DUPLICATE

Zydus Pharmaceuticals (USA) Inc.

Zydus Cadila

508 Carnegie Center, First Floor,
Princeton, NJ 08540 USA
Phone: 609-275-5125
Fax: 609-275-3711

Dated 30th March 2007

1135 7 APR 13 P3:55

Dr. Gary Buehler
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park, North II
7519 Standish Place
Rockville, MD 20855

SPECIAL AMENDMENT
N-000-MC

REF: Amlodipine Besylate Tablets 2.5mg, 5mg and 10mg – ANDA # 78-226

Respected Sir,

This has reference to the written communication we received from you with respect to above referenced ANDA of Zydus Pharmaceuticals USA Inc. We understand from your communication that because of the recent developments in the Amlodipine Besylate patent litigation presented several regulatory issues that need to be resolved before any applications could be approved.

Detailed response/comments to the questions agency is considering on the patent issues of subject ANDA is enclosed with this communication for your kind consideration and further advice.

A copy of this cover letter is enclosed in a self-enclosed, stamped envelope. Please stamp the copy as 'Received' with the date, as acknowledgment of receipt of these documents.

If there are any questions or comments, please do not hesitate to contact me via telephone at (609) 275-5125, via facsimile at (609) 275-3711 or via e-mail: gsrinivas@zydususa.com.

We thank you for your co-operation.

Sincerely,

03/30/07

G. Srinivas
Drug Regulatory Affairs

2007N-0123

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Zydus Pharmaceuticals USA Inc.	03/30/2007
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
609-275-5125	609-275-3711
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* Zydus Pharmaceuticals USA Inc. 508 Carnegie Center, 1st Floor, Suite 101 Princeton, NJ-08540	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE G. Srinivas Zydus Pharmaceuticals USA Inc., 508 Carnegie Center, 1st Floor, Suite 101 Princeton, NJ-08540

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* -

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Amlodipine Besylate Tablets	-

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate

CODE NAME *(If any)*: -

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	2.5 mg, 5 mg and 10 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
See Attachment I

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: Norvasc® (amlodipine besylate) Tablets — Holder of Approved Application: Pfizer Inc., USA

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Special Amendment (Response to Patent issues dated 29th March 2007)

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

No change from original ANDA

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Amlodipine Besylate DMF # 18827

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	G. Srinivas, Senior Director – Regulatory Affairs Zydus Pharmaceuticals (USA) Inc.	03/30/2007

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Zydus Pharmaceuticals USA Inc., 508 Carnegie Center, 1st Floor, Princeton, NJ - 08540	(609) 275-5125

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling & Program Support
Rockville, Maryland

To: Zydus Pharmaceutical
ATTN: Ravindra Patel

Phone: _____ Fax: 609-275-3711

From: Tracy Buehler

Phone: (301) 827-5846 Fax: (301) 827-5911

Number of Pages: 4
(Including Cover Sheet)

Comments:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-226

Zydus Pharmaceuticals USA, Inc.
Attention: Ravindra Patel
508 Carnegie Center
First Floor, Suite 101
Princeton, NJ 08540

Dear Mr. Patel:

This letter is in reference to your pending ANDA for amlodipine besylate tablets. As you may be aware, on March 26, 2007, Mylan Laboratories, Inc. filed a complaint against the Food and Drug Administration ("FDA") seeking to enjoin FDA from immediately approving abbreviated new drug applications for amlodipine besylate products. *Mylan Laboratories, Inc. v. Michael Leavitt*, CA No. 07-579 (RMU) (D.D.C.). Because the recent developments in the amlodipine besylate patent litigation (in particular, the Federal Circuit's March 22, 2007 decision in *Pfizer Inc. v Apotex, Inc.*, No. 2006-1261 (Fed. Cir. March 22, 2007)) presented several regulatory issues that need to be resolved before any applications could be approved, FDA informed the court (in CA No. 07-579) that it planned to solicit comments from interested parties before it reached decisions on the matters that Mylan sought to enjoin. The court has memorialized FDA's proposal, and enjoined the agency from implementing its decisions once made, until 5:00 pm on April 13, 2007, to allow the court the opportunity to review the FDA decisions. *Mylan Laboratories*, CA No. 07-579, Order (March 26, 2007).

