" <Keith.Kiedrow@fda.hhs.gov>

To "Matt Kuntz" <KUNTZ\_MATT@LILLY.COM>

cc

07/16/2009 02:07 PM

Subject RE: NDA 22173, Zyprexa Relprevv

Matt,

From our OSE group (who's helping us review the REMS) -

As far the forms are concerned they can be called patient enrollment or registry forms. But all the other REMS materials including the training, the website etc. the sponsor needs to indicate that this is a risk evaluation and mitigation strategy that restricts the distribution to ensure safe use of the drug. They cannot refer to it solely as a registry.

Let me know if you require further clarification.

Keith

*Keith J. Kiedrow, Pharm.D., RAC, LCDR USPHS  
Team Leader, Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1924  
Fax: (301) 796-9838  
Email: keith.kiedrow@fda.hhs.gov*

---

**From:** Matt Kuntz [mailto:KUNTZ\_MATT@LILLY.COM]  
**Sent:** Tuesday, July 14, 2009 12:41 PM  
**To:** Kiedrow, Keith  
**Subject:** RE: NDA 22173, Zyprexa Relprevv

Hi Keith,

Just checking in. Were you able to confirm that our interpretation of your 7/6/09 email is accurate?

The REMS response that I emailed to you on Friday should be transmitted via the WebTrader Gateway tomorrow.

Thanks,  
Matt

-----  
Matt Kuntz, RPh, MBA, RAC  
U.S. Regulatory Affairs  
Eli Lilly and Company  
Office 317.433.1766  
(b) (4)

-----  
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**Matt Kuntz/AMLLY**

07/07/2009 03:11 PM

To "Kiedrow, Keith" <Keith.Kiedrow@fda.hhs.gov>  
cc

Subject RE: NDA 22173, Zyprexa Relprevv [Link](#)

Keith,

We've had the opportunity to discuss this and would like to ensure our understanding is accurate.

We will remove the term (b) (4) from the REMS and REMS Supporting document. For example, the revised REMS document would read (excerpt with changes tracked):

Zyprexa Relprevv will be available only through a REMS program (b) (4) (b) (4) in which participants must be registered in order to prescribe, dispense, administer, or receive Zyprexa Relprevv. Distribution of Zyprexa Relprevv will be controlled by Lilly and limited only to those participants who are certified through the (b) (4) REMS enrollment process.

Based on our interpretation of the feedback in your email, "Registry" can remain on participant materials

appended to the REMS (i.e. prescriber, facility, pharmacy and patient registration forms, injection collection forms, training materials, program website, etc.). Please confirm this is correct.

Thanks  
Matt

-----  
Matt Kuntz, RPh, MBA, RAC  
U.S. Regulatory Affairs  
Eli Lilly and Company  
Office 317.433.1766  
(b) (4)  
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"Kiedrow, Keith" <Keith.Kiedrow@fda.hhs.gov>

07/07/2009 12:12 PM

To "Matt Kuntz" <KUNTZ\_MATT@LILLY.COM>

cc

Subject RE: NDA 22173, Zyrexia Relprevv

Yes, this is acceptable. Thanks.

Keith

*Keith J. Kiedrow, Pharm.D., RAC, LCDR USPHS  
Team Leader, Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1924  
Fax: (301) 796-9838  
Email: keith.kiedrow@fda.hhs.gov*

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**From:** Matt Kuntz [mailto:KUNTZ\_MATT@LILLY.COM]  
**Sent:** Monday, July 06, 2009 7:45 PM  
**To:** Kiedrow, Keith  
**Subject:** Re: NDA 22173, Zyrexia Relprevv

Keith,  
I'll share this with the team here. We may have additional questions.

Since changing "Registry" would require updating all our materials, and therefore delay our response to the 02June2009 OSE comments, I'll plan to submit the current versions containing "Registry" so the review can continue. I'm hopeful I'll have most REMS items to email to you by the end of this week. Please confirm this is acceptable.

Thanks,  
Matt

-----  
Matt Kuntz, RPh, MBA, RAC  
U.S. Regulatory Affairs  
Eli Lilly and Company  
Office 317.433.1766  
[REDACTED] (b) (4)

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"Kiedrow, Keith" <Keith.Kiedrow@fda.hhs.gov>

07/06/2009 05:45 PM

To "Matt Kuntz" <KUNTZ\_MATT@LILLY.COM>  
cc

Subject NDA 22173, Zyrexia Relprevv

Matt,

With the help of the Office of Safety and Epidemiology, we have the following response to your "registry" question -

On December 15, 2008, you received a complete response letter from the Agency notifying you that the Agency has determined that a REMS is necessary to ensure the benefits of the drug outweigh the known risk of post-injection delirium and sedation syndrome (PDSS) that occurs with NDA 22-173 , Zyrexia Relprevv (olanzapine). The Agency's decision is based on the clinical safety information submitted under this NDA.

The CR letter specified that your REMS include the following elements:

- A plan to ensure that Zyrexia TRADENAME (olanzapine) for Extended Release Injectable Suspension will only be prescribed by prescribers who are specially certified under 505- 1(f)(3)(A) through the certification process.

- A plan to ensure that Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension is only dispensed/administered in healthcare settings that are specially certified under 505-1(f)(3)(B) through the certification process.
- A plan to ensure that the drug is dispensed to patients with documentation of the following safe use conditions under 505-1 (f) (3)(D):
  - Prescribers have enrolled each patient in a program by obtaining, at the time of the first prescription and on a specific periodic schedule thereafter, a signed physician-patient agreement form that documents safe use conditions
  - Healthcare setting staff or prescriber must document that patients have been monitored for sedation or other symptoms of PDSS in a controlled environment.

Your REMS proposal described as a "registry" is insufficient in defining the program. A REMS is not a "registry" and the term registry may be construed as an observational required postmarketing study. Revise the Zyprexa Relprevv REMS and REMS Supporting Document to appropriately refer to the program as a REMS.

Let us know if you have any questions regarding this.

