

FOR FURTHER INFORMATION CONTACT:

Na'im R. Moses, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave. Bldg. 51, Rm. 6226, Silver Spring, MD 20993-0002, 240-402-3990.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is known generally as the "Orange Book." Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale, but must be made prior to approving an ANDA that refers to the listed drug (§ 314.161 (21 CFR 314.161)). FDA may not approve an ANDA that does not refer to a listed drug.

PREZISTA (darunavir) tablets, 400 mg, is the subject of NDA 21-976, held by Janssen Products, LP, and initially approved on June 23, 2006. PREZISTA is a human immunodeficiency virus (HIV-1) protease inhibitor indicated for the treatment of HIV-1 infection in adult patients. It is also indicated for the treatment of HIV-1 infection in pediatric patients 3 years of age and older. PREZISTA must be coadministered with ritonavir

(PREZISTA/ritonavir) and with other antiretroviral agents.

In an email dated July 30, 2013, Janssen Products, LP, notified FDA that PREZISTA (darunavir) tablets, 400 mg, was being discontinued for the U.S. market only. The PREZISTA 800-mg tablet continues to be marketed in the United States. Lachman Consultant Services, Inc., submitted a citizen petition dated October 21, 2013 (Docket No. FDA-2013-P-1379), under 21 CFR 10.30, requesting that the Agency determine whether PREZISTA (darunavir) tablets, 400 mg, was withdrawn from sale for reasons of safety or effectiveness. In January 2014, FDA moved the 400-mg dosage strength of this drug product to the "Discontinued Drug Product List" section of the Orange Book.

After considering the citizen petition and reviewing Agency records and based on the information we have at this time, FDA has determined under § 314.161 that PREZISTA (darunavir) tablets, 400 mg, was not withdrawn for reasons of safety or effectiveness. The petitioner has identified no data or other information suggesting that PREZISTA (darunavir) tablets, 400 mg, was withdrawn for reasons of safety or effectiveness. We have carefully reviewed our files for records concerning the withdrawal of PREZISTA (darunavir) tablets, 400 mg, from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. We have reviewed the available evidence and determined that the product was not withdrawn from sale for reasons of safety or effectiveness.

Accordingly, the Agency will continue to list PREZISTA (darunavir) tablets, 400 mg, in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. ANDAs that refer to PREZISTA (darunavir) tablets, 400 mg, may be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs. If FDA determines that labeling for this drug product should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.

Dated: March 27, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration**

[Docket No. FDA-2011-P-0267]

Determination That NIMOTOP (Nimodipine) Capsules, 30 Milligrams, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) has determined that NIMOTOP (Nimodipine) Capsules, 30 milligrams (mg), was not withdrawn from sale for reasons of safety or effectiveness. This determination means that FDA will not begin procedures to withdraw approval of the abbreviated new drug applications (ANDAs) that refer to nimodipine capsules, 30 mg, and it will allow FDA to approve ANDAs that refer to this drug as long as they meet relevant legal and regulatory requirements.

FOR FURTHER INFORMATION CONTACT:

Rachel Turow, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave. Bldg. 51, Rm. 6236, Silver Spring, MD 20993-0002, 301-796-5094.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed drug," which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is known generally as the "Orange Book." Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends

approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

Under § 314.161(a) (21 CFR 314.161(a)), the Agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness: (1) Before an ANDA that refers to that listed drug may be approved; (2) whenever a listed drug is voluntarily withdrawn from sale and ANDAs that refer to the listed drug have been approved; and (3) when a person petitions for such a determination under §§ 10.25(a) and 10.30 (21 CFR 10.25(a) and 10.30). Section 314.161(d) provides that if FDA determines that a listed drug

was withdrawn from sale for reasons of safety or effectiveness, the Agency will initiate proceedings that could result in the withdrawal of approval of the ANDAs that refer to the listed drug. FDA may not approve an ANDA that does not refer to a listed drug.

NIMOTOP (Nimodipine) Capsules, 30 mg, the subject of NDA 18-869, held by Bayer HealthCare Pharmaceuticals Inc., was initially approved on December 28, 1988. The most recent labeling for NIMOTOP states that the product is indicated for the improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in patients with subarachnoid hemorrhage (ruptured blood vessels in the brain) from ruptured intracranial

berry aneurysms regardless of their post-ictus neurological condition (i.e., Hunt and Hess Grades I–V).