The FDA is considering the following questions. Should you wish to comment on them, your response will be posted at http://www.fda.gov/cder/ogd/index.htm. Other submissions relevant to these issues will also be posted at this address. Please send your response, if any, by close of business on April 4, 2007 to:

Food and Drug Administration
Office of Generic Drugs, HFD-600
Attention: Gary J. Buehler, Director
7519 Standish Place
Rockville, MD 20855

1. What date controls FDA's giving effect to the decision in *Pfizer Inc. v Apotex, Inc.*, No. 2006-1261 (Fed. Cir. March 22, 2007) ("*Apotex* decision") holding that Pfizer's patent 4,879,303 ("the '303 patent") is invalid? Can FDA treat the '303 patent as invalid as of March 22, 2007, or must FDA await the issuance of the mandate? Is the answer the same for all purposes, that is, for determining the applicability of pediatric exclusivity, the triggering of 180-day exclusivity, and the eligibility of other ANDA applicants for final approval?

2. If FDA must await the issuance of the mandate, does pediatric exclusivity bar approval of all unapproved ANDAs in the meantime?

3. If and when the *Apotex* decision is implemented, what is the effect of the decision that the '303 patent is invalid on the obligation of an ANDA applicant to change its certification? Must Pfizer delist its patent, so that certifications can be withdrawn? Or can FDA treat an invalid patent as delisted as a matter of law, and presume the withdrawal of the certifications? Or must the ANDA applicants file paragraph II certifications stating that the '303 patent has expired?

4. If and when the *Apotex* decision is implemented and the patent is treated as invalid, does pediatric exclusivity attach to the '303 patent with respect to any unapproved ANDAs? Does it matter whether the ANDA applicant filed a paragraph III or IV certification before patent expiration?

5. Does 180-day exclusivity triggered before a patent expires continue to bar approvals of other ANDAs after the patent expires, even if other ANDA applicants change their certifications to paragraph II or withdraw their certifications altogether?

We note that several citizen petitions have been submitted that also raise issues relevant to approval of ANDAs for products containing amlodipine. The petition docket numbers are: 2007P-0116, submitted by Mylan Pharmaceuticals, Inc; 2007P-0110 and 2007P-0111 submitted by Pfizer Inc. If you believe your comments are also relevant to consideration of those petitions, you may submit your comments to the petitions dockets as well. In addition, FDA may consider relevant comments received in this context when answering the petitions.

Thank you for your consideration of these questions. If you have any questions regarding this letter, please contact Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at 240-276-9310.

Sincerely,

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

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

/s/

Gary Buehler
3/28/2007 12:27:47 PM

1. ***What date controls FDA's giving to the decision in Pfizer Inc. V Apotex, Inc., No. 2006-1261 (Fed. Cir. March 22, 2007) ("Apotex decision") holding that Pfizer's patent 4,879,303 ("the '303 patent") is invalid? Can FDA treat the '303 patent as invalid as of March 22, 2007, or must FDA await the issuance of the mandate? Is the answer the same for all purposes, that is, for determining the applicability of pediatric exclusivity, the triggering of 180-day exclusivity, and the eligibility of other ANDA applicants for final approval?***

   In our opinion, the date that controls the FDA's giving effect to the decision in *Pfizer Inc. vs. Apotex, Inc.,* No. 2006-1261 (Fed. Cir. March 22, 2007) ("Apotex decision") holding that the Pfizers Patent 4,879,303 ("the '303 patent") is the day of issuance of the mandate.

   Rule 41 of the Federal Rules of Appellate Procedure ("FRAP") states that "the court's mandate must issue 7 days after the time to file a petition for rehearing expires, or 7 days after entry of an order denying a timely petition for panel rehearing, rehearing en banc, or motion for stay of mandate, whichever is later". *See Rule 41(b).* Subdivision (c) of the Rule introduced by way of the 1998 amendment stating that "The mandate is effective when issued". The Advisory Committee Notes on the Rules to this amendment clearly stated that "A court of appeals' judgment or order is not final until issuance of the mandate; at that time the parties' obligations become fixed".

   The congressional intent is clear. The requirement that a mandate be issued following a decision makes decision of the Appellate Court final and binding on the parties after affording opportunity to the aggrieved party to file a petition for rehearing.

   Hence we submit that the date controlling FDAs giving effect to the Apotex decision is the date of issuance of the mandate. Hence FDA must await the issuance of mandate before treating the '303 patent as invalid.