Thanks,  
Keith

*Keith J. Kiedrow, Pharm.D., RAC, LCDR USPHS  
Team Leader, Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1924  
Fax: (301) 796-9838  
Email: keith.kiedrow@fda.hhs.gov*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KEITH J KIEDROW  
07/29/2009

# MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** July 8, 2009

**FROM:** David J. Claffey, Ph.D., ONDQA

**SUBJECT:** **Evaluation of dissolution of recent drug product lots and final CMC recommendation for NDA 22-173, Zyprexa (olanzapine) for extended release injectable suspension**

On November 7, 2008 the OCP review team completed their evaluation of the proposed drug product dissolution specification. They recommended that the acceptance criterion for the 2-hour time point for the 210 mg strength be limited to a (b) (4) range rather than the proposed (b) (4) range.

In the previous memo by this reviewer (13 November 2009) it was mentioned that one of the validation lots for the 210 mg strength failed to meet the revised (tighter) drug product dissolution specification at the 2-hour time point. A request was made of the applicant to provide CoAs of recent lots of drug product to ensure that their full-scale commercial manufacturing process is capable of producing drug product that meet the revised drug product dissolution specification.

The applicant responded in the 29 May 2009 amendment by providing batch analysis data of nine drug product lots (A312411, A316427, A445705, A482296, A523270, A527341, A528201, A528203, and A576393) manufactured after production of the lots detailed in the application. All the lots met the proposed specification and each of the three 210 mg strength lots met the (b) (4) 2-hour acceptance criterion – in fact these results were within a relatively tight range of (b) (4).

These data do not change our previous approval recommendation from a CMC perspective.

For the record, the drug product specification which incorporates the recent change in the dissolution acceptance criterion for the 210 mg strength is included in Attachment 1 of this memo.

7 pages of Admin/Dissolution specs. has been withheld in full immediately following this page as B4 CCI/TS

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

-----  
David Claffey  
7/8/2009 09:52:48 AM  
CHEMIST

Ramesh Sood  
7/8/2009 10:17:34 AM  
CHEMIST



NDA 22-173

Eli Lilly and Company  
Attention: Gregory T. Brophy  
Director, U.S. Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Mr. Brophy:

Please refer to your New Drug Application, submitted April 30, 2007, resubmitted March 11, 2009, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa Relprevv (olanzapine for injectable suspension).

With the aid of the Office of Surveillance and Epidemiology, we have the following requests/comments regarding your application.

**1. REMS Goals and Objectives:**

A REMS is intended to ensure that the benefits outweigh the risks of the drug. Revise the goals of the REMS as follows:

- a. To mitigate negative outcomes associated with Zyprexa Relprevv induced post-injection delirium/sedation syndrome (PDSS).
- b. To establish long-term safety and safe use of Zyprexa Relprevv through periodic monitoring of all patients who receive Zyprexa Relprevv for the risk of PDSS events.

**2. Medication Guide:**

The Medication Guide has not been reviewed for content but for overall readability and format. We refer you to Appendix A for high level comments on the proposed Medication Guide. Submit the revised proposed Medication Guide for review and describe how you will ensure that a Medication Guide will be dispensed with each prescription of Zyprexa Relprevv as required by 21 CFR 208.24 in the REMS document.

**3. Communication Plan:**

You have submitted the Dear Health Care Professional (DHCP) as an optional tool and not part of the REMS materials. Since the proposed DHCP letter describes the REMS program we request that it be included in the REMS under a Communication Plan. Submit the DHCP letter as part of the REMS with the following revisions:

- a. Use verbatim language from the boxed warning in the prescribing information.

- b. Include as a safe use condition that healthcare facilities should make sure that the patient has transportation provided by someone other than themselves to their destination prior to administering the injection.
- c. Delete the statement: (b) (4)

(b) (4)

**4. Elements to Assure Safe Use (ETASU):** Address the following concerns regarding the ETASU in the proposed REMS.

- A. Reference is made in the REMS Document and REMS Supporting Document to the “Registry” which will “systematically follow and actively solicit information regarding the occurrence of signs and symptoms of PDSS.”

We remind you that a REMS will require a number of elements to assure safe use, not only 505-1(f)(3)(F). Revise the submission and remove references to the Registry and refer to the program as a REMS rather than a registry.

- B. Both the REMS and the supporting document state that the specialty distributors and pharmacy service providers will confirm enrollments before distributing the product. The flowchart (Figure 5.1 of the supporting document) indicates this confirmation will be via the Registry Database. The actual procedures for accessing the database are not provided in either document. Please provide the details.
- C. Describe the drug-handling processes and methods that will be used to ensure:
  - i. Zyprexa Relprevv goes directly from a pharmacy to a physician or the health care facility where the patient will receive the drug, without going through the patient’s hands.
  - ii. no patient will receive an injection of Zyprexa Relprevv unless he or she will be accompanied when leaving the injection facility
- D. You have defined the Pharmacy Service Provider (PSP) as any hospital, pharmacy, physician, or properly licensed healthcare facility (or “entity” as described in Appendix 3 Registry Design Document) that can order and dispense Zyprexa Relprevv. Specify the role of the pharmacy service providers and how they will ensure that the drug is only administered in certified healthcare facilities.
- E. Describe the mechanism for distributing patient identification numbers to prescribers or healthcare facilities.
- F. How and by whom will healthcare facility eligibility be confirmed?
- G. The pharmacy and healthcare facility attestation forms do not explicitly state what the different entities are agreeing to or what the specific program requirements are. Revise the forms to specify what the requirements are.
- H. Provide detailed information about the dissemination of educational material to HCPs and patients.

- i. Provide a dissemination plan for the training information to prescribers and healthcare facilities. It is unclear how the prescriber and healthcare facilities will receive the Zyprexa Relprevv Training Material Kit.
- ii. Include as an instruction that training and enrollment are required to prescribe and dispense Zyprexa Relprevv to patients.

**5. Prescriber Attestation:** Revise the first prescriber attestation in section 4.2.1 and the corresponding prescriber enrollment form to: “I have completed the mandatory Zyprexa Relprevv training and understand the risks and benefits associated with its use.”

