

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-864**

**PROPRIETARY NAME REVIEW(S)**

|                   |   |
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| <b>MEMORANDUM</b> | <b>Division of Medication Errors and Technical Support</b><br><b>Office of Surveillance and Epidemiology</b><br><b>HFD-420; WO 22, Mail Stop 4447</b><br><b>Center for Drug Evaluation and Research</b> |
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**To:** Scott Monroe, MD, Acting Director  
Division of Reproductive and Urologic Products, HFD-580

**Through:** Linda Kim-Jung, PharmD, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Errors and Technical Support, HFD-420

**From:** Todd Bridges, RPh, Safety Evaluator  
Division of Medication Errors and Technical Support, HFD-420

**Date:** May 7, 2007

**Subject:** OSE Review #2007-949, Lybrel (Levonorgestrel and Ethinyl Estradiol Tablets) 90 mcg/20 mcg  
NDA #: 21-864

This memorandum is in response to the April 23, 2007, request from your Division for a re-review of the proprietary name, Lybrel. The revised label, carton and insert labeling, and patient insert labeling were also submitted for review and comment at this time.

The proposed proprietary name was found acceptable by DMETS in OSE Reviews 05-0076 and 05-0076-2, dated September 29, 2005 and March 8, 2006, respectively. Since the completion of our previous review, DMETS has not identified any additional proprietary or established drug names which have the potential for confusion with Lybrel. Therefore, we have no objections to the use of the proprietary name, Lybrel.

Upon review of the revised label and labeling for Lybrel, DMETS has identified the following areas of improvement, in the interest of minimizing user error and maximizing patient safety.

A. General Comments

1. Ensure that the established name is one-half the size of the proprietary name.  
See 21 CFR 201.10(g)(2).
2. Revise the established name and product strength on all labels and labeling to read:

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3. Throughout the labels and labeling, delete the large green graphic art (as indicated by the arrow below) following the proprietary name as it distracts attention away from important statements such as the proprietary name, established name, and product strength.

Delete

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B. Plastic Tray Labeling

See General Comments A1 through A3.

C. Wallet Stiffening Card Labeling

See General Comments A1 through A3.

D. Carton Labeling (Trade and Professional Sample)

See General Comments A1 through A3.

E. Packer Carton Labeling (Professional Sample)

See General Comments A1 through A3.

F. ClickCase Single Unit Dispenser Instruction Labeling

See General Comments A1 through A3.

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G. Insert Labeling

1. See General Comments A2 and A3.
2. Delete the use of \_\_\_\_\_ throughout the insert labeling. FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols. The \_\_\_\_\_ is listed as one of those dangerous abbreviations. Thus, we request that the Divisions not approve or use \_\_\_\_\_ in their labels and labeling as the potential for a ten-fold dosing error exists if the decimal point is not readily apparent.

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Additionally, the use of a terminal zero in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "... to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." We further note that the trailing zero is specifically listed as a dangerous abbreviations, acronyms, or symbols in the 2006 National Patient Safety Goals of The Joint Commission for Accreditation of Hospitals (JCAHO). Lastly, safety groups, such as the Institute for Safe Medication Practices (ISMP), also list the trailing zero on their dangerous abbreviations and dose designations list.

H. Patient Insert Labeling

No Comments.

I. ClickCase Single Unit Dispenser

DMETS has identified the following potential safety concern regarding the Single Unit Dispenser. After a preliminary overview of the device, DMETS has concerns about the potential for damage to the device, spring, or casing of this item (e.g. misalignment of the spring and subsequent inability to dispense the medication, cracking and breaking of the plastic case). DMETS questions the durability of the device under routine handling, and how the patient would dispense the medication if the device is damaged or becomes non-operational at any time. Additionally, has any usability testing been performed on the device? Please forward our concerns to the CDRH reviewer.

In summary, DMETS has no objections to the use of the proprietary name, Lybrel. Additionally, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the name, Lybrel, acceptable from a promotional perspective. DMETS request implementation of the above label/labeling revisions prior to approval. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any correspondence. If you have any questions or need clarification, please contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

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/s/

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Linda Kim-Jung  
5/18/2007 09:50:17 AM  
DRUG SAFETY OFFICE REVIEWER  
Also signing for Todd Bridges 5/18/07.

