CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-023s000

ADMINISTRATION and CORRESPONDENCE DOCUMENTS Part 2

Emend Exclusivity Determination

M E M O R A N D U M

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

DATE: December 1, 2009

FROM: Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Gary Buehler 12/1/09

SUBJECT: Addendum to Emend NCE Exclusivity Determination

TO: NDA 022023 - Emend for Injection
Merck and Co. Inc.

Upon further review of the exclusivity record for NDA 022023, I have determined that at the time of approval, Emend for Injection was not granted any exclusivity. The January 25, 2008 Exclusivity Summary indicated that because Study 07L1 supported only the safety of the drug and not the efficacy, it was not "essential for approval of [sic] exclusivity purposes." This appears to have been the basis for not granting Emend for Injection three years of exclusivity.

In light of the conclusion that Emend for Injection is a new chemical entity, we need not further address whether the previous determination that Emend for Injection was not eligible for three years of exclusivity was correct.

EXCLUSIVITY DETERMINATION CHECKLIST

NDA # 22023 SUPPL. # _____ APPLICANT Merck TR. NAME Emend

ACTIVE INGRED Fosaprepitant Dimeglumine POTENCY eq 115 mg base/me DOSAGE FORM/ROUTE powder, intravenous

APPROVAL DATE 25 Jan 2008

TYPE OF APPLICATION: FULL NDA ✓ 505(b)(2) ___ EFFIC. SUPP. ___ OTHER (SPECIFY) ___

EXCLUSIVITY REQUESTED: 5 YR ___ 3 YR ___ NONE ___

QUALIFICATIONS FOR 5 YR EXCLUSIVITY:

Approved for NCE, no salt or ester of which previously approved ✓

QUALIFICATIONS FOR 3 YR EXCLUSIVITY:

Approval based on clinical study (other than BIO)?	Y___	N___	
New Studies:			
Previously relied on by Agency for efficacy?		Y___	N___
Essential for Approval:			
Approval could have been based on literature?		Y___	N___
Previously approved in another application?		Y___	N___
Studies conducted by or for applicant:			
IND sponsored by applicant?	Y___	N___	
or Certification of principal support?	Y___	N___	

NOTE: If any checks appear in shaded area, it is likely that exclusivity should not be granted. Any exclus. recommendations should be explained below:

This document serves to change exclusivity on NDA 22023 from 3 year to 5 year NCE.

EXCLUSIVITY RECOMMENDED: 5 YR ✓ 3 YR ___ NONE ___

CONCUR ✓
NON CONCUR ___ }

SIGNED [signature]
DIRECTOR, OFFICE OF GENERIC DRUGS

MEMORANDUM

To: Gary Buehler, Director, Office of Generic Drugs/OPS/CDER

From: Moheb Nasr, Ph.D., Director, Office of New Drug Quality Assessment/OPS/CDER

RE: Exclusivity Determination for Emend (fosaprepitant dimeglumine) for Injection

Date: November 4, 2009

FDA approved NDA 22-023 for Emend® (fosaprepitant dimeglumine) for Injection (Emend for Injection), on January 25, 2008. At that time, FDA granted Emend for Injection 3 years of exclusivity under 21 CFR § 314.108.[1] Recently, as part of the review of Actavis' challenge to FDA's grant of new chemical entity (NCE) exclusivity to Vyvanse (lisdexamfetamine dimesylate) Capsules (Docket No. FDA-2009-N-0184), FDA has had occasion to review the exclusivity decision regarding Emend for Injection. After further review of the information before the Agency at the time NDA 22-023 was approved, we have determined that Emend (fosaprepitant dimeglumine) for Injection is an NCE entitled to 5 years of exclusivity. A brief description of the reasons for this decision is set out below. The attached October 23, 2009 letter from FDA responding to Actavis' challenge (Vyvanse Letter) contains a complete description of the facts related to the Vyvanse matter, and of the applicable legal and regulatory authorities.

I. Statutory and Regulatory Background

The 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) provide for the granting of marketing exclusivity to certain drug products. Under the statute, a 5-year exclusivity period is provided for drug products that do not contain a previously approved active ingredient (including any ester or salt of the active ingredient).[2] This

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[1] Documents explaining the basis at the time for the 3 year exclusivity are attached. The reasoning is not consistent with FDA's longstanding application of 21 CFR § 314.108.

[2] Section 505(j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act provides

> If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

exclusivity generally prevents FDA from accepting a 505(b)(2) application or ANDA that contains the protected drug (active moiety) for a 5-year period from the date of approval of the protected drug.[3] Sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the Act. The exclusivity does not block acceptance and review of stand-alone NDAs containing the same active moiety, that is those NDAs supported entirely by data developed by the applicant or to which the applicant has a right of reference.

The Act also provides for a 3-year period of exclusivity. This is available for drug products that contain a previously approved active ingredient (including any ester or salt of the active ingredient), when that application includes new clinical investigations essential to the approval of the application and conducted or sponsored by the applicant.[4] This marketing exclusivity prevents FDA from approving 505(b)(2) applications and ANDAs for the same conditions of approval for 3 years from the date of approval of the drug with exclusivity. Sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the Act.

FDA's regulation at 21 CFR § 314.108 implements the statutory exclusivity provisions. In this regulation FDA has interpreted sections 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Act to preclude the Agency from accepting ANDAs for drugs that contain the same "active moiety" as in a previously approved new chemical entity. The regulation provides

> If a drug product that contains a new chemical entity was approved . . . in an application submitted under section 505(b) of the act, no person may submit a[n] . . . abbreviated new drug application under section 505(j) of the act for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application. . . .

21 CFR § 314.108(b)(2). Thus, under FDA's interpretation of the statute embodied in the regulations, a drug that is a new chemical entity will receive 5 years of exclusivity. If a drug product is not a new chemical entity (i.e., it contains any previously approved active moiety), it may be eligible for 3 years of exclusivity, but will not be eligible for 5 years of exclusivity.

See also section 505(c)(3)(E)(ii) of the Act.

[3] An applicant may submit an ANDA or 505(b)(2) application after 4 years if the application includes a paragraph IV certification to a patent listed in the Orange Book for the referenced drug.

[4] Section 505(j)(5)(F)(iii) of the Act provides

> If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section for such drug.

See also section 505(c)(3)(E)(iii) of the Act.

The Agency has defined "new chemical entity" to mean "a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act." 21 CFR § 314.108(a). "Active moiety" in turn is defined as

> [T]he molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

As discussed in detail in the Vyvanse Letter, under FDA's regulation at 21 CFR § 314.108, a non-ester covalently bonded molecule is considered the active moiety of a drug and, if not previously approved, it will be considered a new chemical entity entitled to 5 years of exclusivity. A non-ester that requires metabolic conversion to produce a previously approved active moiety is considered a new chemical entity.[5]

II. Exclusivity for Emend (fosaprepitant dimeglumine) for Injection

FDA approved your NDA, 21-549 for Emend (aprepitant) Capsules (Emend Capsules), 40 mg, 80 mg, and 125 mg, on March 27, 2003.

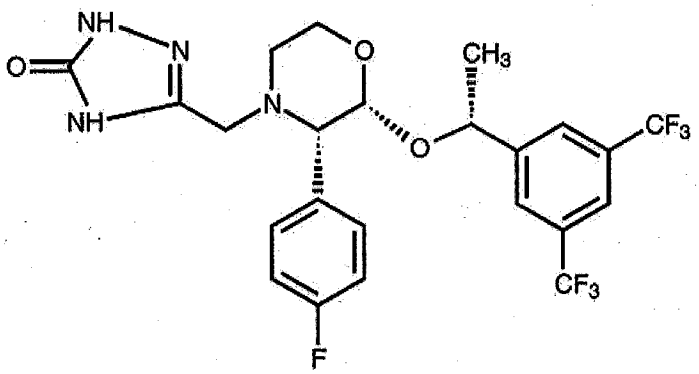


Figure 1. Aprepitant

[5] As noted in the Vyvanse Letter, FDA's Exclusivity Summary Form asks that the following be assessed in determining whether a drug is an NCE:

> 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.

Exclusivity Summary at 2.

Aprepitant is an antiemetic agent indicated for the prevention of nausea and vomiting. It was classified as a new molecular entity and granted NCE exclusivity.