**6. Patient Attestation:** Revise the patient attestation in section 4.2.4 and the corresponding patient enrollment form as follows:

- A. Revise the eighth attestation to: *“I agree to seek medical care right away if I have a reaction such as excessive sleepiness, dizziness, confusion, difficulty talking, difficulty walking, muscle stiffness or shaking, weakness, irritability, aggression, anxiety, increase in blood pressure or convulsions.”*
- B. Revise the tenth attestation to: *“I may be asked to complete occasional surveys about my understanding of the risks and benefits of treatment with Zyprexa Relprevv.”*
- C. Add the following attestations:
  - i. the patient received a copy of the Medication Guide;
  - ii. your doctor has explained the risks and benefits of using Zyprexa;
  - iii. you or your caregiver has discussed any questions or concerns about your treatment with Zyprexa Relprevv.

**7. Implementation System:** Address the following concerns regarding the implementation system in the proposed REMS.

- A. Provide details on the processes and procedures for verifying and collecting information on the administration of Zyprexa Relprevv.
- B. How will the healthcare facilities be monitored to ensure that they are administering Zyprexa Relprevv in accordance with the program requirements?
- C. Will there be reminder systems or alerts in place to ensure that the facilities responsible for administering Zyprexa Relprevv are in compliance with the program requirements (i.e. injection forms submitted within 7 days, PDSS forms submitted within 24 hours)?
- D. Describe plans to monitor the coordinating center and certified pharmacies and correct any deficiencies, including at a minimum
  - i. Training
  - ii. Adequacy and implementation of written procedures related to Zyprexa Relprevv registration, distribution, and dispensing
  - iii. Deviations definition, tracking, and resolution
  - iv. Fulfillment of reporting requirements

**8. Comments on specific materials:**

- A. We were not able to locate the Zyprexa Relprevv Registry Welcome Letter that was mentioned in the REMS supporting document. If this letter is part of the REMS materials, please submit for review.

- B. The following materials were submitted as part of the REMS but were considered to be promotional in nature

(b) (4)

Remove these materials from the REMS. Materials intended for promotion should be submitted to DDMAC for review prior to distribution.

- C. Healthcare Training Program: The training program for healthcare providers submitted as part of the REMS is not acceptable. The slides are promotional in nature and include information about the clinical studies. Revise the training slides as follows:
- i. Provide instructions about the risks associated with the use of this drug per the PI, registration, prescribing and dispensing the medication, dosing and administration, how to recognize PDSS in patients and the need for risk minimization.
  - ii. Remove the slides that refer to clinical trials unless they provide important information about the appropriate use of Zyprexa Relprevv.
- D. Reconstitution and Administration Recorded Presentation Script: Revise this material as follows:
- i. Provide the instruction that all HCPs that administer this product must view this video before giving the injection.
  - ii. Provide the instruction that the HCP should make sure that patients receiving injections have adequate transportation to their destination following the injection and 3 hour waiting period. Provide a definition of adequate transportation as transportation being provided by someone other than the patient.
  - iii. Add the following statement to the *instructions to patients*. Advise patients *and their caregiver* to be vigilant for symptoms of a post-injection delirium/sedation syndrome event for the remainder of the day and to obtain assistance if needed.
  - iv. In Chapter 4: Step Two, HCPs are instructed to refer to the table in the full color reconstitution and administration instructions for proper volumes of diluent to add for each vial strength. Revise this instruction. The full color reconstitution and administration instructions should be referring the HCP to the full color poster.
  - v. In Chapter 6: Step Four, HCPs are instructed to refer to the table in the instructions for the correct injection volume. This instruction is not clear. Provide a location for these instructions and the table.
- E. Registry Instruction Brochure: Currently #2 in the Prescriber Information section (Three Steps to Patient Enrollment) states that prescribers should provide patients or their guardians with a copy of the registration form only if requested. Revise the instruction to state that a copy of the registration form should be provided to each patient or their guardian.
- F. In the Pharmacy Service Provider Information three steps to enrollment, include in the review section that *Pharmacy staff should review the training and education material within this document before dispensing the medication.*
- G. Zyprexa Relprevv Registry Website Screenshots:

- i. Provide the instruction that prescribers and all healthcare professionals should refer to the full prescribing information for full details about the risks associated with the use of Zyprexa Relprevv.
- ii. For first time users, provide instructions for obtaining the username and password.
- iii. It is not clear if the healthcare administer will be able to download the poster for future reference.
- iv. It is unclear what training is specific to staff that monitors patients. Will they be required to complete the healthcare professional training?
- v. Provide the content for the pharmacy service provider.

## 9. Participant Registration Forms

### A. Prescriber Registration Forms

- i. Provide an instruction at the top of the page that training must be completed before they can enroll in the program.
- ii. The REMS does not mention the use of a Data Entry Delegate. Please provide an explanation of their responsibility in the REMS.
- iii. Revise the prescriber attestation per comments made above.

### B. Pharmacy Registration Forms

- i. Provide an instruction at the top of the page that training must be completed before they can enroll in the program.
- ii. Revise the pharmacy attestation to specify the program requirements as applicable. For example, verifying patient eligibility/enrollment, prescriber enrollment, and healthcare facility enrollment.

### C. Patient Registration Form

- i. Revise the patient attestation statements as described above.
- ii. Remove the patient agreement section. This section is redundant. A full explanation of the registry is found in a later section on the form.
- iii. The form includes a signature line for the individual conducting the consent discussion. Is this considered a consent or registration form? Please make this clear on the form and in the REMS document.
- iv. Provide a signature for the prescriber or healthcare provider completing the form. We recommend changing “signature of individual conducting consent discussion” to “prescriber signature.”
- v. Add a checkbox for the prescriber to document on the patient enrollment form that patient has been shown to be tolerant of oral olanzapine.

### D. Healthcare Facility Registration Form

- i. Provide an instruction at the top of the page that training must be completed before they can enroll in the program.
- ii. Revise “contact name” to “institutional representative name” and include his/her position title.

## 10. Data Collection Forms

### A. Injection Form

- i. Revise the form to verify the following information prior to administration of the drug:

- Does the patient have someone accompanying them to their destination after leaving the clinic?

**11. REMS Supporting Document:**

- A. Section 6.2 of the REMS Supporting Document states that noncompliant prescribers, prescriber/dispensers, healthcare facilities, or pharmacy service providers may be de-enrolled. Describe the criteria and procedures that will be used to determine when to de-enroll a participant and the circumstances under which the participant may be re-enrolled.
- B. Section 6.2, fourth bullet states “*An assessment of compliance with the requirement that all patients are associated with a registered healthcare facility prior to enrollment.*” The patient enrollment form does not include information to link a patient to a particular healthcare facility. Clarify how this is achieved.