In a letter dated July 30, 2010, Bayer HealthCare Pharmaceuticals Inc. notified FDA that NIMOTOP (Nimodipine) Capsules, 30 mg, was being discontinued, and FDA moved the drug product to the “Discontinued Drug Product List” section of the Orange Book. Currently, there are three approved ANDAs for nimodipine capsules, 30 mg. The following table lists the approved ANDAs for nimodipine capsules that are listed in the “Active Drug Product List” of the Orange Book and their sponsors.

Applicant	Application No.	Dosage form; route	Strength
Banner Pharmacaps	ANDA 076740	Capsule; Oral	30 mg.
Barr Labs, Inc.	ANDA 077811	Capsule; Oral	30 mg.
Sun Pharmaceuticals Inds., Inc.	ANDA 077067	Capsule; Oral	30 mg.

Lachman Consultant Services, Inc., submitted a citizen petition dated April 11, 2011 (Docket No. FDA-2011-P-0267) (Petition), under § 10.30, requesting that the Agency determine whether NIMOTOP (Nimodipine) Capsules, 30 mg, was withdrawn from sale for reasons of safety or effectiveness. In the Petition, the petitioner identified no data or other information suggesting that NIMOTOP (Nimodipine) Capsules, 30 mg, was withdrawn for reasons of safety or effectiveness.

In responding to the Petition, we have carefully reviewed our files for records concerning the withdrawal of NIMOTOP (Nimodipine) Capsules, 30 mg. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. The adverse event reports included 36 reports of medication errors associated with the administration or prescribing of nimodipine capsules, 30 mg, which were received between 1989 (the initial marketing of NIMOTOP) and November 2013.¹ Of these 36 reports, 27

involved the erroneous intravenous administration of nimodipine.² The intravenous injection of nimodipine can result in cardiac arrest, severe drop in blood pressure, other cardiac-related complications, and death. In almost all of the cases involving erroneous intravenous administration, there were serious or potentially serious outcomes, with 5 of the 27 cases resulting in the death of the patient. FDA has attributed these medication errors to the use of an intravenous needle and syringe at bedside to extract the capsule contents for administration to patients that are unconscious or cannot swallow the capsules. In such cases, the professional labeling instructions call for using an 18-gauge needle to make a hole on both ends of the capsule to extract the capsule's liquid contents into a syringe, and then administering the extracted liquid to the patient orally or via a nasogastric tube (feeding tube). Because a needle will not fit on an oral syringe, the health care provider must use a parenteral syringe to extract the liquid from the capsule. Once the drug is prepared in a parenteral syringe, rather than administering it orally or through a nasogastric tube as further directed in the drug's labeling, a conditioned response can occur where the drug is erroneously administered intravenously. Most patients receiving nimodipine

capsules require complex care, are hospitalized in critical care units, and are receiving other intravenous medications, which may further contribute to the occurrence of such errors.

Each year, between 20,000 and 30,000 patients in the United States³ are administered nimodipine for the emergency treatment of subarachnoid hemorrhage. Since NIMOTOP was approved in 1988, FDA has taken several actions to reduce these medication errors. These include labeling changes, a Dear Healthcare Professional Letter, two FDA Patient Safety News Webcasts, and a Drug Safety Communication.⁴ As recently as August 2010, FDA issued a safety alert, again emphasizing to health care professionals that nimodipine capsules should be given only by mouth or through a nasogastric tube and that they should never be given by intravenous administration.⁵ In addition, in

¹ FDA became aware of these reports through a search of the FDA Adverse Event Reporting System (FAERS), the Pennsylvania Patient Safety Reporting System (PA-PSRS), the Institute for Safe Medication Practices' (ISMP) Quantros MEDMARX database, the Council for International Organizations of Medical Sciences (CIOMS) II database, or through their publication in the medical literature. Thirty-one of the 36 cases occurred between 1989 and 2009. (See FDA Drug Safety Communication: Serious medication errors from intravenous administration of nimodipine oral capsules, available at <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm220386.htm>.) FDA identified five additional cases through searches of

the Agency's FAERS database conducted in 2012 and 2013.

² The remaining reports of medication errors involved prescribing errors (i.e., physician erroneously prescribed that the drug be administered intravenously), sublingual administration, or drug name confusion.

³ American Heart Association Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage, 2009, *Stroke*, 40:994–1025; see also, National Institute of Neurological Disorders and Stroke—Cerebral Aneurysms Fact Sheet, available at http://www.ninds.nih.gov/disorders/cerebral_aneurysm/detail_cerebral_aneurysms.htm#228933098.

⁴ Nimodipine (marketed as Nimotop)—Healthcare Professional Sheet, text version, available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm129297.htm>; NIMOTOP Safety alert, available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm150728.htm>.