As described above, Emend for Injection, was approved on January 25, 2008 in your NDA 22-023. At that time, it was granted 3 years of exclusivity. See attached January 25, 2008 Exclusivity Summary. In consultation with Norman Schmuff, a Branch Chief in the Office of New Drug Quality Assessment, I have reviewed the exclusivity documents describing the basis for the grant of 3 year exclusivity, including a March 16, 2006 e-mail from Moo Jhong Rhee, Chief of the ONDQA review branch that reviewed the Emend NDA, as well as documentation of the chemical structure and characteristics of Emend for Injection.

Based on my analysis, Emend for Injection under FDA's interpretation of 21 CFR § 314.108 should have been classified at the time of approval as an NCE.

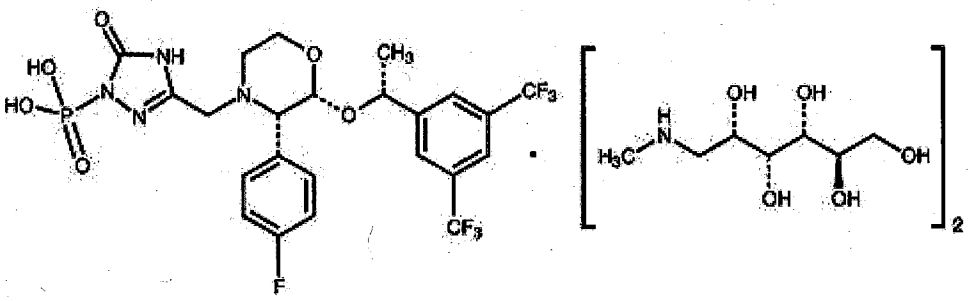


Figure 2. Fosaprepitant Dimeglumine

The active ingredient in Emend for Injection is fosaprepitant dimeglumine. As described in the approved labeling for Emend for Injection, fosaprepitant dimeglumine is a prodrug of aprepitant. When administered intravenously, fosaprepitant dimeglumine is rapidly converted to aprepitant, which is responsible for the antiemetic effect. It appears that the conversion of fosaprepitant to aprepitant can occur in multiple extrahepatic tissues in addition to the liver.

Fosaprepitant dimeglumine is a pro-drug phosphoramide derivative of aprepitant. A phosphoramide is a compound in which one or more of the OH groups of phosphoric acid have been replaced with covalent bonds to an amino or substituted amino group. Fosaprepitant dimeglumine is neither an ester, salt (including a salt with hydrogen or coordination bonds), nor other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule aprepitant. It is a covalent phosphoramide derivative. As a non-ester covalent derivative of aprepitant, under 21 CFR § 314.108, fosaprepitant dimeglumine is a new chemical entity entitled to 5 years of exclusivity.

III. CONCLUSION

Based on FDA's longstanding interpretation of the exclusivity regulation at 21 CFR § 314.108, fosaprepitant dimeglumine is a new chemical entity. Therefore, at the time of approval, Merck's NDA 22-023 for Emend (fosaprepitant dimeglumine) for Injection should have been granted 5 years of NCE exclusivity. Please revise FDA's exclusivity data base to reflect the correct exclusivity for this drug.

cc: John Jenkins, M.D., Director, Office of New Drugs, CDER
Julie Beitz, M.D., Director, Office of New Drug Evaluation III, OND
Donna Griebel, M.D., Director, Division of Gastroenterology Products
Michael Landa, Acting Chief Counsel, OCC/FDA
Helen Winkle, Director, Office of Pharmaceutical Science, CDER
Keith Webber, Ph.D., Deputy Director, Office of Pharmaceutical Science, CDER

Attachments

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

NDA 021977

Chad A. Landmon
Axinn Veltrop & Harkrider LLP
90 State House Square
Hartford, CT 06103-3702

Docket No. FDA-2009-N-0184

Dear Mr. Landmon:

Actavis Elizabeth LLC (“Actavis”) has requested that the Food and Drug Administration ("FDA" or "Agency") reconsider its grant of new chemical entity exclusivity to Vyvanse (lisdexamfetamine dimesylate) Capsules under sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or "the Act") and the implementing regulation at 21 CFR § 314.108. Actavis asserts that FDA should have granted Vyvanse a shorter period of exclusivity under sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the Act, and permitted the company to submit its abbreviated new drug application (“ANDA”) for lisdexamfetamine dimesylate (“lisdexamfetamine”) on January 28, 2009.

We have carefully reviewed the submissions made to the Agency on this issue and additional relevant materials. For the reasons set forth below, we deny Actavis' request and affirm that lisdexamfetamine is entitled to NCE exclusivity.

I. Summary

Vyvanse Capsules contain lisdexamfetamine dimesylate as the active ingredient. Lisdexamfetamine consists of dextroamphetamine bonded covalently to lysine through an amide bond. Lisdexamfetamine is a prodrug that is metabolically converted to produce dextroamphetamine, which is responsible for the drug's activity. Under FDA's regulation at 21 CFR § 314.108, a non-ester covalently bonded molecule is considered the active moiety of a drug and, if not previously approved, it will be considered a new chemical entity entitled to 5 years of exclusivity. A non-ester that requires metabolic conversion to produce a previously approved active moiety is considered a new chemical entity. Because lisdexamfetamine is a non-ester covalently bonded molecule, and because it requires metabolic conversion to produce dextroamphetamine, lisdexamfetamine is a new chemical entity and is thus entitled to 5 years of exclusivity.

II. Factual and Procedural Background

A. Approval of Vyvanse Capsules

FDA approved Shire's new drug application ("NDA") 21-977 for Vyvanse (lisdexamfetamine dimesylate) Capsules ("Vyvanse") 30 mg, 50 mg, and 70 mg on February 23, 2007. The 20 mg,

40 mg, and 60 mg strengths were approved on December 10, 2007. Vyvanse is approved for the treatment of Attention Deficit Hyperactivity Disorder ("ADHD").

Sections 505(c) and (j) of the FDCA provide for 3 years or 5 years of marketing exclusivity for drugs approved in NDAs, depending upon the characteristics of the drug and the type of information needed to support its approval. FDA applied these statutory exclusivity provisions and the corresponding implementing regulations, and classified Vyvanse as a new chemical entity ("NCE") entitled to 5 years of exclusivity beginning on the date of approval. Pursuant to the grant of NCE exclusivity, with certain limited exceptions, FDA may not accept an ANDA or so-called "505(b)(2) application" (i.e., an application described in section 505(b)(2) of the Act) for a drug that contains the same active moiety as Vyvanse for 5 years from the date of approval of the Vyvanse NDA.[1] Therefore, with certain exceptions, FDA may not accept an ANDA based on Vyvanse until February 23, 2012.[2]

B. Actavis' ANDA

On January 29, 2009, Actavis submitted an ANDA for lisdexamfetamine dimesylate capsules that references Vyvanse. On February 6, 2009, Actavis provided the Agency a position paper arguing that FDA should reconsider its decision to classify Vyvanse as an NCE entitled to 5 years of exclusivity. Also on February 6, 2009, FDA returned[3] Actavis' ANDA because, as explained above, FDA had awarded Vyvanse 5-year NCE exclusivity, and that exclusivity was a bar on receiving an ANDA at that time.

After FDA declined receipt of the ANDA, Actavis initiated litigation in the United States District Court for the District of Columbia on February 24, 2009, alleging that FDA had erroneously granted Vyvanse NCE exclusivity. Actavis argued that because Vyvanse should not have been awarded NCE exclusivity, FDA should not have refused to receive Actavis' ANDA for review. Actavis sought entry of an injunction directing FDA to rescind the NCE exclusivity for Vyvanse and to accept Actavis' ANDA with an effective filing date of January 28, 2009.

Actavis sued FDA before the Agency had a meaningful opportunity to consider the arguments that Actavis had raised in its February 6, 2009 submission concerning the application of the governing statutory provisions and regulation to lisdexamfetamine. Following the initiation of litigation, FDA determined that these issues should be considered administratively through a

[1] An exception to the 5-year prohibition applies when an ANDA includes a certification described in section 505(j)(2)(A)(vii)(IV) of the Act ("a paragraph IV certification") that a patent listed in *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) for the referenced drug is invalid or would not be infringed by the proposed drug product. Section 505(j)(5)(F)(ii). In those circumstances, FDA may accept the ANDA at the end of 4 years. Parallel provisions in section 505(c)(3)(E)(ii) of the Act apply to the submission of 505(b)(2) applications.