**12. Surveys:** Address the following concerns regarding the surveys in the proposed REMS.

- A. Clarify which method of sampling will be used for each of the surveys? Random sampling or sampling by site?
- B. The method you have proposed to define adequate comprehension of the education materials will not reveal if specific educational messages are being conveyed to the respondents. The evaluation is to assess the effectiveness of conveying specific educational messages about Zyprexa Relprevv to the healthcare professionals and patients; the evaluation is not a test of an individual respondent but rather an individual risk or concept that is conveyed (or tested) in a particular question. A more appropriate way to assess the effectiveness of conveying the specific educational messages would be to look at individual questions and determine if X% of respondents answered that question correctly.
  - i. Evaluate the effectiveness of the educational materials based on X% of respondents answering each individual question correctly.
  - ii. Specify what percentage of total respondents have to get an individual question correct to consider the educational message successfully conveyed.
- C. Revise the healthcare professional survey as follows:
  - i. For questions #1, #2, #4 and #5 add an answer choice of “I don’t know”; add “select all that apply” to questions #4 and #5
  - ii. Re-word question #4 to read “Zyprexa Relprevv can be administered at which of the following sites: Select all that apply.” Add two more possible responses to this question. “in the patient’s home” and “in my office” (my referring to the doctor or respondent)
  - iii. Change the answer choices for question #3 to True/False/I don’t know
  - iv. Add a question about the symptoms of PDSS. For example:
    - Which of the following are symptoms of PDSS? Select all that apply.
      - Dizziness
      - Confusion
      - Difficulty talking
      - Difficulty walking
      - Aggression
      - Convulsions
      - Excessive sleepiness

- Stomachache
- Headache
- I don't know

D. Revise the patient survey as follows:

- i.** Clarify if caregivers will be allowed to complete the survey if the patient is unable.
- ii.** Clarify how the healthcare professional will notify selected patients. Will it be by telephone, mail or when the patient comes into the office?
- iii.** Add text explaining what the Medication Guide is or an image of it to help with recall for these questions below
- iv.** Add questions to the survey that ask if a patient read and understood the Medication Guide. For example:
  - Did you read the Medication Guide?
    - a. All
    - b. Most
    - c. Some
    - d. None
    - e. I did not get a Medication Guide
  - Did you understand what you read in the Medication Guide?
    - a. All
    - b. Most
    - c. Some
    - d. None
    - e. I did not get a Medication Guide
  - Did your healthcare provider offer to explain to you the information in the Medication Guide?
    - a. Yes
    - b. No
    - c. I did not receive the Medication Guide
  - Did you accept the offer? Yes or No
  - Did you understand the explanation that was given to you?
    - a) All
    - b) Most
    - c) Some
    - d) None
  - Did or do you have any question about the Medication Guide? Yes or No (If Yes, list your question below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA
- v.** For questions #1, #2, #3, #4, #5, #6 and #7 add an answer choice of “I don't know”
- vi.** Add “select all that apply “ to questions 2 and 4
- vii.** In question #5 add an answer choice of “Rest and see if it goes away”; add “select all that apply”; separate the response “call my doctor” and “get medical assistance” because it makes the correct answers less obvious

- viii.** Re-word question #6. For example:
- For the rest of the day after the injection, I should (select all that apply):
    - a. Watch out for symptoms of PDSS
    - b. Call my doctor after I get home
    - c. Not drive my car
    - d. Take a shower
    - e. Exercise
    - f. None of the above
    - g. I don't know
- ix.** Add a question about the symptoms of PDSS. For example:
- Which of the following are symptoms of PDSS? Select all that apply.
    - a. Dizziness
    - b. Confusion
    - c. Difficulty talking
    - d. Difficulty walking
    - e. Aggression
    - f. Convulsions
    - g. Excessive sleepiness
    - h. Stomachache
    - i. Headache
    - j. I don't know

**13. Optional Patient Tools:** Patient ID Card, Patient Wristband, and Patient Brochure were submitted but are not considered as part of the REMS. Remove these materials from the REMS. Materials intended for promotion should be submitted to DDMAC for review prior to distribution.

#### **Additional Comment**

- 14.** Format Request: The numerical system for the appendices was identical for the REMS document and REMS Supporting Document and thus made it very difficult to follow. For example, Appendix 1 in the REMS was the Healthcare Provider Training while the Appendix 1 in the Supporting Document was the Dear Healthcare Professional Letter. Revise the REMS and REMS Supporting Document using both a numeric and alpha numeric systems instead to differentiate the appendices.
- 15.** Please submit the revised Proposed REMS with appended materials and the REMS Supporting Document with a track changes and clean version of all revised materials and documents. Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant.

#### **Appendix A – High level comments on Zyprexa Relprevv Medication Guide**

- The readability scores for the MG that the applicant submitted on March 11, 2009 are not within the acceptable range. The proposed MG has a Flesch reading grade level of 10.3 and a Flesch reading ease score of 48.0%. To enhance patient comprehension, patient-directed materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. Simplify the language in the MG accordingly.
- The terms “doctor” and “healthcare provider” are used in the MG. We recommend using either “doctor” or “healthcare provider” consistently throughout the MG, except in the required verbatim

statement at the end of the section "What are the possible side effects of Zyprexa Relprevv?" where the term "doctor" is required.

- The following proposed section titles should be revised as follows:
  - [REDACTED] (b) (4) should be renamed "What should I tell my doctor before taking Zyprexa Relprevv?"
  - [REDACTED] (b) (4) should be deleted. This information goes at the end of the section "What should I tell my doctor before taking Zyprexa Relprevv." The applicant should refer to the MG approved for Zyprexa on March 19, 2009, which includes the following language:

**Tell your doctor about all the medicines that you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. ZYPREXA and some medicines may interact with each other and may not work as well, or cause possible serious side effects. Your doctor can tell you if it is safe to take ZYPREXA with your other medicines. Do not start or stop any medicine while taking ZYPREXA without talking to your doctor first.