⁵ FDA Drug Safety Communication: Serious Medication Errors from Intravenous Administration of Nimodipine oral Capsules (August 2010), available at <http://www.fda.gov/Drugs/DrugSafety/>

February 2012, Barr Pharmaceuticals added the following statement to the labeling directing health care professionals to transfer the capsule contents to a syringe that cannot accept a needle: "A parenteral syringe can be used to extract the liquid inside the capsule, but the liquid should always be transferred to a syringe that cannot accept a needle and that is designed for administration orally or via a nasogastric tube or PEG."⁶

Despite these efforts by FDA and the drug's sponsor, a small number of adverse events due to erroneous intravenous administration continue to be reported to the Agency. Nevertheless, FDA believes that it is in the best interest of the public health for patients to continue to have access to this lifesaving drug for a number of reasons. First, only a portion of the patients treated with nimodipine capsules are unconscious and unable to swallow—these are the patients who are most vulnerable to the medication errors identified. Of those patients that begin their course of treatment (two capsules every 4 hours for 21 days) while unable to swallow, many improve to the point where they are awake and able to swallow a capsule soon after treatment begins. Hence, for many patients, the risk of erroneous intravenous administration is only present during a small percentage of their overall duration of treatment.

Second, we believe the approval of a nimodipine oral solution⁷ that is administered via an oral syringe only will further prevent erroneous intravenous administration because it can be used for those patients who are unconscious or unable to swallow and eliminates the need for use of a parenteral syringe, which is the source of the medication errors. And third, we believe the capsules play an important role in treating patients with subarachnoid hemorrhage because many are discharged from the hospital while taking capsules, and capsules provide a more convenient route of administration that increases patient compliance.

As a result, we believe that the benefits of having nimodipine capsules on the market to treat these extremely sick patients, who could die or have serious permanent injury without

treatment, outweigh the risks of medication errors.

Therefore, after considering the Petition and reviewing Agency records, and based on the information we have at this time, FDA has determined under § 314.161 that NIMOTOP (nimodipine) Capsules, 30 mg, was not withdrawn for reasons of safety or effectiveness.

Accordingly, the Agency will continue to list NIMOTOP (Nimodipine) Capsules, 30 mg, in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. FDA will not begin procedures to withdraw approval of the approved ANDAs that refer to NIMOTOP (Nimodipine) Capsules, 30 mg. Additional ANDAs that refer to NIMOTOP (Nimodipine) Capsules, 30 mg, may also be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs. If FDA determines that labeling for this drug product should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.

Dated: March 27, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2007-D-0369]

Draft and Revised Draft Guidances for Industry Describing Product-Specific Bioequivalence Recommendations; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of additional draft and revised draft product-specific bioequivalence (BE) recommendations. The recommendations provide product-specific guidance on the design of BE studies to support abbreviated new drug applications (ANDAs). In the **Federal Register** of June 11, 2010, FDA announced the availability of a guidance for industry entitled "Guidance for Industry on Bioequivalence Recommendations for Specific Products;

Availability," which explained the process that would be used to make product-specific BE recommendations available to the public on FDA's Web site. The BE recommendations identified in this notice were developed using the process described in that guidance.

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comments on these draft and revised draft guidances before it begins work on the final versions of the guidances, submit either electronic or written comments on the draft and revised draft product-specific BE recommendations listed in this notice by June 2, 2014.

ADDRESSES: Submit written requests for single copies of the individual BE guidances to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance recommendations.

Submit electronic comments on the draft product-specific BE recommendations to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Kris André, Center for Drug Evaluation and Research (HFD-600), Food and Drug Administration, 7520 Standish Pl., Rockville, MD 20855, 240-276-8866.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of June 11, 2010 (75 FR 33311), FDA announced the availability of a guidance for industry entitled "Guidance for Industry on Bioequivalence Recommendations for Specific Products; Availability," which explained the process that would be used to make product-specific BE recommendations available to the public on FDA's Web site at <http://www.fda.gov/Drugs/Guidance/ComplianceRegulatoryInformation/Guidances/default.htm>.

As described in that guidance, FDA adopted this process as a means to develop and disseminate product-specific BE recommendations and provide a meaningful opportunity for the public to consider and comment on those recommendations. Under that

PostmarketDrugSafetyInformationforPatientsand Providers/ucm220386.htm.

⁶ As used here, PEG refers to a percutaneous endoscopic gastrostomy tube.

⁷ Nymalize was approved on May 10, 2013. See FDA's News Release, "FDA Approves Nymalize—First Nimodipine Oral Solution for Use in Certain Brain Hemorrhage Patients," available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm352280.htm>.