[2] Actavis would be permitted to submit its ANDA on February 23, 2011, because the ANDA contained a paragraph IV certification to a listed patent for Vyvanse.

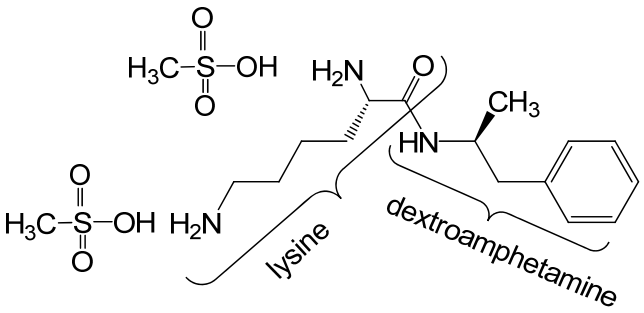
[3] FDA's return of the Actavis ANDA was pursuant to 21 CFR § 314.101(e)(2) ("The agency … will consider an abbreviated new drug application not to have been received if …the drug product contains the same active moiety as a drug that: (i) Was approved after September 24, 1984, in an application under section 505(b) of the Act, and (ii) Is entitled to a 5-year period of exclusivity under [the relevant provisions of section 505(c) and (j) of the Act] and § 314.108(b)(2), unless the 5-year exclusivity period has elapsed or unless 4 years of the 5-year period have elapsed and the [ANDA] contains a [paragraph IV certification]."). A "refusal to receive" an ANDA is generally analogous to a "refusal to file" an NDA. *Compare* 21 CFR § 314.101(a)(1) *with* § 314.101(b)(1).

public process to permit comment by interested parties. Accordingly, the parties agreed to stay the litigation until the administrative process is completed. On April 13, 2009, FDA opened a public docket to receive comments from interested parties on the legal and regulatory issues raised by Actavis' submissions. After reviewing the submissions to the docket[4] and additional relevant material, the Agency has determined that the grant of NCE exclusivity to Vyvanse was consistent with the statute and regulations, and therefore affirms its original decision.

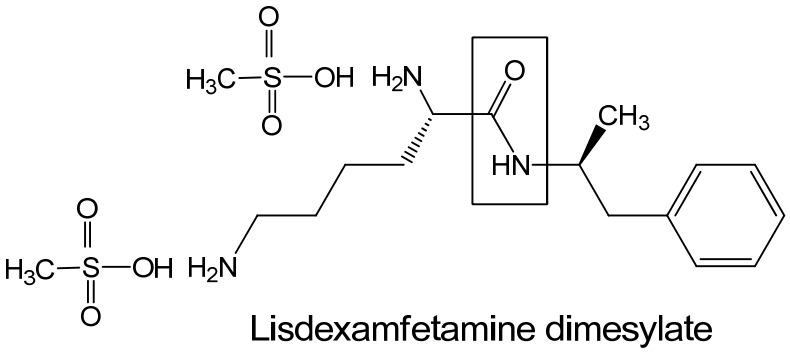
C. Vyvanse (lisdexamfetamine dimesylate) Capsules

Vyvanse Capsules contain lisdexamfetamine dimesylate as the active ingredient. Lisdexamfetamine dimesylate is lisdexamfetamine as the dimesylate salt.

Lisdexamfetamine dimesylate

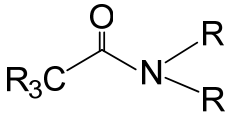


Lisdexamfetamine consists of dextroamphetamine bonded covalently to lysine through an amide bond. See detail of amide bond in box in figure below. Amides are carboxylic acid derivatives in which the acid hydroxyl group has been replaced by an amino group.[5]



[4] A list of the submissions to Docket No. FDA-2009-N-0184 is attached at APPENDIX A.

[5]



Illustrates an amide: carbonyl group (C=O) connected to an amino group (NR_2).

Lisdexamfetamine is a prodrug[6] of dextroamphetamine. Vyvanse Labeling at Sec. 12.1 Mechanism of Action. Dextroamphetamine is the active moiety in a number of drugs approved by FDA prior to its approval of Vyvanse. Examples of these include Dexedrine (dextroamphetamine sulfate) (a salt of dextroamphetamine) and Adderall (amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate), both of which are also approved for the treatment of ADHD. Lisdexamfetamine has not been previously identified as the active moiety in any drug approved by FDA.

III. Statutory and Regulatory Authorities

A. New Drug Applications and Abbreviated New Drug Applications

Section 505(b) of the Act establishes the approval requirements for NDAs. To be approved, an application submitted under 505(b) must, among other things, be supported by investigations showing the drug product to be safe and effective. Section 505(b)(1) of the Act. 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 (a "stand-alone NDA"). The 1984 Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman Amendments") provided an alternate pathway under subsection 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 (a "505(b)(2) application"). Like a stand-alone NDA, a 505(b)(2) application is submitted under section 505(b)(1) of the Act and approved under section 505(c) of the Act. Both types of NDA are eligible for exclusivity under relevant provisions of section 505(c) and 505(j) of the Act.

The Hatch-Waxman Amendments also provided for submission of ANDAs for approval of generic versions of listed drugs. Section 505(j) of the Act. A listed drug is a drug product with an effective approval under section 505(c). 21 CFR § 314.3(b). 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 as the listed drug with respect to active ingredient, dosage form, strength, route of administration, and, with certain narrow exceptions, labeling, and that its product is bioequivalent to the listed drug. Section 505(j)(2) of the Act.

[6] Prodrugs generally are drugs that are themselves pharmacologically inactive compounds that are converted into biologically active substances in a variety of ways, including by hydrolysis of ester or amide linkages, or by other metabolic processes such as oxidation by a CYP450 enzyme. See generally Goodman & Gilman, The Pharmacological Basis of Therapeutics at 11 (9th ed. 1996); Remington, The Science and Practice of Pharmacy at 913 (20th ed. 2000).

B. Five-Year and Three-Year Marketing Exclusivity

In addition to establishing the abbreviated drug approval pathways in sections 505(b)(2) and 505(j) of the Act, the Hatch-Waxman Amendments provided incentives for pharmaceutical innovation in the form of marketing exclusivity to protect qualified drug products approved under section 505(b) from competition for certain periods. Under the statute, a 5-year exclusivity period is provided for drug products that do not contain a previously approved active ingredient (including any ester or salt of the active ingredient).[7] This exclusivity generally prevents FDA from accepting a 505(b)(2) or ANDA that contains the protected drug (active moiety) for a 5-year period from the date of approval of the protected drug.[8] Sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the Act. The exclusivity does not block acceptance and review of stand-alone NDAs containing the same active moiety, that is those NDAs supported entirely by data developed by the applicant or to which the applicant has a right of reference.

The Act also provides for a 3-year period of exclusivity. This is available for drug products that contain a previously approved active ingredient (including any ester or salt of the active ingredient), when that application includes new clinical investigations essential to the approval of the application and conducted or sponsored by the applicant.[9] This marketing exclusivity prevents FDA from approving 505(b)(2) applications and ANDAs for the same conditions of approval for 3 years from the date of approval of the drug with exclusivity. Sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the Act.

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[7] Section 505(j)(5)(F)(ii) of the Act provides

> If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

See also section 505(c)(3)(E)(ii) of the Act.

[8] As described above at fn. 1, an applicant may submit an ANDA or 505(b)(2) application after 4 years if the application includes a paragraph IV certification to a patent listed in the Orange Book for the referenced drug.

[9] Section 505(j)(5)(F)(iii) of the Act provides

> If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section for such drug.

See also section 505(c)(3)(E)(iii) of the Act.

C. FDA's Regulations Governing Five-Year NCE Exclusivity

FDA's regulation at 21 CFR § 314.108 implements the statutory exclusivity provisions. In this regulation FDA has interpreted sections 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the Act, which award 5 years of exclusivity to drugs "no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application,"[10] to preclude the Agency from accepting ANDAs for drugs that contain the same active moiety as in a previously approved new chemical entity. The regulation provides

> If a drug product that contains a new chemical entity was approved. . . in an application submitted under section 505(b) of the act, no person may submit a[n] . . . abbreviated new drug application under section 505(j) of the act for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application. . . .