- [REDACTED] (b) (4) should be renamed "What are the possible side effects of Zyprexa Relprevv?"
- Add the section "What should I avoid while taking Zyprexa Relprevv?" Information about avoiding alcohol and the need for caution when driving or operating machinery should be added. Refer to the Zyprexa MG.
- Revise the Zyprexa Relprevv MG to make it consistent with the MG for Zyprexa and Zyprexa Zydis, to the extent possible, given the differences in formulation, setting of use, the risk of Post-injection Delirium/Sedation Syndrome (PDSS) and the fact that patients go home after receiving these injections.
- Submit the revised proposed MG for our review.

If you have any questions, call Keith Kiedrow, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1924.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

-----  
Thomas Laughren  
6/2/2009 03:41:15 PM



NDA 22-173

**INFORMATION REQUEST LETTER**

Eli Lilly and Company  
Attention: Gregory T. Brophy, Ph. D., Director, US Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to your April 30, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa Adhera (olanzapine) long acting injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- Provide Certificates of Analysis for all drug product lots manufactured subsequent to those detailed in the initial application (after lots A302103, A303416 and A303418).

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief, Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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Ramesh Sood

5/7/2009 04:28:57 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>HFD-860/ Biopharm/ Ray Baweja</b>		FROM: <b>HFD-130 (Division of Psychiatry Products); Keith Kiedrow</b>		
DATE <b>April 1, 2009</b>	IND NO.	NDA NO. <b>22-173</b>	TYPE OF DOCUMENT <b>Type II resubmission</b>	DATE OF DOCUMENT <b>March 11, 2009</b>
NAME OF DRUG <b>Zypraxa Relprevv (depot injection)</b>		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE <b>Final discipline reviews should be signed off to the CDTL by 7/26/09</b>
NAME OF FIRM: <b>Lilly</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: <b>Lilly has responded to our CR letter of 12/15/08 for Zypraxa depot injection for schizophrenia. Please review the resubmission from a biopharm standpoint and provide feedback as appropriate. The submission can be found at the following link - <a href="http://FDSWA150\NONECTD\N22173\N_000\2009-03-11">\FDSWA150\NONECTD\N22173\N_000\2009-03-11</a>. The PDUFA goal date is 9/12/09. Let me know if you have any questions regarding this.</b>				
SIGNATURE OF REQUESTER <b>Keith Kiedrow, Pharm.D.</b> <b>Regulatory Project Manager</b> <b>301-796-1924</b> <b>keith.kiedrow@fda.hhs.gov</b>		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

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Keith Kiedrow

4/1/2009 05:31:21 PM

**From:** Kiedrow, Keith  
**Sent:** Tuesday, March 31, 2009 6:13 PM  
**To:** 'Matt Kuntz'  
**Subject:** NDA 22-173 Zyprexa Relprevv Resubmission  
Matt,

Sorry for the delay with this - been busy here. We met when the submission came in to discuss whether this would be a type 1 or 2 resubmission and it was decided that, due to the submission of the REMS, it would be a type 2 classification. The PDUFA goal date is 9/12/09. We do not have filing meetings regarding resubmissions, but we do have a brief classification meeting which is scheduled soon after a resubmission arrives. Let me know if you have any questions. This will serve as the acknowledgement of the submission.

Thanks!  
Keith

*Keith J. Kiedrow, Pharm.D., RAC, LCDR USPHS  
Team Leader, Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1924  
Fax: (301) 796-9838  
Email: keith.kiedrow@fda.hhs.gov*

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/s/

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Keith Kiedrow  
4/6/2009 02:53:36 PM  
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IND 60,701  
NDA 22-173

Eli Lilly and Company  
Attention: Gregory T. Brophy, Ph.D.  
Director, U.S. Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Dr. Brophy:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension.

We also refer to your submission dated November 4, 2008 to IND 60,701, and your submission dated November 19, 2008, to NDA 22-173, containing the request to evaluate the proposed tradename Zyprexa RELPREVV.

With the aid of the Division of Medication Error Prevention and Analysis of the Office of Surveillance and Epidemiology we have completed the review of your submission and have the following comments.

### **Proprietary Name**

We have completed our review of the proposed proprietary name, Zyprexa Relprevv, and have concluded that it is acceptable at this time. The proprietary name, Zyprexa Relprevv, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics are altered prior to approval of the marketing of this application, the proprietary name must be resubmitted for review.

### **Labels and Labeling**

#### **A. All Labels and Labeling**

Revise the font of the established name so that it is at least one half as large as the letters comprising the proprietary name. The established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).

**B. Container Labels**

1. Revise the presentation of the proprietary name so that the entire name appears in a print font of the same color. Additionally, ensure that the font color utilized for the proprietary name contrasts with the background color and is not the same as any color used for product strength differentiation. As currently presented, the yellow-green color used for “Relprevv” and the 300 mg strength is difficult to because of the minimal contrast it provides against the grey/white background.
2. On the side panel delete the phrase [REDACTED] (b) (4) and revise to read: “Each vial contains...”
3. Revise the sentence [REDACTED] (b) (4) to read: “Reconstitute each vial with XX mL of enclosed diluent. The resultant solution will contain 150 mg/mL.” Additionally, increase the prominence of these instructions through bolding, as currently presented the labels appear crowded and the instructions are difficult to locate amongst the text.

**C. Diluent Label**

1. Reduce the prominence of the proprietary name “Zyprexa Relprevv”. Additionally, “Diluent for” should appear more prominent (by bolding, underlining, or some other means) than the drug name, Zyprexa Relprevv”.
2. Revise the font color of the statement “Diluent for Zyprexa Relprevv should not be used to reconstitute any other product” to black in order that it does not compete with the “Important: This vial...reconstitution” statement.
3. Revise the statement “IMPORTANT: This vial contains more diluent than is needed for reconstitution.” to appear more prominent by changing the font color to red and relocate it to appear immediately below the active ingredient list.
4. Delete the phrase [REDACTED] (b) (4) and revise to read: “Each vial contains...”