Carol Holquist  
5/18/2007 10:28:05 AM  
DRUG SAFETY OFFICE REVIEWER

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|-------------------|--|
| <b>MEMORANDUM</b> | <b>Division of Medication Errors and Technical Support</b><br><b>Office of Drug Safety</b><br><b>HFD-420; WO22, Mail Stop 4447</b><br><b>Center for Drug Evaluation and Research</b> |
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**To:** Daniel Shames, MD  
 Director, Division of Reproductive and Urologic Products, HFD-580

**Through:** Alina R. Mahmud, RPh, MS, Team Leader  
 Denise Toyer, PharmD, Deputy Director  
 Carol Holquist, RPh, Director  
 Division of Medication Errors and Technical Support, HFD-420

**From:** Nora Roselle, PharmD, Safety Evaluator  
 Division of Medication Errors and Technical Support, HFD-420

**Date:** January 12, 2006

**Re:** ODS Consult #05-0076-2; Lybrel (Levonorgestrel and Ethinyl Estradiol Tablets)  
 90 mcg/20 mcg; NDA 21-864

This memorandum is in response to the December 27, 2005 request from your Division for a re-review of the proprietary name, Lybrel. Revised labels and labeling were not provided for review and comment at this time.

The proposed proprietary name was previously found acceptable by the Division of Medication Errors and Technical Support (DMETS) on September 29, 2005 (ODS Consult 05-0076). Since we conducted our previous review, DMETS has identified two additional proprietary names, Sabril\*\*\* and Enbrel, which have the potential for confusion with Lybrel.

Sabril\*\*\* was identified as a name with slight look-alike similarity to Lybrel. Sabril\*\*\* is a proposed proprietary name \_\_\_\_\_ currently under review in the Agency. DMETS has not yet completed the tradename review for this NDA. Sabril\*\*\* \_\_\_\_\_ is proposed as add on therapy for the treatment of certain serious and/or refractory epilepsies. Sabril\*\*\* will be available as a 500 mg oral tablet. The proposed dosing for Sabril\*\*\* is 500 mg twice daily up to 1500 mg twice daily. Sabril\*\*\* and Lybrel can look similar in that each name has six letters and has four almost identical ending letters (-BRIL vs. -BREL). Likewise, when scripted in cursive the beginning letters (S vs. L) can look alike. However, the downstroke letter "y" in Lybrel helps differentiate one name from the other (see below). While the two drugs do share an overlapping dosage form (tablet), route of administration (oral), and are available in single strengths, there are some product differences. Sabril\*\*\* and Lybrel have different dosing regimens and indications for use (seizures vs. oral contraceptive). Sabril\*\*\* is dosed as one tablet (500 mg) twice daily up to three tablets (1500 mg) twice daily. Lybrel, on the other hand, is dosed as one tablet once daily. While there are overlapping product similarities, the differences in dosing as well as written characteristics help decrease the risk for confusion and error between Sabril\*\*\* and Lybrel.

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\*\*\*NOTE: This review contains proprietary and confidential information that should not be released to the public.\*\*\*

Enbrel was identified as a name with look-alike potential to Lybrel. Enbrel (etanercept) is a tumor necrosis factor (TNF) blocker indicated for the treatment of Juvenile Rheumatoid Arthritis (JRA), plaque psoriasis, rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. Enbrel is available in a 50 mg/mL pre-filled injectable syringe and a 25 mg powder for injection. Enbrel and Lybrel have four overlapping ending letters (-BREL) and the two beginning letters (EN- vs. LY-) can look similar when scripted in cursive (see below).