21 CFR § 314.108(b)(2). Thus, under FDA's interpretation of the statute embodied in the regulations, a drug that is a new chemical entity will receive 5 years of exclusivity. If a drug product is not a new chemical entity (i.e., it contains any previously approved active moiety), it may be eligible for 3 years of exclusivity, but will not be eligible for 5 years of exclusivity.

The Agency has defined "new chemical entity" to mean "a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act." 21 CFR § 314.108(a). "Active moiety" in turn is defined as

> [T]he molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

Id. "Drug substance" is further defined as

> [A]n active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use [sic] in the synthesis of such ingredient.

21 CFR § 314.3(b). Active ingredient[11] is defined at 21 CFR § 210.3(b)(7) as

> [A]ny component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease,

[10] 35 U.S.C. § 156(a)(5)(A) and (f), also enacted as part of the Hatch-Waxman Amendments, apply almost identical language in provisions applicable to patent term extensions.

[11] An "inactive ingredient" means any component other than an active ingredient. 21 CFR § 210.3(b)(8).

> or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.

For drug labeling and ANDA approval purposes, the active ingredient is "the active ingredient in the finished drug product prior to its administration." 54 Fed. Reg. 28872, 28881 (July 10, 1989). An applicant seeking approval of an ANDA referencing Vyvanse would be required to provide adequate evidence that the proposed generic product contains the same active ingredient as Vyvanse (i.e., lisdexamfetamine dimesylate) and is labeled as having the same active ingredient. Section 505(j)(2)(A)(i) and (v) of the Act; 21 CFR § 314.94(a)(5) and (8). Vyvanse is labeled as having lisdexamfetamine dimesylate as its active ingredient. 21 CFR § 201.100(b).

D. Development of the Regulation Describing Five-Year NCE Exclusivity and Defining Active Moiety

FDA's interpretation of the NCE exclusivity provisions has consistently focused on the specific chemical structure of the drug under consideration. In the 1989 preamble to the proposed regulation defining an NCE, the Agency explained that it interpreted the statutory requirement that, to receive 5 years of exclusivity, a drug must contain no previously approved "active ingredient (including any ester or salt of the active ingredient)" to mean that the drug must not contain any previously approved active moiety. FDA based its interpretation on the statutory language and on the definition of "new molecular entity" or "Type 1" drug in FDA's IND/NDA classification scheme (used to classify new drugs by chemical type and therapeutic significance), which was in effect when Congress was considering the Hatch-Waxman Amendments. FDA stated that its interpretation of the 5-year exclusivity provision was consistent with the legislative history, which showed that Congress was aware of FDA's drug classification scheme and did not intend to confer significant periods of exclusivity on minor variations of previously approved chemical compounds. 54 Fed. Reg. at 28897-98.

Under the drug classification scheme, a "new molecular entity" is a compound containing an entirely new (i.e., never previously approved) active moiety. FDA elaborated on the definition of active moiety in the preamble to the 1989 proposed regulation, as follows:

> The “active moiety” in a drug is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance. A drug product will thus not be considered a “new chemical entity” entitled to 5 years of exclusivity if it contains a previously approved active moiety, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative has not been previously approved. A compound (other than an ester) that requires metabolic conversion to produce an already approved active moiety is considered a “new molecular entity,” however, and will be considered a new chemical entity entitled to 5 years of exclusivity. FDA will consider whether a drug contains a previously approved active moiety on a case-by-case basis.

54 Fed. Reg. at 28898.[12]

In proposing the regulation, FDA described the chemical structure of the types of molecules that would be considered to be an active moiety. The preamble explained that salts (including certain specific types of salts) and other derivatives, which - like salts - are noncovalently bonded, would not be considered the active moiety of a drug. In addition, and of particular application to the matter at hand, the Agency recognized that the only type of covalently bonded molecule that would not be considered an active moiety is an ester. At the same time, FDA stated that a molecule with a non-ester bond that requires metabolic conversion (i.e., a pro-drug) would be eligible for NCE exclusivity, and specifically noted that this analysis would apply even if the molecule resulting from the metabolic conversion is a previously approved active moiety. The Agency noted that exclusivity would be determined on a case-by-case basis.

FDA promulgated its final rule describing NCE exclusivity in 1994. 59 Fed. Reg. 50338 (Oct. 3, 1994). The preamble to the final rule described the basis for the Agency's adoption of the active moiety approach in light of Abbott Labs. v. Young, 920 F.2d 984 (D.C. Cir. 1990), in which the D.C. Circuit had addressed and rejected FDA's interpretation of a similar Hatch-Waxman marketing exclusivity before FDA had proposed its regulation. Id. at 988. [13] FDA stated that the "active moiety" approach in the context of the phrase "active ingredient (including any ester or salt of the active ingredient)" was not foreclosed by the D.C. Circuit, explaining as follows:

> Although the court of appeals appeared to agree with the agency's conclusion that exclusivity should be limited to the first approved product containing the active moiety, the court found the agency's parsing of the operative statutory phrase "active ingredient (including any salt or ester of the active ingredient)" to be linguistically impermissible as set forth in the agency's administrative decision denying 10-year exclusivity to Abbott. Rather than interpret the term "active ingredient" broadly to include the concept of active moiety, the agency interpreted the term narrowly to refer to the form of the moiety in the product, but interpreted the parenthetical phrase "(including any salt or ester of the active ingredient)"

[12] This interpretation had also been described generally in an April 28, 1988 "Dear Industry" letter ("the sixth in a series of letters intended to provide informal notice to all affected parties of developments in the policy and interpretation of the Drug Price Competition and Patent Term Restoration Act of 1984"). In that letter, FDA stated that "[t]he Agency considers a drug product eligible for the five-year period if it contains no active moiety that was previously approved by the Agency." April 28, 1988 letter at 2. The letter further stated in a footnote that:

> The "active moiety" in a drug product is the molecule or ion, excluding esterified forms, salts, complexes, chelates, or clathrates of the molecule, responsible for the physiological or pharmacological action of the drug substance. A drug product will not be considered a "new chemical entity" entitled to five years of exclusivity if it contains a previously approved active moiety, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or other non-covalent derivative (such as a complex, chelate or clathrates) has not been previously approved. A compound (other than an ester) that requires metabolic conversion to produce an already approved active moiety, however, is considered a "'new chemical entity" entitled to five years of exclusivity.

[13] The issue in *Abbott* was whether Abbott's drug was eligible for 10 years of exclusivity under section 505(j)(4)(D)(i) of the Act. Section 505(j)(4)(D)(i) (now section 505(j)(5)(F)(i)) provided 10 years of exclusivity for drugs approved between January 1, 1982, and September 24, 1984. The pertinent language describing the exclusivity in this subsection is identical to the relevant language of the 5-year exclusivity provision at issue here.

> broadly to include all active ingredients that are different but contain the same active moiety. Although the court noted that the agency had, subsequent to the administrative decision, voiced the more linguistically permissible construction (interpreting the term "active ingredient" to refer to active moiety), the court found that it could not consider this construction because it was not relied upon in the administrative decision.

59 Fed. Reg. at 50357-58. In promulgating its final rule, FDA concluded that the active ingredient, as used in the phrase "active ingredient (including any salt or ester of the active ingredient)," is the active moiety, as the Agency defines the term in 21 CFR § 314.108. Id. at 50358.[14]

The regulation promulgated by FDA relies on a relatively straightforward analysis of the chemical structure of the drug when analyzing eligibility for exclusivity. FDA adopted this approach based upon certain reasonable assumptions regarding the activity of different types of molecules, which can be applied to a range of drugs. FDA's regulation provides that, although neither esters nor salts will be a unique active moiety (as recognized in the statutory parenthetical), covalently bonded molecules that are not esters will be considered separate active moieties.[15] If a drug product contains a covalently bonded molecule as its active moiety and if this covalently bonded molecule was not previously approved as an active moiety, the drug is entitled to NCE exclusivity. As described more fully below at VI. C., the Agency has established a reasonable scientific basis for adopting this approach to NCE exclusivity.