**D. Convenience Kit Labeling**

1. Revise the presentation of the proprietary name to assure that the font color utilized for the proprietary name contrasts with the background color and is not the same as any color used for product strength differentiation.
2. Increase the prominence of the route of administration statement by increasing the font size, bolding, coloring or some other means.
3. On the back panel delete the phrase [REDACTED] (b) (4) and revise to read: “Each vial contains...”
4. Revise the sentence [REDACTED] (b) (4) to read: “Reconstitute each vial with XX mL of enclosed diluent. The resultant solution will contain 150 mg/mL.”

**E. Insert Labeling**

1. Place the column and rows that appear in Section 2.2, Step 2 into a table with gridlines. Additionally, increase the prominence of the Header (Determining Reconstitution Volume) through bolding or some other means to minimize potential confusion with the table in Step 4.
2. Place the column and rows that appear in Section 2.2, Step 4 into a table with gridlines. Additionally, revise the header to read: Determining the final volume to inject.

3. In Section 2.2, Step 4, delete the [REDACTED] <sup>(b) (4)</sup> as the concentration for the product is 150 mg/mL regardless of the vial size used, therefore, this information is unnecessary.

**F. Instructions to Reconstitute and Administer Zyprexa Relprev Education Sheet**

In Step 4, delete the [REDACTED] <sup>(b) (4)</sup> as the concentration for the product is 150 mg/mL regardless of the vial size used, therefore, this information is unnecessary.

If you have any questions, call Keith Kiedrow, Pharm.D., Regulatory Project Manager, at 301-796-1924.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Thomas Laughren  
1/9/2009 04:32:58 PM

**Kiedrow, Keith**

---

**From:** Kiedrow, Keith  
**Sent:** Monday, January 05, 2009 4:13 PM  
**To:** 'Matt Kuntz'  
**Subject:** RE: NDA 22-173 Zyprexa Action Letter

Matt,

Regarding the facility certification question/issue - we still believe that a separate certification procedure is needed for facilities. We are willing to have a tcon to discuss this. Let me know if that would interest you all.

With regard to the latest question on dosing - no, we cannot agree to this at this time. The information you provided was reviewed and was considered prior to our action letter. Anything provided in a resubmission will also be considered.

Thanks,  
Keith

*Keith J. Kiedrow, Pharm.D., RAC, LCDR USPHS  
Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1924  
Fax: (301) 796-9838  
Email: keith.kiedrow@fda.hhs.gov*

---

**From:** Matt Kuntz [mailto:KUNTZ\_MATT@LILLY.COM]  
**Sent:** Monday, January 05, 2009 2:11 PM  
**To:** Kiedrow, Keith  
**Subject:** RE: NDA 22-173 Zyprexa Action Letter

Hi Keith,  
Happy New Year!

Any estimate when the clinical review team will have a response to the Lilly REMS proposal (in my 12/22/08 email)?

On a separate note, we are working through labeling and had a question about the following highlighted comment:

**["Starting Dose" in the table below must be more explicitly defined. Do you intend to use only one injection at the higher starting dose, or more? Please be more clear for the prescriber. Please identify where the data are to support this argument for a higher starting dose.]**

**Table 1: Recommended Dosing For Patients Taking Oral ZYPREXA Switching to ZYPREXA Relprev**

--	--	--	--

Target Oral ZYPREXA Dose	Starting Dose of ZYPREXA Relprev	Maintenance Dose After 2 Months of ZYPREXA Relprev Treatment
10 mg/day	210 mg/2 weeks or 405 mg/4 weeks	150 mg/2 weeks or 300 mg/4 weeks
15 mg/day	300 mg/2 weeks	210 mg/2 weeks or 405 mg/4 weeks
20 mg/day	300 mg/2 weeks	300 mg/2 weeks

The amendment to support this labeling change was submitted on 12/20/07. The hazard ratio analyses (attached) to support the higher starting dose were included at that time. Because this table was updated during the initial review cycle, and prior to our 6/13/08 complete response, I wanted to ensure the review team was aware of this previously submitted data. Or does the review team feel additional justification beyond what was provided 12/20/07 is needed to support the higher starting dose? Clarification on this point would be appreciated.

Thanks,  
Matt

-----  
Matt Kuntz, RPh, MBA  
U.S. Regulatory Affairs  
Eli Lilly and Company  
Office 317.433.1766  
(b) (4)

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"Kiedrow, Keith" <Keith.Kiedrow@fda.hhs.gov>

12/23/2008 07:43 AM

To "Matt Kuntz" <KUNTZ\_MATT@LILLY.COM>

CC "Brounstein, Daniel" <Daniel.Brounstein@fda.hhs.gov>

Subject RE: NDA 22-173 Zyprexa Action Letter

Matt,

We will get back to you with a response regarding this - It most likely will not be this week though since most of the clinical review staff is out of the office.

Keith

*Keith J. Kiedrow, Pharm.D., RAC, LCDR USPHS  
Regulatory Project Manager*

Division of Psychiatry Products  
 Center For Drug Evaluation and Research, FDA  
 Office of Drug Evaluation I  
 Ph: (301) 796-1924  
 Fax: (301) 796-9838  
 Email: keith.kiedrow@fda.hhs.gov

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**From:** Matt Kuntz [mailto:KUNTZ\_MATT@LILLY.COM]  
**Sent:** Monday, December 22, 2008 4:48 PM  
**To:** Kiedrow, Keith  
**Cc:** Brounstein, Daniel  
**Subject:** RE: NDA 22-173 Zyprexa Action Letter

Hi Keith,

Lilly seeks to clarify the REMS requirements in the 15 December 2008 Complete Response letter, in particular, the registration of facilities and the training of personnel administering OP Depot described on pages 3 and 4 of the letter:

*2. A plan to ensure that Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension is only dispensed/administered in healthcare settings that are specially certified under 505-1(f)(3)(B) through the certification process described below.*

Prescribers of depot antipsychotics typically work very closely with the clinics that administer the depot medications, versus infusion centers, for example. Due to this close working relationship, the physician is the best qualified person to ascertain the conditions of safe use for a given facility and also to ensure appropriate personnel have been trained prior to commencing treatment.

Lilly commits to training all physicians who wish to prescribe this product about the conditions of safe use. Further, Lilly proposes to fulfill the healthcare setting certification objectives set forward by FDA through physician attestation of the conditions of safe use within the facility as opposed to the separate, distinct certification process for each facility conveyed in the complete response letter.

