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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	September 18, 2014
From	Mary H. Parks
Subject	Office Director Decisional Memo
NDA/BLA #	BLA 125469
Supplement #	
Applicant Name	Eli Lilly and Company
Date of Submission	September 18, 2013
PDUFA Goal Date	September 18, 2014
Proprietary Name / Established (USAN) Name	Trulicity (dulaglutide)
Dosage Forms / Strength	0.75 mg and 1.5 mg sc once weekly
Proposed Indication(s)	Improve glycemic control in adults with type 2 diabetes mellitus
Action:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Suchitra Balakrishnan
Statistical Review	Janelle Charles/Bradley McEvoy
Pharmacology Toxicology Review	Brian Hummer
CMC Review/OBP Review	Joel Welch
Microbiology Review	Colleen Thomas (DP), Bo Chi (DS)
Clinical Pharmacology Review	Sang Chung
OPDP	Tara Turner
DSI	Cynthia Kleppinger
CDTL Review	Bill Chong
OSE/DEpi	Christian Hampp
OSE/DMEPA	Sarah Vee
OSE/DRISK	Naomi Redd
RPM	Bola Adeolu
DMA (labeling)	Jibril Abdus-Samad

OND=Office of New Drugs
 DDMAC=Division of Drug Marketing, Advertising and Communication
 DSI=Division of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 OSE= Office of Surveillance and Epidemiology
 DEPi= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management
 RPM = Regulatory Project Manager

Introduction

This biologics licensing application is for the glucagon-like peptide 1 (GLP-1) analogue, dulaglutide, indicated for the improvement of glycemic control in adults with type 2 diabetes mellitus.

GLP-1 is an incretin hormone that increases insulin secretion in response to an ingested meal. Unlike other anti-diabetic therapies, which control hyperglycemia through stimulation of insulin release from the pancreas (e.g. sulfonylureas or glinides), incretin-based therapies control hyperglycemia through a glucose-dependent manner thereby mitigating the risk of hypoglycemia. Because human GLP-1 is rapidly degraded by the serine protease, dipeptidyl peptidase IV (DPPIV), it has limited clinical use.

Dulaglutide is a fusion protein containing the N-terminal amino acid sequence of GLP-1 linked to the Fc portion of a modified human IgG4 heavy chain produced through a mammalian cell bank. (b) (4)

There are currently four GLP-1 analogues approved and marketed: exenatide is available as a twice-daily injection in the form of Byetta and a once-weekly injection in the form of Bydureon; liraglutide is available as a once-daily injection available as Victoza; and albiglutide is available as a once-weekly injection available as Tanzeum.

The review team has concluded that dulaglutide (Trulicity) should be approved. Although the applicant originally proposed one dosage strength for marketing, the review team has deemed that a lower dose studied is efficacious and should also be made available. The proposed dosages and dosing regimen for dulaglutide are 0.75 mg and 1.5 mg to be administered subcutaneously once-weekly. (b) (4)

My memo will summarize the efficacy findings from 5 Phase 3 trials, including criticism (b) (4)

No unique safety concerns outside those already observed within the class were identified. The applicant submitted the results of a meta-analysis of their Phase 2 and 3 controlled trials to evaluate CV risk as outlined in the FDA Guidance for Industry titled *Diabetes Mellitus – Evaluating CV Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. The results of the meta-analysis provide adequate assurance of pre-marketing CV safety. Overall, labeling will be similar to other approved GLP-1 analogues, including a boxed warning on the risk of thyroid c-cell tumors. Similar to other GLP-1 analogues, dulaglutide will be approved with a REMS, Medication Guide, and several PMRs including a dedicated CV outcomes trial.

I concur with the reviewers' recommendations for approval.

Clinical Efficacy

Both doses of dulaglutide were studied in 5 Phase 2/3 clinical trials evaluating its use as monotherapy and in combination with a variety of other approved anti-diabetic therapies. All the trials had an active control arm and two trials included a placebo group. The following table from Dr. Brad McEvoy’s statistical review provides an overview of these trials. I refer the reader to Dr. McEvoy’s review for a thorough discussion of each study’s design, patient population, trial execution, and results.

Table 2. Summary of Trial Designs

Study	Design	Controlled Data (wks)	Primary Endpoint (wk)	Number of Subjects Randomized
Metformin add-on				
H9X-MC-GBCF (Stage II)	R, PG, DB, PC, AC, ADF	104 weeks	Sitagliptin: week 52 Placebo: week 26	Dula 0.75 mg-281 Dula 1.5 mg-279 Sitagliptin-273 Pbo/sitagliptin*-139
Monotherapy				
H9X-MC-GBDC	R, PG, DB, DD, AC	52 weeks	week 26	Dula 0.75 mg-270 Dula 1.5 mg-269 Metformin-268
Met and Pio add-on				
H9X-MC-GBDA	R, PG, DB PC, DB Dula, OL AC,	52 weeks	week 26	Dula 0.75 mg-280 Dula 1.5 mg-279 Pbo/Dulaglutide*-141 Exenatide-278
Met and SU add-on				
H9X-MC-GBDB	R, PG, OL, AC	78 weeks	week 52	Dula 0.75 mg-272 Dula 1.5 mg-279 Insulin glargine-265
Insulin Lispro add-on				
H9X-MC-GBDD	R, PG, OL, DBDA Dula, AC	52 weeks	week 26	Dula 0.75 mg-293 Dula 1.5 mg-295 Insulin glargine-296