IV. Summary of Vyvanse Exclusivity Determination

Exclusivity for Vyvanse Capsules is governed by 21 CFR § 314.108, which as discussed above implements the applicable statutory provisions. Because of the chemical structure of the active ingredient in Vyvanse, the analysis under the regulation entails a number of steps. Pursuant to FDA's interpretation of 21 CFR § 314.108, a salt will not be considered an active moiety. Therefore, although lisdexamfetamine dimesylate is the active ingredient of Vyvanse, because lisdexamfetamine dimesylate is a salt, lisdexamfetamine dimesylate is not the active moiety. The exclusivity analysis then turns to the lisdexamfetamine molecule.

As FDA interprets and applies 21 CFR § 314.108, a non-esterified covalently bonded molecule will be considered an active moiety in a drug. FDA has determined that lisdexamfetamine is a non-esterified covalently bonded molecule and thus lisdexamfetamine is the active moiety in Vyvanse. Further, lisdexamfetamine has not been previously approved as an active moiety in a drug product under section 505(b) of the Act, and is therefore a new chemical entity entitled to 5 years of exclusivity. Vyvanse Exclusivity Summary at 2. Lisdexamfetamine is a non-ester prodrug that requires metabolic conversion to produce dextroamphetamine, the previously approved active moiety.

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[14] In 1991, prior to the finalization of the applicable regulations, FDA granted NCE exclusivity to isosorbide mononitrate, a molecule that is an ester of previously approved isosorbide dinitrate. Isosorbide mononitrate is a stable ester in which the esterified portion of the molecule is responsible for the molecule's activity; isosorbide alone is inactive.

[15] Notably, the Agency did not adopt a rule that eligibility for exclusivity depends solely upon whether the specific molecule responsible for the therapeutic effect has been previously approved.

V. Actavis' Position

Actavis asserts that under the standard set out in FDA's regulation at 21 CFR § 314.108, lisdexamfetamine is not the active moiety in Vyvanse. Instead, Actavis maintains that dextroamphetamine is responsible for the therapeutic effect of Vyvanse, and thus FDA must disregard the portion of lisdexamfetamine linked to dextroamphetamine by the covalent amide bond and apply the regulation to conclude that dextroamphetamine is the active moiety in Vyvanse. February 6, 2009 Letter at 7-8. Because dextroamphetamine was previously approved as an active moiety, Actavis concludes that Vyvanse is not eligible for NCE exclusivity. Actavis claims it does not challenge the applicable regulation at 21 CFR § 314.108 on its face; rather Actavis states that it challenges FDA's application of 21 CFR § 314.108 to Vyvanse. February 6, 2009 Letter at 9; June 24, 2009 Supplement at 6.

In support of its argument, Actavis relies on the Vyvanse labeling, as well as on published literature and FDA's Pharmacology/Toxicology Review and Evaluation of Vyvanse to establish certain facts. Actavis asserts that:

i. dextroamphetamine is the molecule that is responsible for the therapeutic effect of lisdexamfetamine;
ii. lisdexamfetamine does not have therapeutic effect, i.e., is therapeutically inactive;
iii. lisdexamfetamine does not travel to the site of drug action; and
iv. lisdexamfetamine cleaves in vivo to release dextroamphetamine.

See generally, February 6, 2009 Letter at 1-3; June 24, 2009 Supplement at 1-6. Actavis argues that these facts require the conclusion that, under 21 CFR § 314.108, dextroamphetamine is the active moiety in lisdexamfetamine. According to Actavis, an active moiety must be the molecule or ion that provides the therapeutic effect at the site of action. Actavis points to FDA's "indisputable" definition of active moiety as the molecule that is "responsible for the physiological or pharmacological action of the drug substance," and to "the plain meaning of the NCE statute, Congressional intent and modern scientific understanding." June 24, 2009 Supplement at 2. Actavis contends that these factors support its view that the award of exclusivity to Vyvanse was arbitrary and capricious, and cannot stand. June 24, 2009 Supplement at 19; see also February 6, 2009 Letter at 4-6.

Actavis further maintains that FDA's regulations distinguish between active and inactive ingredients based upon whether the component provides the therapeutic effect, and argues that, because lisdexamfetamine is not active, it is not the active ingredient - or the active moiety - of Vyvanse.

VI. Discussion

Actavis' principal argument is that FDA has not interpreted and applied its own regulation correctly to determine the appropriate exclusivity for Vyvanse. Actavis asserts that, when properly interpreted, an active moiety as described at 21 CFR § 314.108(a) is "the 'molecule' that 'is responsible for the physiological or pharmacological action of the drug substance,' less the salt, ester or non covalent appendage to that molecule." February 6, 2009 Letter at 9. Actavis recognizes that this is not the Agency's current interpretation of the regulation, but urges that we adopt it nonetheless to determine exclusivity for Vyvanse. Id.

A. Actavis' proposed new interpretation of FDA's regulation at 21 CFR § 314.108 is not persuasive.

Actavis' interpretation would have the Agency apply 21 CFR § 314.108(a) so that the active moiety inquiry would identify the specific molecule, or portion of the molecule, that is responsible for the physiological or pharmacological action of the drug substance, and then treat as the active moiety that molecule, minus "the salt, ester, or non-covalent appendage to that molecule." Actavis' proposed interpretation is flawed because, although it addresses esters, salts, or other non-covalent forms of a drug, it fails to address the distinction FDA has drawn between these types of molecules and molecules with non-ester covalent bonds. Specifically, Actavis does not propose a reading of the regulation that would apply when, as they argue is the case with lisdexamfetamine, the molecule responsible for the physiological and pharmacological action of the drug has a covalent appendage. The regulation specifically directs that the active moiety is to be identified by "excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule." The regulation does not, however, state that covalent derivatives (other than esters) are to be excluded. Actavis ignores this aspect of the regulation when it makes the leap from asserting that dextroamphetamine is the molecule responsible for the pharmacological action of lisdexamfetamine to the conclusion that dextroamphetamine is the active moiety, without explaining the basis for discounting the covalently bonded appendage.

Actavis is in essence seeking to rewrite FDA's definition of active moiety to be "the molecule or ion, excluding any appended portions of the molecule, responsible for the physiological or pharmacological action of the drug substance." See May 19, 2009 Letter at 2. That is not the regulation in force. Nor, as Actavis acknowledges, is this the interpretation of 21 CFR § 314.108 FDA applies in making exclusivity decisions. FDA interprets and applies 21 CFR § 314.108 so that the relevant inquiry addresses the structure of the molecule that forms the drug substance, and whether that molecule has been previously approved as an active moiety.[16] Whether a molecule will be considered to be responsible for the physiological or pharmacological action of the drug substance depends upon on the chemical structure of that molecule, which in turn depend on certain reasonable assumptions FDA had adopted about the activity of these classes of molecules. If the molecules in the drug substance are salts or esters or other non covalent derivatives, the active moiety will be the molecule minus the appendage. If the drug substance is composed of non-ester covalently bonded molecules, the covalently bonded molecule is considered the active moiety. Actavis has provided no persuasive reason for FDA to depart in this case from its consistent practice.

[16] For small molecule chemically synthesized active ingredients, there is generally only one molecular structure to be assessed in the exclusivity analysis. However, on occasion the Agency must make an exclusivity determination for a drug that has more than one active ingredient (e.g., Coartem (artemether/lumefantrine) Tablets which was granted NCE exclusivity in April 2009). In addition, for certain drugs with active ingredients that are heterogeneous and/or not fully characterized (e.g., hyaluronidase, pancreatic enzyme products), these inquiries are much more complicated. In some cases it may be difficult or impossible to make the threshold determination of which molecules among the different types of molecules present in this type of active ingredient should be assessed with respect to molecular structure under the active moiety approach described under 21 CFR § 314.108.

FDA's longstanding interpretation of its regulation is reflected in the "Exclusivity Summary" form that guides the review divisions' analysis of eligibility for different periods of marketing exclusivity under the Hatch-Waxman Amendments. FDA's analysis of the eligibility of a drug for 5 years of exclusivity focuses on the following question:

> 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.

Exclusivity Summary at 2.

