DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
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Silver Spring, MD 20993

JUL 3 2014

Timothy P. Walbert
Chairman, President, and CEO
Horizon Pharma, Inc.
520 Lake Cook Road, Suite 520
Deerfield, IL 60015

Re: Docket No. FDA-2014-P-0209

Dear Mr. Walbert:

This letter responds to the citizen petition submitted to the Food and Drug Administration (FDA) by Horizon Pharma, Inc. (Horizon), dated February 3, 2014 (Petition). In the Petition, Horizon asks FDA to take certain actions with regard to any abbreviated new drug application (ANDA) for which Vimovo (naproxen and esomeprazole magnesium) Delayed-Release Tablets (new drug application (NDA) 022511, held by Horizon) is the reference listed drug (RLD).

Specifically, Horizon requests that FDA:

1. Require that any application listing Vimovo as the RLD, which seeks approval for a generic product that employs less than a complete enteric coating around the naproxen component, be supported by either
    a. pharmacokinetic data sufficient to show that the timing of release of naproxen in the generic product is equivalent to that of Vimovo, or
    b. data from clinical trials demonstrating that the proposed generic product does not cause more frequent or more severe gastrointestinal adverse events than does Vimovo;
2. If additional clinical trials described above are necessary to support safety of the proposed generic product, require that any such application be filed as a 505(b)(2) application,[1] rather than as an ANDA; and
3. Refuse to approve any currently pending ANDA for such a product, and require the applicant to withdraw its ANDA and resubmit it as a 505(b)(2) application, accompanied by the additional clinical testing described above.

Petition at 2.

[1] An application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)(2)).

We have carefully considered the information submitted in the Petition. For the reasons stated below, the Petition is denied.

I. BACKGROUND

A. Vimovo

On April 30, 2010, FDA approved an NDA for Vimovo (naproxen and esomeprazole magnesium) Delayed-Release Tablets (NDA 022511, held by Horizon). Vimovo is currently approved for relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, and to decrease the risk of developing gastric ulcers in patients at risk of developing non-steroidal anti-inflammatory drug (NSAID)-associated gastric ulcers.[2] Vimovo is available in two strengths: 375 milligrams (mg) of naproxen with 20 mg of esomeprazole, and 500 mg of naproxen with 20 mg of esomeprazole. The 500-mg naproxen/20-mg esomeprazole strength is the RLD.

The active ingredients of Vimovo are naproxen, which is an NSAID with analgesic and antipyretic properties, and esomeprazole magnesium, which is a proton pump inhibitor (PPI) that suppresses gastric acid secretion. Vimovo tablets consist of an enteric-coated naproxen core surrounded by an immediate-release esomeprazole magnesium layer. The enteric coating prevents naproxen from being released when gastric pH is under 5.5.[3]

The Vimovo application referenced two previously approved NDAs:

- EC-Naprosyn (naproxen) Delayed-Release Tablets (NDA 020067, held by Roche Palo), and
- Nexium (esomeprazole magnesium) Delayed-Release Capsules (NDA 021153, held by AstraZeneca).

EC-Naprosyn is available as enteric-coated tablets containing 375 or 500 mg of naproxen for oral administration. The dissolution of the enteric-coated naproxen tablet is pH-dependent with rapid dissolution above pH level 6. There is no dissolution below pH level 4.[4] Nexium is available as delayed-release capsules containing 20 or 40 mg of esomeprazole (present as 22.3 mg or 44.5 mg of esomeprazole magnesium trihydrate) in the form of enteric-coated granules[5] that protect the esomeprazole from being degraded in the stomach's acidic environment.

[2] See labeling for Vimovo approved on March 27, 2014, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022511s010lbl.pdf.

[3] Id. at section 12.1 (Clinical Pharmacology: Mechanism of Action).

[4] EC-Naprosyn label approved on March 22, 2013, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017581s111,018164s061,018965s020,020067s018lbl.pdf.

[5] Nexium label approved on March 27, 2014, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021153s046,021957s015,022101s012lbl.pdf.

The Vimovo application was also supported by two clinical studies that were submitted to support the efficacy of Vimovo in reducing the risk of developing NSAID-associated gastric ulcers. The 500-mg naproxen dose of the fixed-combination Vimovo was compared with enteric-coated naproxen in both studies. Both studies showed that Vimovo, given as a 500-mg naproxen/20-mg esomeprazole tablet twice daily, showed a statistically significant reduction in the 6-month cumulative incidence of gastric ulcers, as compared to enteric-coated naproxen given as a 500 mg tablet twice daily.[6] The approval of the other dose level of Vimovo (375-mg naproxen/20-mg esomeprazole) and approval of the indications for use in treatment of rheumatoid arthritis and ankylosing spondylitis were based on the approval of EC-Naprosyn and bioequivalence (BE) studies between Vimovo and EC-Naprosyn.[7]

B. Statutory and Regulatory Basis for Approving 505(b)(2) Applications and ANDAs

Section 505(b) of the FD&C Act establishes the approval requirements for NDAs. To be approved, an application submitted under 505(b) must, among other things, be supported by well-controlled investigations showing the drug product to be safe and effective.[8] One pathway under section 505(b) provides for approval of NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference (stand-alone NDA). The 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) provided an alternate pathway under section 505(b)(2) for approval of an NDA for which some or all of the safety and efficacy investigations relied upon for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.[9] Like a stand-alone NDA, a 505(b)(2) application is approved under section 505(c) of the FD&C Act.