*enbrel*      *lybrel*

However, Enbrel and Lybrel have many product characteristics which help differentiate one drug from the other (see chart below). Enbrel and Lybrel differ with respect to dosage form, route of administration, strength, dosing frequency, dosing regimen, and how supplied.

| Product Characteristic  | Lybrel                                | Enbrel  |
|-------------------------|---------------------------------------|---|
| Established Name        | Levonorgestrel and Ethinyl Estradiol  | Etanercept  |
| Dosage Form             | Tablet                                | Injection, prefilled syringe and Powder for Injection   |
| Route of Administration | Oral                                  | Subcutaneous injection  |
| Strength                | 90 mcg/20 mcg                         | Injection, prefilled syringe: 50 mg/mL<br>Powder for Injection: 25 mg (needs to be reconstituted prior to use)  |
| Dosing Frequency        | Daily                                 | Once or twice weekly  |
| Dosing Regimen          | One tablet once daily                 | Juvenile Rheumatoid Arthritis (JRA): 0.8 mg/kg/week, as a single dose or divided into two injections given on the same day or 3 to 4 days apart<br>Plaque Psoriasis: 50 mg twice a week for 3 months followed by a maintenance injection of 50 mg/week<br>Rheumatoid Arthritis, spondylitis, and psoriatic arthritis: 50 mg/week as one SQ injection using a 50 mg/mL prefilled syringe. Administer this dose as two 25 mg injections given either on the same day or 3 - 4 days apart. |
| How Supplied            | 28-tablets per pack, 3 packs in a box | Prefilled syringe: carton of 4 syringes<br>Powder for Injection: multiple use vials supplied with Bacteriostatic water for Injection  |

From the chart above, patients who are dosed with Enbrel 50 mg need to be instructed by their healthcare practitioner as to whether they should use 50 mg per week as one subcutaneous injection using a 50 mg/mL prefilled syringe or administer as two 25 mg injections either given on the same day or three to four days apart. Lybrel, on the other hand, is an oral tablet administered once daily. Likewise, Lybrel is available in a single strength which does not need to be indicated when prescribed. Enbrel, in contrast, is available in two strengths and dosage forms (vial and prefilled syringe) each of which would need to be identified prior to prescription filling and dispensing. Prescriptions for Enbrel will be further differentiated from prescriptions for Lybrel since Enbrel will need to be prescribed with a dose to be administered to the patient. While, Lybrel may be ordered as 1 tablet daily or even "use as directed. Additionally, since Enbrel is an injectable product, an order would most likely include the route of administration. Thus, despite orthographic similarities the numerous product differences minimize the likelihood for confusion between Enbrel and Lybrel.

Additionally, "upon further review, DDMAC is objecting to the proposed trade name Lybrel."  
Comments from DDMAC are as follows:

Of note, we did not object to Lybrel in the first review. However, we did object to the proposed trade name "Librel" in July 2004 as being \_\_\_\_\_ and thus unacceptable from a promotional perspective. The components and subsequent combination of Levonorgestrel and Ethinyl Estradiol are common substances, but the proposed trade name implies a unique composition and drug combination \_\_\_\_\_

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\_\_\_\_\_ both of which make a similar representation about the effectiveness of the drug product. For example, this trade name misleadingly implies patients can be free (or \_\_\_\_\_) from getting a period, suffering the psychiatric and physiological effects of getting a monthly period (PMS, headaches, cramping, bloating), experiencing side effects because it is a low dose option, or worrying about pregnancy. Without substantial evidence to support such claims, the proposed trade name misleadingly implies that the drug is more effective and/or safer than demonstrated.

Please note that 21 CFR 201.10(c)(3) states that a proprietary name that implies that the drug or ingredient has some \_\_\_\_\_ effectiveness or composition would be misleading, if the drug or ingredient is a common substance, the limitations of which are readily recognized when the drug or ingredient is listed by its established name. In addition, the statute also provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

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The sponsor submitted a rebuttal to DDMAC's objection to the proprietary name Lybrel. After reviewing the rebuttal, DDMAC withdrew their objection to Lybrel on February 17, 2006.

In summary, DMETS does not have any objections to the use of the proprietary name Lybrel from a look- or sound-alike perspective. DDMAC finds the proprietary name Lybrel acceptable from a promotional perspective. DMETS recommends implementation of the label and labeling revisions outlined in our original review (ODS Consult 05-0076). DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward. If you have any questions or need clarification, please contact Diane Smith at 301-796-0538.

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/s/  
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3/8/2006 01:41:50 PM  
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       Trade Secret / Confidential

       Draft Labeling

8 Deliberative Process