Thus, the inquiry is whether the Agency has already approved a drug that contains the active moiety, as defined by its chemical structure.

B. FDA may not discount the non-ester covalent bond in lisdexamfetamine when determining the “active moiety” of the drug.

Under FDA's interpretation of its regulation, the active moiety of a molecule with a non-ester covalent bond is the entire molecule, even if the molecule includes a covalent bond to a molecule that was itself previously an active moiety. Thus, a molecule (such as lisdexamfetamine) which includes an amide bond will be a different active moiety from the molecule absent the amide bond. If not previously approved in a drug product under section 505(b) of the Act, the molecule with the amide bond will be considered a new chemical entity eligible for NCE exclusivity. This application of the term active moiety is consistent with FDA’s implementation of the FDCA and its interpretation of the regulation since 1994.

In contrast, Actavis’ interpretation would deny exclusivity in any case in which a molecule, even one with a non-ester covalent bond, included a constituent “responsible for the physiological or pharmacological action of the drug substance” that it shared with a previously approved drug. June 24 Supplement at 2. This broad interpretation does not, however, comport with the FDCA, 21 CFR § 314.108, or Agency practice.

Actavis' arguments fail to adequately consider FDA’s definition of active moiety in its entirety. Actavis asserts that "'[a]ctive moiety' moiety means the molecule or ion responsible for the physiological or pharmacological action of the drug substance.” May 19, 2009 Letter at 2. That characterization of the regulation is incomplete and therefore misleading; it omits a crucial requirement that the active moiety exclude “those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule.” 21 CFR § 314.108(a)(emphasis added). These requirements are specific. The only covalent bond that both the FDCA and the regulation carve out from the identification of the active moiety is an ester

bond.[17] For purposes of determining active moiety, the regulation excludes only those molecules that are esters, salts, or other non-covalent derivatives. Actavis inappropriately broadens the limitation on the active moiety definition.

Lisdexamfetamine is a molecule with an amide covalent bond, not an ester covalent bond. The regulation exempts only those covalently bonded molecules that are esters from active moiety status, not covalently bonded molecules that are amides. In lisdexamfetamine, the amide bond between dextroamphetamine and lysine does not "cause lisdexamfetamine to be an ester." 21 CFR § 314.108(a). Therefore, the covalently bonded portion of the molecule cannot be excluded from the molecule in identifying the active moiety; lisdexamfetamine in its entirety is the active moiety. Since lisdexamfetamine is not a previously approved active moiety, FDA's grant of 5-year exclusivity to Vyvanse was consistent with the regulation and not arbitrary or capricious.

C. FDA's "blanket" distinction between covalent and non-covalent derivatives is neither arbitrary nor contrary to statutory language and legislative history.

Actavis argues that FDA's regulation which treats covalent and non-covalent bonds differently is contrary to the statutory language and legislative history, does not reflect what happens when Vyvanse is administered, and does not support the award of NCE exclusivity. February 6, 2009 Letter at 4, 6. Actavis claims that "FDA arbitrarily drew a rigid distinction between covalent and non-covalent derivatives" in promulgating 21 CFR § 314.108(a). Id. at 4. Actavis points out that FDA's regulation results in a situation in which a non-covalent derivative of a previously-approved active moiety will not be entitled to NCE exclusivity, but a covalent derivative of a previously approved active moiety will be, regardless of the molecule or ion or portion thereof that is responsible for the therapeutic action. Id. at 5. Actavis argues that FDA's reasoning for distinguishing between covalent and non-covalent bonds is not supported by the actual effects of Vyvanse in vivo and does not support the award of NCE exclusivity. Id.

FDA's definition of active moiety depends in part on distinctions between non-covalent and covalently bonded molecules, and - further - between covalently bonded molecules that are esters and covalently bonded molecules that are not esters. In a 1989 Citizen Petition Response, FDA explained its reasoning for distinguishing between covalent and non-covalent bonds in identifying an active moiety, which it identified as "the molecule or ion, excluding those appended portions that cause it to be an ester, a salt, or other noncovalent derivative, such as a complex, chelate, or clathrate, responsible for the physiological or pharmacological action of the drug substance." July 26, 1989 Citizen Petition Response, Docket No. 1987P-0339 at 10. The Agency stated:

17

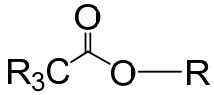

Illustration of an ester: carbonyl group (C=O) connected to an alkoxy, O-R group.

> [I]t has been FDA's longstanding experience that even minor covalent structural changes are capable of producing not only major changes in the activity of the drug but changes that are not readily predicted. Because of their potential significance, FDA has always identified changes in covalent structure, including minor changes, … as sufficient to create a new "active moiety," and thereby to create a new chemical entity.
>
> The potential significance of modifications in covalent structure, even where previously approved drugs contain the same "active site," is reflected in the amount and kind of data required for approval of such changes. Such a change requires submission of an amount of data comparable to that required for an entirely new molecule.
> …
>
> In contrast to most changes in the covalent structure of a molecule, the formation of a salt or a complex, or of an ester, is not intended to, and generally cannot, alter the basic pharmacologic or toxicologic properties of the molecule.

Id. at 11-12.[18]

In the 1994 preamble to its final regulations adopting the "active moiety" definition, FDA further explained the reasonableness of treating non-covalent derivatives differently from covalent derivatives:

> FDA disagrees with the assertion that the definition of "active moiety" should not exclude chelates, clathrates, and other noncovalent derivatives. As stated in the preamble to the proposed rule, exclusivity is intended to provide incentives for innovation (see 54 FR 28872 at 28898 and 28899). The addition of a chelate, clathrate, or other noncovalent derivative generally does not affect the active moiety of a drug product. The agency, therefore, does not believe that providing exclusivity for chelates, clathrates, and other noncovalent derivatives of a previously approved active moiety would be consistent with the statutory intent.

59 Fed. Reg. at 50358. Therefore, the Agency has a reasonable basis for its treatment of non-covalent derivatives, which comports with legislative intent to provide incentives for innovation.

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[18] The Agency also noted that:

> [T]he "active moiety" of a drug is the molecule or ion responsible for the pharmacological action of the drug, excluding only those appended portions that cause it to be an ester or a salt or other non-covalent derivative. Although the "active site" of the molecule may be responsible for a specific pharmacological action of the drug, other portions of the active moiety affect the activity of the drug, e.g., by affecting its distribution within the body, its metabolism, its excretion, or its toxicity. The "active moiety" of a drug thus consists of both the active site, if that is known, and those other portions of the molecule affecting the drug's activity that remain after absorption of the drug into systemic circulation and after exclusion of the appended portions that cause the molecule to be an ester [sic] salt or other noncovalent derivative.

Id. at 11.

In the 1989 Citizen Petition Response, FDA also explained its reasoning for distinguishing between esters and other covalent bonds:

> Although forming an ester causes a change in the covalent structure of the molecule, formation of an ester is more analogous to changes in noncovalent structures than to other changes in covalent structure. Portions of a molecule that are not covalently bound to the molecule, such as those portions that cause a drug to be a salt or complex, are designed to be separated from the "active moiety" before the drug is absorbed into the circulation. These noncovalently bound portions do not travel to, or act on, the site of drug action. Covalently bound portions, on the other hand, generally remain part of the active moiety and travel to the site of drug action. The formation of an ester, unlike other covalently bound groups, is in almost all cases designed to be removed before, or just after, absorption by gut or blood esterases; at that point there ester portion is cleaved from the "active moiety," and only the active moiety travels to, and acts on, the receptor site.

Id. at 12 n.5.

For the reasons described at the time of the rule-making, the distinctions FDA draws between non-covalently and covalently bonded molecules, and between ester and non-ester covalently bonded molecules are - like the distinctions drawn by Congress in the exclusivity provisions of the Act between salts and esters and other types of molecules - based on reasonable assumptions regarding the pharmaceutical activity of the molecules.