The Hatch-Waxman Amendments also provide for submission of ANDAs for approval of generic versions of listed drugs.[10] A listed drug is a drug product with an effective approval under section 505(c).[11] The ANDA process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to repeat the studies conducted to support approval of the listed drug. To rely on such a finding, the ANDA applicant must show that, among other things, its proposed drug product is the same

[6] Vimovo label approved on March 27, 2014 (supra note 2) at section 14 (Clinical Studies). See also Goldstein JL1, Hochberg MC, Fort JG, Zhang Y, Hwang C, Sostek M. Clinical trial: the incidence of NSAID-associated endoscopic gastric ulcers in patients treated with PN 400 (naproxen plus esomeprazole magnesium) vs. enteric-coated naproxen alone. Aliment Pharmacol Ther. 2010 Aug; 32(3):401-413.

[7] In addition, two clinical studies were conducted to evaluate the efficacy of the 500 mg naproxen component of Vimovo for treating the signs and symptoms of osteoarthritis. The results of these two studies provided sufficient evidence to support the efficacy of Vimovo for the indication of treatment of signs and symptoms of osteoarthritis.

[8] Section 505(b)(1) of the FD&C Act.

[9] The Vimovo NDA was itself submitted under section 505(b)(2).

[10] Section 505(j) of the FD&C Act.

[11] 21 CFR 314.3(b).

as the listed drug with respect to its active ingredient, dosage form, strength, route of administration, and, with certain exceptions, labeling, and that the proposed product is bioequivalent to the listed drug.[12]

C. Bioequivalence and ANDAs

The basic assumption underlying the Hatch-Waxman Amendments is that bioequivalent drug products that meet the FD&C Act's criteria are therapeutically equivalent and may be substituted for each other. A generic drug product is bioequivalent to the RLD "if the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient" (section 505(j)(8)(B)(i) of the FD&C Act). FDA regulations at 21 CFR 320.1(e) specify that

> *[B]ioequivalence* means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.[13]

FDA's regulations at 21 CFR 314.94(a)(7) set forth the BE requirements for an ANDA, and the regulations in part 320 (21 CFR Part 320) set forth the procedures for determining BE. The regulations discuss the various methods of establishing BE in general descending order of accuracy, sensitivity, and reproducibility. These methods include pharmacokinetic (PK) studies, pharmacodynamic (PD) studies, comparative clinical trials, and in vitro studies (21 CFR 320.24). In addition, as under section 505(j)(8)(C) of the FD&C Act, section 320.24(b)(6) of the regulations states that FDA has the flexibility to use "[a]ny other approach deemed adequate by FDA to . . . establish [BE]." It is well-accepted that FDA has considerable discretion in determining how the BE requirement is met. FDA's discretion need only be based on a "reasonable and scientifically supported criterion, whether [the Agency] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs. . . ."[14] Courts have expressly upheld FDA's regulatory implementation of the FD&C Act's BE requirements.[15]

Standard BE PK studies are conducted using a two-treatment crossover study design. Single oral doses of the test and reference drugs are administered, and blood or plasma levels of the drug are measured over time. The rate and extent of drug absorption are statistically measured. The relevant PK parameters calculated from these data include the area under the

[12] Section 505(j)(2) of the FD&C Act.

[13] See also 21 CFR 320.23(b).

[14] *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp 212, 218 (D.D.C. 1996) (quoting *Schering Corp. v. Sullivan*, 782 F. Supp 645, 651 (D.D.C. 1992), vacated as moot sub nom, *Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993).

[15] See, e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 397-400 (3d Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 863-67 (D.D.C. 1994).

plasma concentration versus time curve (AUC), calculated to the last measured concentration time (AUC_{0-t}), and AUC extrapolated to infinity (AUC_{∞}). These parameters represent the extent of absorption. Another relevant PK parameter is the maximum or peak drug concentration (C_{max}). C_{max} is used to reflect the rate of absorption.

To establish BE, the calculated 90 percent confidence interval for the log transformed ratio of geometric means for AUC and C_{max} values between the generic product and the RLD should fall entirely within an 80 percent to 125 percent acceptance interval (0.8 to 1.25).[16] The use of an 80 to 125 percent acceptance interval to compare two products with the same active ingredient, dosage form, route of administration, and strength is a scientific judgment about the best statistical practices for BE determinations. It reflects decades of scientific data on the variability of product characteristics within and between batches, as well as biological variability in patients. Because the point estimate of the test/reference ratio lies in the center of the 90 percent confidence interval, the mean of the data is usually close to 100 percent (a test/reference ratio of 1).[17] The PK parameter time to reach maximum concentration (T_{max}) is also a rough indicator of the rate of drug absorption and serves as supportive data in evaluating BE.

For modified-release drug products, FDA may consider an additional PK parameter, lag time.[18] Lag time means the time from administration of a drug product until release and absorption of one or more active ingredients of that product (as reflected by quantifiable plasma concentrations).[19] For example, for an oral delayed-release tablet, the effect of an enteric coating intended to slow release of the active ingredient would be reflected in PK data as the lag time.

D. Product-Specific Bioequivalence Guidance

Under a process set forth in the guidance for industry on *Bioequivalence Recommendations for Specific Products* (BE Recommendation Process Guidance), FDA develops

[16] See FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book), Chapter 1.3, "Statistical Criteria for Bioequivalence," available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf; See also FDA guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (Revision 1), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[17] In general, for the 90 percent BE confidence interval to fall between 0.8 and 1.25, the point estimate should fall within .90 and 1.11.

[18] See, e.g., FDA guidance for industry on *Food-Effect Bioavailability and Fed Bioequivalence Studies*, available at http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126833.pdf at 6-7.

[19] See, e.g, description of lag time with regard to delayed-release products in FDA guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (Revision 1), supra note 16, at 14 (stating "[a]s defined in the USP, delayed-release drug products are dosage forms that release the drugs at a time later than immediately after administration (i.e., these drug products exhibit a lag time in quantifiable plasma concentrations)").

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