   We further submit that this date is the same for determining the applicability of pediatric exclusivity, triggering of 180-day exclusivity and the eligibility of other ANDA applicants final approval since all these events are governed by the final decision of the Court as stated in 21 U.S.C §355(j)(5)(B)(iii), 21 U.S.C. § 355(j)(5), 21 U.S.C §355(a)(b)(2)(B) and 21 USC §355(a)(c)(2)(B).

2. ***If FDA must await the issuance of the mandate, does pediatric exclusivity bar approval of all unapproved ANDAs in the meantime?***

   We believe that until a mandate is issued by the Court, pediatric exclusivity does bar approval of all unapproved ANDAs.

As stated in 21 U.S.C §355(a)(b)(2)(A,B) and 21 USC §355(a)(c)(2)(A,B), pediatric exclusivity is attached to patent listed for which a certification has been submitted under subsection (b)(2)(A)(ii) or (j)(2)(A)(vii)(II) of section 355 and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iii) or (j)(2)(A)(vii)(III) of section 355 or of a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 355 of this title, and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed.

Thus a pediatric exclusivity is valid and existent till there is a final decision by the court regarding the validity of the patent. As stated in Response to Question 1, an issuance of the mandate is determinative of final decision of the court. Hence he FDA should await the issuance of the mandate until when pediatric exclusivity will bar all unapproved ANDAs.

3. ***If and when the Apotex decision is implemented, what is the effect of the decision that the '303 patent is invalid on the obligation of an ANDA applicant to change its certifications? Must Pfizer delist its patent, so that certifications can be withdrawn? Or can FDA treat an invalid patent as delisted as a matter of law, and presume the withdrawal of the certifications? Or must the ANDA applicants file paragraph II certifications stating that the '303 patent has expired?***

We believe that once Apotex decision is implemented, Pfizer should delist the '303 patent and the certifications filed by the ANDA holders should be withdrawn.

In our opinion, such delisting would enable future ANDA filers to submit appropriate certification. An express delisting of the '303 patent by Pfizer would enable future ANDA filers to submit suitable certification without ambiguity.

4. ***If and when the Apotex decision is implemented and the patent is treated as invalid, does pediatric exclusivity attach to the '303 patent with respect to any unapproved ANDAs? Does it matter whether the ANDA applicant filed a paragraph III or IV certification before patent expiration?***

We believe that if the Apotex decision is implemented and the patent is treated as invalid, the pediatric exclusivity will no longer be attached to the '303 patent with respect to unapproved ANDAs and that the FDA should give final approvals to all such ANDAs

21 U.S.C §355(a)(b)(2)(B) and 21 USC §355(a)(c)(2)(B) state pediatric exclusivity for a new drug and an already existing drug respectively would be

granted for a period of six months after the date the patent expires (including any patent extensions) if "the drug is the subject of a listed patent for which a certification has been submitted under subsection (b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) of section 355 of this title, and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed ..."

The section clearly indicates that a pediatric exclusivity with respect to an unapproved ANDA is attached only to patents which are valid and non-infringed by the ANDA holder. In the Apotex decision, the issue concerns a patent which has been invalidated by the court. The pediatric exclusivity hence cannot be attached to this patent once the Apotex decision is implemented. Implementation of the decision should be followed by immediate approval of all unapproved ANDAs.

Since the Apotex decision invalidates the patent, we believe that it does not matter whether the ANDA applicant has filed a Paragraph III or paragraph IV certification. Since the '303 patent is invalid, there cannot be a pediatric exclusivity attached to it which is applicable to all unapproved ANDA holders.

We also believe, that the type of certification to the '303 patent would have become a matter of concern for the unapproved ANDA holders other than Apotex had the court given a finding of validity and non-infringement instead of invalidity. Since, this is not the case; the type of certification should not be a factor determining the approval to the unapproved ANDA holders.

5. ***Does 180-day exclusivity triggered before a patent expires continue to bar approvals of other ANDAs after the patent expires, even if other ANDA applicants change their certifications to paragraph II or withdraw their certifications altogether?***

We believe that 180-day exclusivity triggering before the patent expires does not bar approval of other ANDAs after the patent expires. 21 U.S.C. § 355(j)(5)(D)(i)(VI), states that the 180-day exclusivity would be forfeited if all of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired