

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125469Orig1s000

APPROVAL LETTER



BLA 125469/0

BLA APPROVAL

Eli Lilly and Company
Attention: Kenneth Mace, PhD
Advisor, Global Regulatory Affairs-US
Lilly Corporate Center, DC 2543
Indianapolis, IN 46285

Dear Dr. Mace:

Please refer to your Biologics License Application (BLA) dated September 17, 2014, received September 18, 2014, submitted under section 351(a) of the Public Health Service Act for Trulicity (dulaglutide).

We also refer to our approval letter dated September 18, 2014, which contained errors in the Manufacturing Locations and Dating Period sections of the letter.

This replacement approval letter incorporates the correction of the errors. The effective approval date will remain September 18, 2014, the date of the original approval letter.

We acknowledge receipt of your amendments dated October 8 and 14, November 22, December 6, 2013, and January 10 and 13 (2), February 6, 21, and 28, April 4, 11, 14, 17, 18, 21 (3), 24, and 29, May 5, 6, 8, 27, and 30, June 9, 11, 13, 18, 24, 27, and 30, July 17, August 5, 25, and 27, and September 9 and 18, 2014.

We also acknowledge receipt of your email dated September 18, 2014, which includes the agreed-upon labeling.

LICENSING

We have approved your BLA for Trulicity (dulaglutide) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Trulicity, under your existing department of Health and Human Services U.S. License No. 1891. Trulicity is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture dulaglutide drug substance at Eli-Lilly S.A, Kinsale, Ireland (FEI number 3002806888). The final formulated product will be manufactured and filled at Eli Lilly and Company, Indianapolis, IN (FEI number 1819470) and (b)(4) (FEI number (b)(4)). The semi-finished syringes will be assembled into pre-filled syringes, labeled, and packaged at (b)(4) (FEI (b)(4)). The semi-finished syringes will be assembled into pre-filled pens, labeled, and packaged at Eli Lilly and Company, Indianapolis, IN (FEI number 1819470). You may label your product with the proprietary name, Trulicity, and will market it in 1.5 mg/0.5 mL and 0.75 mg/0.5 mL single dose pre-filled syringes and pre-filled pens.

DATING PERIOD

The dating period for Trulicity shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the (b)(4) (b)(4). The dating period for your drug substance shall be (b)(4) months from the date of manufacture when stored at (b)(4).

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Trulicity to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2a (specified product). We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot

Any changes in the manufacturing, testing, packaging, or labeling of Trulicity, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your August 27, 2014, submission containing final printed carton and container labels

ADVISORY COMMITTEE

Your application for Trulicity (dulaglutide) was not referred to an FDA advisory committee because this biologic is not first in class, the safety profile is similar to that of other drugs approved for this indication, and the application did not raise significant safety or efficacy issues that were unexpected for a biologic of this class.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years (inclusive) for this application because necessary studies are impossible or highly impracticable. This is because there are too few children in this age range with type 2 diabetes mellitus to study.

We are deferring submission of your pediatric studies for ages 10 to 17 years (inclusive), because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

2781-1 A 26-week randomized, double-blind, placebo controlled study of the safety, efficacy, and pharmacokinetics (PK) of Trulicity (dulaglutide) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive) with or without concomitant metformin therapy, followed by a 26-week open-label extension. As part of this study, sparse blood samples for population PK and exposures-response analysis will be collected. This trial should not be initiated until after the data from the juvenile toxicity study have been submitted to and reviewed by the Agency.

Final Protocol Submission: February 2016
Study Completion: August 2022
Final Report Submission: January 2023

2781-2 A study to evaluate dulaglutide toxicity in immature rats.

Study Completion: January 2015
Final Report Submission: March 2015

Submit the protocols to your IND 070930, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of medullary thyroid carcinoma associated with Trulicity (dulaglutide).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2781-3 A medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Trulicity (dulaglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Trulicity (dulaglutide).

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	June 2015
Study Completion:	December 2030
Final Report Submission:	March 2032

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to:

- Assess signals of a serious risk of worsening renal function and other serious adverse events in patients with renal impairment treated with Trulicity (dulaglutide).
- Assess signals of a serious risk of major adverse cardiovascular events (MACE) with Trulicity (dulaglutide). There have been signals of a serious risk of cardiovascular events with some other medications developed for the treatment of type 2 diabetes mellitus and available data have not definitively excluded the potential for this serious risk with Trulicity (dulaglutide).
- Assess signals of the serious risks of pancreatic cancer, pancreatitis, immune-mediated reactions (including serious hypersensitivity reactions), serious hypoglycemic events, hepatic events, serious gastrointestinal events, clinically significant supraventricular arrhythmias and clinically significant conduction disorders.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2781-4 A 26-week randomized, controlled trial comparing once weekly Trulicity (dulaglutide), 0.75 mg and 1.5 mg, with insulin glargine on glycemic control in patients with type 2 diabetes mellitus and moderate or severe renal impairment, with a 26-week controlled extension.