As a condition of physician enrollment in the registry, physicians will be required to report each facility at which they will prescribe the product and to attest to conditions of safe use, including:

- Measures are in place to ensure that Zyprexa TRADENAME is administered only to patients with evidence of safe use conditions
- Facility access to emergency services

Physicians will also attest that appropriate personnel have been trained on:

- Procedures for ordering Zyprexa TRADENAME
- Procedures for administering Zyprexa TRADENAME after ensuring documentation of safe use conditions
- Procedures for reconstitution and proper injection technique
- Appropriate monitoring of patients for early recognition of somnolence and other symptoms of a PDSS event
- Providing patient tools that will be available for distribution to patients (e.g., patient take-away card, wristband, patient brochure, and patient DVD)
- Appropriate documentation of adverse events

Lilly proposes to provide training through multiple methods, including in-person, web-based, and print materials to enable flexibility for facilities' implementation of the requirements.

Lilly believes this is an appropriate approach for certification of facilities given the settings in which patients with schizophrenia receive treatment with depot antipsychotics. As part of the REMS, we will assess the effectiveness of these certification procedures and evaluate the need for modifications.

Does FDA agree with this approach? We would appreciate a response by 30 December 2008.

Please let us know if you feel it would be more advisable to discuss this in a meeting.

Happy holidays and best regards,  
Matt

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Matt Kuntz, RPh, MBA  
U.S. Regulatory Affairs  
Eli Lilly and Company  
Office 317.433.1766  
(b) (4)  
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"Kiedrow, Keith" <Keith.Kiedrow@fda.hhs.gov>

12/18/2008 03:46 PM

To "Matt Kuntz" <KUNTZ\_MATT@LILLY.COM>  
cc  
Subject RE: NDA 22-173 Zyprexa Action Letter

You're correct, you do not need to notify us.

Keith

*Keith J. Kiedrow, Pharm.D., LCDR USPHS  
Regulatory Project Manager  
Division of Psychiatry Products  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1924  
Fax: (301) 796-9838  
Email: keith.kiedrow@fda.hhs.gov*

---

**From:** Matt Kuntz [mailto:KUNTZ\_MATT@LILLY.COM]

**Sent:** Thursday, December 18, 2008 1:08 PM  
**To:** Kiedrow, Keith  
**Subject:** Re: NDA 22-173 Zyprexa Action Letter

Hi Keith,

I wanted to make sure that I don't need to submit a notice of our intent to amend the application in response to the CR letter within 10 days per the revised 314.110. Would you please confirm, or let me know if I need to take this step?

Thanks,  
 Matt

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 Matt Kuntz, RPh, MBA  
 U.S. Regulatory Affairs  
 Eli Lilly and Company  
 Office 317.433.1766  
 (b) (4)

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**Matt Kuntz/AM/LLY**

12/15/2008 04:51 PM

To "Kiedrow, Keith" <Keith.Kiedrow@fda.hhs.gov>  
 cc  
 Subject Re: NDA 22-173 Zyprexa Action Letter [Link](#)

Thanks Keith. I'll share with this with the team.  
 I really appreciate the word version of labeling.  
 Best regards,  
 Matt

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 Matt Kuntz, RPh, MBA  
 U.S. Regulatory Affairs  
 Eli Lilly and Company  
 Office 317.433.1766  
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**"Kiedrow, Keith" <Keith.Kiedrow@fda.hhs.gov>**

12/15/2008 04:23 PM

To "Matt Kuntz" <KUNTZ\_MATT@LILLY.COM>  
 cc

Subject NDA 22-173 Zyprexa Action Letter

Matt,

Attached is the action letter for NDA 22173. I've also attached a word version of the labeling with track changes shown for your convenience.

Regards,  
Keith

*Keith J. Kiedrow, Pharm.D., LCDR USPHS*

*Regulatory Project Manager*

*Division of Psychiatry Products*

*Center For Drug Evaluation and Research, FDA*

*Office of Drug Evaluation I*

*Ph: (301) 796-1924*

*Fax: (301) 796-9838*

*Email: keith.kiedrow@fda.hhs.gov [attachment "22173 to sponsor.pdf" deleted by Matt Kuntz/AM/LLY] [attachment "NDA 22173 OP Depot Labeling 12-16-08.doc" deleted by Matt Kuntz/AM/LLY]*

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/s/

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Keith Kiedrow  
1/5/2009 06:18:49 PM  
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## Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE of New Drugs  
DIVISION of Psychiatry Products

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**NDA:** 22-173  
**Product:** TRADENAME (olanzapine pamoate) for Extended Release Injectable Suspension  
**SPONSOR:** Eli Lilly and Company  
**FROM:** Thomas P. Laughren, M.D.  
**DATE:** December 16, 2008

---

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

ZYPREXA (olanzapine) tablets, orally disintegrating tablets, and intramuscular injection are approved for the treatment of schizophrenia as well as bipolar mania (monotherapy or in combination with lithium or valproate) in adults. The accumulated data indicate that patients across the age spectrum taking olanzapine are at increased risk of clinically important hyperglycemia, hyperlipidemia, and weight gain.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for olanzapine pamoate depot (OP Depot) in the treatment of schizophrenia to ensure that the benefits of the drug outweigh the risks of a serious syndrome characterized by Central Nervous System depression associated a spectrum of symptoms consistent with olanzapine overdose classified as "Post-injection Delirium/Sedation Syndrome" (PDSS). On review of the data submitted to the OP Depot NDA, DPP has determined that patients (regardless of age or gender) and their caregivers should be provided with a Medication Guide to help them understand the additional risk of PDSS in addition to the aforementioned risks of clinically important hyperglycemia, hyperlipidemia, and weight gain. Caregivers must be trained how to recognize and

manage PDSS and should be familiar with how to safely use the product (including enrolling each patient in the REGISTRY program and observing them for at least 3 hours after each injection in a controlled environment, as well as certification of all prescribers, pharmacies and healthcare facilities). In reaching this determination, we considered the following:

- A. The number of patients with Schizophrenia in the United States is estimated to be about 3 million. The number of patients diagnosed with schizophrenia requiring parenteral therapy is estimated to be less than 300,000.
- B. Schizophrenia is a major psychiatric illness, which if left untreated, results in enormous personal, family, and social disability.
- C. Use of OP Depot to treat schizophrenia results in better control of symptoms, decreased hospitalizations, and return to more normal function.
- D. The expected duration of therapy with OP Depot is indefinite and may be used for life.
- E. The most serious acute risk associated with the use of OP Depot is PDSS. In addition, there are other risks associated with the use of ZYPREXA including increased mortality and increased risk of stroke in elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, hyperglycemia, hyperlipidemia, weight gain, tardive dyskinesia, orthostatic hypotension, seizures, impaired cognitive and motor function, and hyperprolactinemia.
- F. Olanzapine is not a new molecular entity.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that OP Depot poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of OP Depot. FDA has determined that OP Depot is a product that has serious risks relative to benefits of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use OP Depot. FDA has also determined that OP Depot is a product for which patient labeling could help prevent serious adverse events.

The four elements of the REMS will be a Medication Guide; elements to assure safe use; an implementation system to monitor and evaluate the implementation of the elements; and a timetable for submission of assessments of the REMS no less frequent than 18 months, 3 years, and 7 years after the REMS is approved is also required.

The elements to assure safe use include: a plan to ensure that OP Depot will only be prescribed by prescribers who are specially certified under 505-1(f)(3)(A); a plan to ensure that OP Depot is administered only in healthcare settings that have been specially certified under 505-1(f)(3)(B); a plan to ensure that the drug is dispensed to patients with

documentation of safe conditions including at least 3 hours of observation by a healthcare professional in a controlled environment post injection; and that healthcare setting staff or prescriber must document that patients have been monitored for sedation or other symptoms of PDSS.

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Thomas P. Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of New Drugs

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/s/

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Keith Kiedrow  
12/5/2008 05:39:24 PM  
CSO



NDA 22-173

Eli Lilly and Company  
Attention: Gregory T. Brophy, Ph.D.  
Director, US Regulatory Affairs  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Dr. Brophy:

Please refer to your new drug application (NDA) dated and received April 30, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension, 210, 300, and 405 mg/vials.

We acknowledge receipt of your submissions dated June 13, 2008, October 1, 2008, November 3, 2008, and November 12, 2008.

Your submission of June 13, 2008, constituted a complete response to our February 25, 2008, letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form.

We recommend that the drug product be labeled as "Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension."

We acknowledge your proposed risk management plan for Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension, submitted with your application. Before we can continue our evaluation of NDA 22-173, you must submit a proposed Risk Evaluation and Mitigation Strategy (REMS) to this application, as described below.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a REMS if FDA has determined that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). This provision took effect on March 25, 2008.

Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension is indicated for acute and maintenance treatment of schizophrenia in adult patients.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension to ensure the benefits of the drug outweigh the risks of post-injection delirium and sedation syndrome (PDSS) that

occurs in this long-acting formulation, in addition to the risks of hyperglycemia, hyperlipidemia, and weight gain associated with all dosage forms of olanzapine. The REMS, once approved, will create enforceable obligations.

Your proposed REMS must include the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension. FDA has determined that Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension. FDA has determined that Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension is a product for which patient labeling could help prevent serious adverse events. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension injections.

The Medication Guide should include information about the risk for PDSS and the need to seek immediate medical assistance should these events occur following discharge from a healthcare facility. The Medication Guide for Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension should also include the final language for the Medication Guide that is under review regarding changes in weight, serum lipids and glucose observed with other dosage forms of olanzapine in response to the approvable letter sent August 1, 2008 (NDA 20-592/s-039/040/041; 21-520/012; 21-086/021; 18-936/077).

**Elements to Assure Safe Use:** We have determined that Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension can be approved only if elements to assure safe use are required as part of the REMS to mitigate the specific risks of serious complications related to PDSS listed in the labeling. Your proposed REMS must include, at minimum the following elements to assure safe use:

1. A plan to ensure that Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension will only be prescribed by prescribers who are specially certified under 505-1(f)(3)(A) through the certification process described below. At a minimum, the plan shall require that:
  - a. Prescribers are trained about:
    - i. Appropriate patient selection
    - ii. The need to establish tolerability with oral olanzapine prior to initiating treatment
    - iii. Proper reconstitution and administration technique
    - iv. Dosing and administration differences between Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension and rapid-acting intramuscular formulation

- v. The risks of Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension, including the risk of PDSS, the clinical presentation of PDSS, and the appropriate way to respond when a PDSS even occurs.
    - b. Prescribers have obtained certification and can attest to the following:
      - i. I have been trained and understand the risks and benefits of Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension.
      - ii. I understand that Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension should only be initiated in patients in whom tolerability with oral olanzapine has been established.
      - iii. I understand the clinical presentation of PDSS and how to manage patients should an event occur while using Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension.
      - iv. I will prescribe Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension under the conditions of safe use indicated in the Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension label.
      - v. I will enroll all patients being treated with Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension into the REMS program.
      - vi. I agree to comply with Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension program monitoring and data collection.
      - vii. I will report information concerning serious adverse events using the specified adverse event form should a patient experience significant clinical adverse events while using Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension
    - c. The sponsor will maintain a list of the prescribers who have obtained the certification, and provide the list to those with a need to know this information.
    - d. Prescribers will be retrained and recertified periodically, at a specified interval. We suggest the training and certification plan be brief and made available using multiple methods to increase participation (e.g., web-based, in-person, and print materials).
2. A plan to ensure that Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension is only dispensed/administered in healthcare settings that are specially certified under 505-1(f)(3)(B) through the certification process described below. At a minimum, the plan shall require that:
  - a. The healthcare settings have:
    - i. Systems, order sets, protocols, or other measures in place to ensure that Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension is administered only to patients with evidence of safe use conditions
    - ii. Access to emergency services
  - b. Sites undergo inservice training from the sponsor. The inservice training will include:
    - i. Procedures for ordering Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension
    - ii. Procedures for administering Zyprexa TRADENAME (olanzapine) for Extended Release Injectable Suspension after ensuring documentation of safe use conditions described below