D. FDA's approach is consistent with Abbott Labs v. Young.

FDA has adopted an interpretation of the NCE exclusivity provisions of the Act that is consistent with the opinion in Abbott. In contrast, Actavis' interpretation of the term "active moiety" is inconsistent with Abbott, the very precedent on which Actavis relies. Actavis cites Abbott as accepting the notion that "'active moiety' [is] 'the substance that creates the actual therapeutic effect within the body.'" June 24, 2009 Supplement at 4 (quoting Abbott, 920 F.2d at 986). Actavis concludes that "this court-sanctioned definition should be applied here." Id. Actavis misstates the applicable law. Elsewhere in the Abbott opinion, the court rejected the precise approach Actavis urges on FDA, that is, an interpretation of the statutory language that would consider a molecule ineligible for NCE exclusivity if that molecule eventually produces a molecule with the therapeutic effect, where the molecule with the therapeutic effect has been previously approved. The court noted, "It is simply not plausible to read 'including any salt or ester' as merely illustrative, to mean including any form that eventually produces the same active moiety." Abbott Labs, 920 F.2d at 988.

In keeping with the court's view, FDA does not consider lisdexamfetamine ineligible for NCE exclusivity because it is a molecule "that eventually produces a previously approved active moiety," (i.e., dextroamphetamine). Instead, the Agency has applied its regulation at 21 CFR § 314.108, which excludes esters, salts, and other non-covalently bonded molecules from eligibility, but recognizes non-ester covalent derivatives as active moieties. Id. Because the covalent bond in lisdexamfetamine is an amide bond (i.e., a non-ester covalent derivative),

lisdexamfetamine is considered the active moiety, even if in vivo lisdexamfetamine eventually produces dextroamphetamine, a previously approved active moiety.

E. FDA does not need to identify precisely what portion of the lisdexamfetamine molecule is responsible for which pharmacological and/or physiological effects to determine that Vyvanse is eligible for NCE exclusivity.

FDA interprets and applies 21 CFR § 314.108 such that, when the molecule in a drug is covalently bonded (and a non-ester), the Agency need not determine which aspects of the physiological or pharmacological effect(s) of the drug are attributable to that molecule or to the molecule minus the covalently bonded portion. Because it is not always feasible to determine precisely which portion of a covalently bonded molecule is responsible for the physiological or pharmacological action, the regulation (like the statute itself) makes certain assumptions about the degree of innovation represented by different types of molecules. The statute and regulation exempt salts and esters from eligibility for NCE exclusivity because these changes to molecules are not expected to result in significantly different pharmaceutical effects. In contrast, molecules that have non-ester covalent bonds are expected to perform differently from molecules with a covalent bond. As discussed above, this assumption is scientifically reasonable.[19] Therefore, FDA may classify Vyvanse as an NCE on the basis of its chemical structure, and we need not determine which of Vyvanse's therapeutic, physiological, and pharmacological effects may be attributable to lisdexamfetamine, and which are attributable to dextroamphetamine.

Permitting the Agency to make exclusivity decisions on the basis of molecular structure is also reasonable in light of the potential difficulty in determining precisely which molecule, or portion

[19] These assumptions regarding the differences in pharmaceutical behavior of certain types of molecules were applied by the Agency in the context of describing the scope and effect of exclusivity under the Orphan Drug Act. See Section 527 of the Act, and corresponding regulations at 21 CFR § 316.3(b)(13) ("Same drug means: (i) If it is a drug composed of small molecules, a drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative such as a complex, chelate or clathrate has not been previously approved, except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug."). As the Agency noted in proposing this approach:

> [I]t appears sound, for the purposes of consideration of exclusive marketing under the Orphan Drug Act, to adopt a policy that regards two drugs as different if they differ with respect to the chemical structure of their active moieties. First, such differences are highly likely to lead to pharmacologic differences. Second, the development of an agent with a novel active moiety is not a financially or intellectually trivial matter; it represents a considerable effort and a substantial risk, as the results of changes in small molecules are difficult to predict.

56 Fed. Reg. 3338, 3341 (Jan. 29, 1991). The Agency further explained in the preamble to the final regulation that:

> For micromolecular products, the active moiety is the whole covalently bound part of the molecule that is active. This means that it generally consists of all of the molecule except added parts that make it a salt or ester. Essentially, any change in covalent structure creates a new active moiety whose properties may well differ from the old active moiety.

59 Fed. Reg. 62076, 62077 (Dec. 29, 1992).

of a molecule, is responsible for a drug's effects. This difficulty is illustrated by the submissions in this case, in which Actavis and Shire make conflicting claims regarding which in vivo effects are meaningful and which molecules or portions of molecules are responsible for those effects. Moreover these claims are based at least in part on information developed since Vyvanse was approved.[20] For example, the parties do not agree upon what effect, if any, inclusion of lisdexamfetamine (instead dextroamphetamine) has on activity of the drug in vivo. Actavis asserts that lisdexamfetamine is merely a carrier used to deliver dextroamphetamine to the site of action, and thus has no physiological or pharmacological effect. February 6, 2009 Letter at 3, 7-8. Shire, in turn asserts that studies have shown that by covalently bonding dextroamphetamine to lysine, it has created a molecule that - without the use of excipients or mechanical formulation - has the characteristics and pharmacokinetics of a sustained release formulation of dextroamphetamine. June 1, 2009 Letter from Covington & Burling at 3. Each party has its experts. Although this debate is interesting, particularly for the light it may shed on the behavior of this covalently bonded molecule, FDA need not, as part of its exclusivity analysis, determine which party is correct.[21]

F. FDA considers molecules that require metabolic conversion to be active moieties eligible for NCE exclusivity, thus providing an additional basis for exclusivity for lisdexamfetamine.

Even if all of the therapeutic effect of Vyvanse were attributable to the conversion of lisdexamfetamine to dextroamphetamine, lisdexamfetamine is eligible for NCE exclusivity because it is a non-ester prodrug that requires metabolic conversion to produce dextroamphetamine. In the preamble to its proposed rule, FDA clarified that "[a] compound (other than an ester) that requires metabolic conversion to produce an already approved active moiety . . . will be considered a new chemical entity entitled to 5 years of exclusivity." 54 Fed. Reg. at 28898. This interpretation of the regulation is also expressly recognized in FDA's Exclusivity Summary, which states that if a compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety, it will be an new chemical entity. Exclusivity Summary at 2.

The Vyvanse labeling and FDA reviews supporting the 2007 NDA approval establish that lisdexamfetamine is a prodrug of dextroamphetamine, and requires metabolic conversion to produce dextroamphetamine. As described above at fn. 7, prodrugs generally are drugs that are themselves pharmacologically inactive compounds that are converted into biologically active

[20] This information is available for consideration in the context of Vyvanse's exclusivity only because of the unusual posture of this matter. Actavis correctly asserts that the additional studies which Shire submitted to the docket on June 1, 2009, were not before FDA when it made its original determination that Vyvanse was entitled to NCE exclusivity. However, FDA stated that it was opening the docket in response to Actavis' request that FDA reconsider its grant of NCE exclusivity to Vyvanse. FDA may consider the results of the studies provided by Shire in its June 1, 2009 filing only because the studies are part of the administrative record in this matter. The submissions made by Shire that are supported by post approval research on Vyvanse underscore the problems associated with basing NCE exclusivity on a finding of which molecule or portion of a molecule is responsible for the action of the drug. Post approval research resulting in new understanding of the activity of the drug could give rise to requests to change the type of exclusivity granted to a given drug, with resulting uncertainty in the industry.

[21] Shire states that information from recent studies of the "active transport process and subsequent cleavage of the lysine molecule from lisdexamfetamine" will be submitted to the Vyvanse NDA "during the second half of 2009," for inclusion in labeling. June 1, 2009 Letter at 13 n. 43. If and when Shire submits this information, FDA will review it to determine whether it is adequate to support changes to the labeling.

substances in a variety of ways, including by hydrolysis of ester or amide linkages, or by other metabolic processes. The labeling for Vyvanse states that "After oral administration, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract. Lisdexamfetamine is converted to dextroamphetamine and l-lysine, which is believed to occur by first-pass intestinal and/or hepatic metabolism." Vyvanse Labeling at Sec. 12.1 Mechanism of Action. Lisdexamfetamine thus requires metabolic conversion to produce dextroamphetamine, which is responsible for the drug's activity. At the time of approval, FDA reviews concluded based on in vitro and in vivo animal data that, in its intact form, lisdexamfetamine dimesylate lacks stimulant properties and is pharmacologically inactive. Therefore, the activity of lisdexamfetamine dimesylate is derived from the compound produced by metabolic conversion, dextroamphetamine.

