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*APPLICATION NUMBER:*

**205692Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

Memorandum to File

Subject: Addendum to Cross Discipline Team Leader Review for NDA 205692 Basaglar (insulin glargine injection): Final Approval Decision

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Division of Metabolism and Endocrinology Products

Application Type	505(b)(2) NDA/Class 1 Resubmission
Application Number(s)	205692
Submit Date(s)	16 Oct 2015
PDUFA Goal Date	16 Dec 2015
Established Name	Insulin glargine injection
Trade Name	Basaglar
Therapeutic Class	insulin
Applicant	Lilly Research Laboratories
Formulation(s)	Subcutaneous injection
Dosing Regimen	individualized
Indication(s)	(b) (4) of diabetes mellitus
Intended Population(s)	Adults and children with type 1 diabetes mellitus and adults with type 2 diabetes mellitus

### **Executive Summary**

NDA 205692 for Basaglar (insulin glargine injection) is acceptable for final approval.

### **Introduction and Background**

This memorandum is an addendum to the original NDA CDTL memo and Clinical review, and serves to document the final approval decision for NDA 205692 for Basaglar (insulin glargine injection). This 505(b)(2) application for Basaglar relies, in part, on FDA's finding of safety and effectiveness for Lantus (insulin glargine injection). Basaglar was tentatively approved on 18 Aug 2014. Tentative approval was appropriate at that time because the NDA was a 505(b)(2) application that otherwise met the requirements for approval under the Federal Food, Drug, and Cosmetic Act (FD&C Act), but could not be approved until the expiration of a period of patent protection for the listed drug relied upon and the expiration of a 30-month stay of approval.

On 16 Oct 2015 the Sponsor submitted an amendment to the NDA requesting final approval. The amendment was classified as a Class 1 resubmission (after withdrawal of certain chemistry, manufacturing, and controls (CMC) information; see below). The resubmission contains a safety update covering the period of 18 Jan 2014 to 8 Sep 2015 and revised draft labeling. These items are reviewed in this memorandum. Note that the NDA resubmission also initially contained CMC updates. However, the Sponsor subsequently withdrew this information (via administrative correction by flagging them as no longer relevant for review) so that the amendment could be reviewed under a 2-month time clock, i.e. a Class 1 resubmission (see General Correspondence dated 21 Oct 2015). The CMC reviewer Dr. Tran confirmed that this withdrawal was acceptable (conditions not changed since the tentative approval

such that any portion of the CMC information was necessary to ensure that the proposed product meets the statutory and regulatory requirements for approval) and that no re-inspection was required by OPQ/Facilities prior to final approval.

The reader is referred to the original Clinical Review and CDTL memo written by myself and the Division Director memo written by Dr. Jean-Marc Guettier for the original review findings and information pertaining to the basis for regulatory action for this NDA.

Note that we are approving Basaglar with the established name “insulin glargine injection,” consistent with current nomenclature practices for products approved under the FD&C Act. A deviation from current nonproprietary naming practices for products approved under the FD&C Act is not warranted for Basaglar at this time. We note, however, that FDA has requested public comment on nomenclature practices for biological products approved under the FD&C Act, and this issue continues to be under review within FDA.

### **Safety Update**

According to the Sponsor’s cover letter the safety update includes:

- an update on blinded safety information from an ongoing phase 3 registration study (ABER) to support registration in countries outside the U.S.
- spontaneously reported adverse events from the brief period Abasaglar<sup>1</sup> has been on the market in a few countries (EU, Japan)
- results from a literature survey for insulin glargine
- relevant safety information on listed drug Lantus

#### *Review findings:*

Study ABER is a Phase 3, prospective, randomized, multinational, multicenter, 2-arm, active control, open-label, parallel-design, 24-week study with a 4-week post-treatment follow-up comparing Lilly’s insulin glargine and Lantus in patients with T2DM. As of 8 September 2015, a total of 328 patients have been randomized (1:1 scheme). The study remains blinded. The majority of subjects are under 65 years of age. 44% of subjects are Asian and 49% White. Approximately half of subjects have completed at least 20 weeks. There have been no deaths. Fourteen patients have had SAEs. The SAEs span multiple system organ classes and preferred terms. There are no concerning SAEs that necessitate unblinding of the data. One patient had a SAE of chronic myelogenous lymphoma (CML) that led to discontinuation. However, a laboratory abnormality in lymphatic/lymphogenic cells was noted prior to enrollment.

See entire list of reported SAEs below. Overall, these data do not change the overall risk benefit of Basaglar.