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Trial Completion: November 2016
Final Report Submission: May 2017

2781-5 A randomized, double-blind, placebo-controlled trial evaluating the effect of Trulicity (dulaglutide) on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) observed with dulaglutide to that observed in the placebo group is less than 1.3. The trial must also assess the following adverse events: thyroid cancer, pancreatic cancer, pancreatitis, immune-mediated reactions (including serious hypersensitivity reactions), serious hypoglycemic events, hepatic events, serious gastrointestinal events, clinically significant supraventricular arrhythmias, clinically significant conduction disorders and worsening renal function.

The timetable you submitted by email on September 17, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: June 2015
Trial Completion: June 2019
Final Report Submission: March 2020

Submit the protocols to your IND 070930, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: “**Required Postmarketing Protocol Under 505(o)**,” “**Required Postmarketing Final Report Under 505(o)**,” “**Required Postmarketing Correspondence Under 505(o)**.”

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 2781-6 To re-evaluate dulaglutide drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process.

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2018

- 2781-7 To re-evaluate dulaglutide drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process.

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2018

- 2781-8 To conduct drug substance and drug product specific leachable and extractable studies on the [REDACTED] (b) (4) used during manufacturing. The drug substance and drug product manufacturing processes will be optimized, as needed, based on the results.

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2016

- 2781-9 To reassess the dulaglutide drug substance and drug product control strategy, and the reference standard qualification/requalification programs, with regards to Fc region modifications and their impact on PK, including neonatal Fc binding.

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2016

- 2781-10 Provide data from one additional (b) (4) batch to support the (b) (4) hour hold time limit (b) (4). Provide this data in the first annual report.

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: November 2015

- 2781-11 Provide summary data from performance qualification shipping studies for shipment of the SFS and PFS from (b) (4) to Eli Lilly in the summer and winter. Provide this data in the first annual report.

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: November 2015

- 2781-12 Explore alternative endotoxin test methods and develop a more suitable endotoxin release test for dulaglutide drug substance and drug product.

The timetable you submitted by email on September 4, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: March 2015
Final Report Submission: December 2016

Submit clinical protocols to your IND 070930 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Trulicity (dulaglutide) to ensure the benefits of the drug outweigh the potential risk of medullary thyroid carcinoma and the risk of pancreatitis.

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on September 18, 2014, and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Trulicity (dulaglutide) into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. REMS communication plan activities:
 - a. Number of healthcare providers (HCPs) and professional societies targeted by the REMS.
 - b. Number of REMS letters sent to HCPs and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via standard mail because the HCP did not have an email address, and the number sent because the email was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
 - c. Number of REMS Factsheets distributed to HCPs during the 12 months after product launch.
 - d. Date when REMS website went live and number of total and unique site visits during the assessment period.
2. Evaluation of HCPs' understanding of:
 - a. The potential risk of medullary thyroid carcinoma (MTC)
 - b. The risk of pancreatitis
 - c. The need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis
 - d. Identification and treatment of pancreatitis after initiation of dulaglutide
 - e. Appropriate dulaglutide patient population characteristics
3. Safety surveillance
 - a. Dulaglutide utilization information including, but not limited to, indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)
 - b. Evaluation and post-marketing case reports of pancreatitis

- c. Evaluation and post-marketing case reports of medullary thyroid carcinoma (MTC)
- d. Any other relevant data and analysis employed to assess if the dulaglutide REMS is meeting its goals
- e. The evaluation shall include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or elements should be modified. If a REMS modification is needed, provide an overview of the impact of the REMS modification on stakeholders and any additional evaluations needed as part of the REMS assessment plan to assess the impact of the proposed REMS modification.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125469 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY)**

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125469 REMS ASSESSMENT
NEW SUPPLEMENT FOR BLA 125469
PROPOSED REMS MODIFICATION**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125469
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals,

complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager, at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

Package Insert
Medication Guide
Instructions for Use
Carton and Container Labeling
REMS

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

/s/

MARY H PARKS
09/18/2014