FDA has granted NCE exclusivity to many prodrugs. In each case, the factors at issue in determining whether the drug is an NCE are whether it is a non-ester, and whether it requires metabolic conversion to produce the active moiety.[22] Actavis argues that FDA should consider other factors in determining whether NCE status for pro-drugs is appropriate, including whether the prodrug travels intact to the site of activity before the final cleaving step occurs, the chemical bonds in the molecules and the mechanism of cleavage, and the number of metabolites produced. June 24, 2009 Supplement at 16-17. Actavis suggests that when applied, these considerations warrant denying lisdexamfetamine NCE exclusivity. This argument fails, however, because the multiple factors Actavis urges FDA to consider are not required by statute or by FDA's regulation.

G. Actavis' arguments regarding the identity of the active ingredient in Vyvanse are not persuasive.

Actavis maintains that FDA's regulations distinguish between active and inactive ingredients based upon whether the component provides the therapeutic effect and argues that, because lisdexamfetamine is not active, it is not the active ingredient - or the active moiety - of Vyvanse. In support of this argument, Actavis points to the definitions in the regulations, asserting that they define active ingredient as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals." February 6, 2009 Letter at 7 (quoting 21 CFR § 210.3(7) (emphasis added)). Actavis also quotes the definition of inactive ingredient in the regulations, which is "any component other than an active ingredient." Id. (quoting 21 CFR § 210.3(8)). A component is "any ingredient intended for use in the manufacture of a drug product, including those that do not appear in such drug product." 21 CFR § 210.3(b)(3).

Actavis argues in essence that lisdexamfetamine is an inactive ingredient of Vyvanse (along with the microcrystalline cellulose, croscarmellose sodium, and magnesium stearate identified in the Vyvanse label). Actavis is incorrect. Lisdexamfetamine dimesylate is the active ingredient in Vyvanse. It is the component of Vyvanse Capsules intended to furnish the effect of Vyvanse through its metabolic conversion into dextroamphetamine. Dextroamphetamine, which is not a

[22] Examples of prodrugs that have received NCE exclusivity include Colazal (balsalizide disodium); Cerebyx (fosphenytoin); and Lusedra (fospropofol disodium).

component of Vyvanse Capsules, is not the active ingredient of Vyvanse. Moreover, after analyzing lisdexamfetamine dimesylate under the standard set out at 21 CFR § 314.108, FDA has determined that dextroamphetamine is not the active moiety in Vyvanse; the active moiety is lisdexamfetamine.

H. FDA grants NCE exclusivity to non-ester covalently bonded molecules; therefore FDA is reviewing the exclusivity determination for Emend for Injection.

Actavis argues that FDA should rescind its grant of NCE exclusivity to Vyvanse because it was inconsistent with FDA's denial of NCE exclusivity to Emend (fosaprepitant dimeglumine) for Injection ("Emend"). According to Actavis, FDA properly determined that Emend was not entitled to NCE exclusivity and therefore Vyvanse, which has similar characteristics, is also not entitled to NCE exclusivity. In light of FDA's review of its interpretation and application of 21 CFR § 314.108 to non-ester covalently bonded molecules, the Agency is reconsidering the decision to deny Emend NCE exclusivity.

VII. CONCLUSION

FDA has correctly applied its regulation at 21 CFR § 314.108 to Vyvanse (lisdexamfetamine dimesylate) to grant it NCE exclusivity. Under the regulation, lisdexamfetamine dimesylate is not the active moiety because lisdexamfetamine dimesylate is a salt of lisdexamfetamine. Lisdexamfetamine in turn consists of dextroamphetamine bonded covalently to lysine through an amide bond. Because lisdexamfetamine is a non-ester covalently bonded molecule, and because it is a non-ester pro-drug, lisdexamfetamine is the active moiety of Vyvanse. Lisdexamfetamine has not been previously approved by FDA, and therefore Vyvanse is an NCE entitled to 5 years of exclusivity.

Sincerely,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: Covington & Burling, Counsel for Shire
Michael Landa, Chief Counsel, FDA/OCC

APPENDIX A

Submissions to Docket No. FDA-2009-N-0184

January 28, 2009 Letter from Axinn, Veltrop & Harkrider LLP on behalf of Actavis Elizabeth, LLC to Gary J. Buehler regarding NCE exclusivity for Lisdexamfetamine Dimesylate Capsules;

February 6, 2009 Letter from Axinn, Veltrop & Harkrider LLP on behalf of Actavis Elizabeth, LLC to Gary J. Buehler regarding NCE exclusivity for Lisdexamfetamine Dimesylate Capsules and attachment entitled "Erroneous Award of NCE Exclusivity to Vyvanse" with exhibits;

May 19, 2009 Letter from Axinn, Veltrop & Harkrider LLP on behalf of Actavis Elizabeth, LLC to Docket No. FDA-2009-N-0184 regarding NCE exclusivity for Lisdexamfetamine Dimesylate Capsules and attached exhibits;

May 29, 2009 Comment to Docket No. FDA-2009-N-0184 regarding NCE exclusivity for Lisdexamfetamine Dimesylate Capsules filed by XenoPort;

June 1, 2009 Letter from Covington & Burling LLP on behalf of Shire Pharmaceuticals to Docket No. FDA-2009-N-0184 regarding NCE exclusivity for Lisdexamfetamine Dimesylate Capsules and attached exhibits;

June 1, 2009 Comment to Docket No. FDA-2009-N-0184 regarding NCE exclusivity for Lisdexamfetamine Dimesylate Capsules filed by Pharmaceutical Research and Manufacturers of America (Pharma);

June 1, 2009 Comment to Docket No. FDA-2009-N-0184 regarding NCE exclusivity for Lisdexamfetamine Dimesylate Capsules filed by Fitzpatrick, Cella, Harper & Scinto and attached exhibits;

June 24, 2009 Supplement to May 19, 2009 letter, filed by Axinn, Veltrop & Harkrider LLP on behalf of Actavis Elizabeth, LLC in response to comments from Shire Pharmaceuticals, XenoPort, Inc., The Pharmaceutical Research and Manufacturers of America, and Fitzpatrick, Cella, Harper, & Scinto;

July 24, 2009 Supplement to June 1, 2009 Letter, filed by Covington & Burling LLP on behalf of Shire Pharmaceuticals and attached exhibits.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21977	ORIG-1	SHIRE DEVELOPMENT INC	VYVANSE (LISDEXAMFETAMINE DIMESYLATE)

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

/s/

GARY J BUEHLER
10/23/2009

EXCLUSIVITY SUMMARY

NDA # 22-023 (Type 2) SUPPL # HFD # 180

Trade Name Emend

Generic Name fosaprepitant dimeglumine

Applicant Name Merck & Co, Inc.

Approval Date, If Known PDUFA date is January 27, 2008

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:

Fosaprepitant dimeglumine, a white to off-white amorphous powder, is a prodrug of aprepitant that is freely soluable in water. When administred intravenously it rapidly converts to aprepitant. Because the administration of fosaprepitant dimeglumine (I.V.) is different than that of aprepitant (oral capsules) clinical data is necessary.

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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?

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).

NDA# 21-549 Emend (aprepitant) Capsules: 40, 80, and 125 mg

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of 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:

NOTE ON QUESTION 2a): Study 07L1 is a clinical study that provided essential support to the safety of Emend. Although efficacy endpoints were measured, the study failed to meet the efficacy endpoints. Therefore, the study only supported safety and not efficacy.

Since Study 07L1 does not support efficacy, we do not consider it essential for approval of exclusivity purposes.

(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:

See PART III, Question 2a)

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:

Question #3) is being answered as Not Applicable (N/A). The clinical study was a safety study/failed efficacy study -- efficacy was demonstrated due to the pK study alone.

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:

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"):

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 # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # 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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(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:

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Name of person completing form: Jagjit Grewal, M.P.H.
Title: Regulartory Project Manager
Date: January 17, 2008

Name of Office/Division Director signing form: Joyce Korvick, M.D., M.P.H.
Title: Deputy Division Director

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

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

/s/

Joyce Korvick
1/25/2008 06:36:06 PM