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<sup>1</sup> Lilly’s “Abasaglar” (different trade name) is a “biosimilar medicinal product” (the EU term) and approved for use in the European Union. We generally consider a U.S.-approved product and an EU-approved product to be distinct products.

612	6552	86	Blinded	43	Female	Black or African American	Head injury/ Head injury	Moderate
203	2103	18	Blinded	43	Female	Asian	Chronic myeloid leukaemia/ Chronic myeloid leukemia	Severe
210	2451	155	Blinded	66	Female	Asian	Gastroenteritis/ Acute gastroenteritis	Severe
304	3162	29	Blinded	65	Female	White	Encephalopathy/ Encephalopathy	Severe
403	4104	64	Blinded	37	Male	Asian	Acute myocardial infarction/ Acute myocardial infarction	Moderate
	4108	58	Blinded	55	Female	Asian	Pyelonephritis/ Pyelonephritis	Mild
404	4151	48	Blinded	70	Male	Asian	Macular hole/ Macular hole	Severe
601	6006	92	Blinded	56	Male	White	Chronic obstructive pulmonary disease/ COPD exacerbation	Moderate
606	6266	17	Blinded	56	Female	White	Supraventricular tachycardia/ Supraventricular tachycardia	Severe
608	6357	-2	Blinded	47	Female	White	Cellulitis/ Cellulitis of foot	Severe
		51					Hypertensive crisis/ Hypertensive crisis	Moderate
		126					Urinary tract infection/ Urinary tract infection	Moderate
		126					Cellulitis/ Cellulitis of leg	Mild
610	6461	29	Blinded	71	Male	White	Pneumonia/ Pneumonia	Severe
	6464	50	Blinded	59	Female	White	Adenocarcinoma of colon/ Adenocarcinoma of sigmoid colon	Moderate
611	6501	49	Blinded	60	Male	White	Hypoglycaemia/ Hypoglycemia	Moderate
	6502	174	Blinded	53	Female	White	Blood creatinine increased/ Creatinine increased	Severe

The Sponsor also submitted 7 spontaneously reported adverse events from the marketing of Abasaglar. Although we consider this a different product than Basaglar, these reports were reviewed for potential new safety information. As of 30 September 2015, (b) (4) units of Lilly's insulin glargine have been sold worldwide. The adverse event spontaneous reports included 4 cases of hyperglycemia, one case of hypoglycemia, and one report each of weight increase and generalized edema in a single patient. These reports comprise known safety issues with insulin glargine and do not raise new safety concerns that change the overall risk benefit of Basaglar.

A literature review for Lantus found one case report of a 72 year old man with a 15-year history of type 2 diabetes who developed bilateral lower limb edema with 'wooden' character after using Lantus. The authors report this is the first such case and this adverse reaction should be considered for patients using insulin glargine. However, this report does not change the overall risk benefit of Basaglar. The Sponsor found no other relevant safety information in the literature with regard to the listed drug Lantus.

Overall, I agree with the Sponsor's statement that the information available for this safety update is consistent with the previous conclusions of safety and thus, does not alter the safety profile or benefit-risk balance of the product and does not suggest any need for labeling changes.

### **Labeling**

Updated labeling submitted by the Sponsor was limited to the following (in addition to correction of typographical errors or formatting inconsistencies):

- Minor revision due to fully incorporating class label language approved for all other insulin products on 25 February 2015 regarding single patient use of prefilled pens.

- Addition of instructions to changing from (b) (4) (now included in 2.3 Changing to BASAGLAR from Other Insulin Therapies) and revisions to study descriptions in Lantus label (see 14. Clinical Studies) as approved by FDA on 17 July 2015.
- A mistake has been corrected in the numbers provided for exposure in subjects over (b) (4) 75 years old (see 8.5 Geriatric Use) for the clinical study in patients with type 2 diabetes. The tentatively approved label provided the percentages for those subjects on BASAGLAR only whereas the text referred to those on BASAGLAR or another insulin glargine product.

These changes were found acceptable by the Division. Additional labeling negotiations occurred including the presentation of adverse reaction information and clinical pharmacology information. At the time of this review labeling negotiations are near complete (final labeling was agreed upon between the Sponsor and Agency and the Agency is awaiting submission of final labeling to the NDA).

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/s/  
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LISA B YANOFF  
12/16/2015

JEAN-MARC P GUETTIER  
12/16/2015

I concur with Dr. Yanoff's assessment and recommend approval.