PC-placebo controlled; AC-Active Comparator; OL-Open Label; R-Randomized, DB-Double Blind; DD-Double dummy; ADF-Adaptive dose finding; DBDA- Double-blind dose assignment; PG-Parallel Group; Pbo-Placebo; Dula-Dulaglutide; Met-Metformin; Pio-Pioglitazone; SU-sulfonylurea

*Placebo given for 26 weeks followed by experimental or active control thereafter.

Dulaglutide 0.75 and 1.5 mg once-weekly statistically lowered HbA1c compared to placebo as demonstrated in Studies GBCF and GBDA. In GBCF, dulaglutide 0.75 and 1.5 mg doses resulted in a greater mean reduction over placebo of 1.04 and 1.23, respectively (see Table 7 from Dr. McEvoy’s review) whereas in GBDA, these same doses resulted in a greater mean reduction over placebo of 0.84 and 1.05, respectively (see Table 19 from Dr. McEvoy’s review). Additional analyses to assess the effect of missing data or initiation of rescue medications continued to support a statistically significant effect of both doses over placebo although attenuated in some analyses.

The inclusion of active comparators in all Phase 2/3 trials allows for comparative efficacy (and safety) evaluation. These trials included objectives to demonstrate both non-inferiority and superiority of dulaglutide to the active controls selected – sitagliptin, metformin, exenatide, and insulin glargine.

Dulaglutide versus Sitagliptin

Study GBCF was pre-specified to test the non-inferiority and superiority of dulaglutide 0.75 and 1.5 mg to sitagliptin 100 mg employing a tree-gatekeeping strategy for the multiple objectives tested. At Month 12, both doses of dulaglutide were non-inferior and superior to sitagliptin 100 mg. Dulaglutide 0.75 and 1.5 mg achieved a greater mean reduction in HbA1c of 0.50 and 0.71 over sitagliptin, respectively, with the 95% CI excluding zero for both doses. Dr. McEvoy conducted several additional analyses to determine if missing data or initiation of rescue medication impacted the superiority results and these analyses supported the primary statistical analysis. The following table is adapted from Dr. McEvoy's Table 7 and shows that in each analysis comparing dulaglutide to sitagliptin the 95% CI excludes zero.

	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Sitagliptin 100 mg
Adjusted Mean Chg (95% CI) from Baseline at Week 52	-0.86 (-0.99, -0.73)	-1.07 (-1.19, -0.94)	-0.36 (-0.49, -0.23)
Dula-Sita (95% CI) at Week 52 (primary analysis model)	-0.50 (-0.67, -0.33)	-0.71 (-0.87, -0.54)	--
Dula-Sita (95% CI) at Week 52 (supportive analyses)			--
MMRM	-0.54 (-0.73, -0.36)	-0.74 (-0.93, -0.56)	
Week 52 assessment	-0.40 (-0.57, -0.23)	-0.66 (-0.83, -0.49)	

Dulaglutide versus Metformin

Study GBDC was pre-specified to test the non-inferiority and superiority of dulaglutide 0.75 and 1.5 mg to metformin (total dose of 2 g/day) at both Week 26 (primary) and Week 52 (secondary). Both doses comfortably excluded the non-inferiority margin of 0.4 and the upper limit of the 95% CI also excluded zero. Based on the pre-specified testing strategy, both doses of dulaglutide would be considered superior to metformin at Week 26. The treatment difference between dulaglutide 0.75 and 1.5 mg relative to placebo was -0.15 (95% CI: -0.29, -0.01) and -0.22 (95% CI: -0.36, -0.08), respectively. At Week 52, only the high dose of dulaglutide demonstrated superiority in HbA1c over metformin; dulaglutide 0.75 mg was non-inferior to metformin at Week 52.

When additional analyses were performed to assess the impact of missing data/rescue medication on efficacy, the results were no longer significant for dulaglutide 0.75 mg at Week 26. Although the efficacy of dulaglutide 1.5 mg versus metformin remained statistically significant, the effect was attenuated and in some analyses the upper limit of the 95% CI *marginally* excluded zero. These observations speak to the lack of robustness of the superiority findings in the primary efficacy analysis. The following table adapted from Table 13 in Dr. McEvoy's review summarizes these additional analyses at Week 26.

	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg	Metformin
Adj. Mean Chg (95% CI) at Week 26	-0.71 (-0.82, -0.59)	-0.78 (-0.90, -0.66)	-0.56 (-0.68, -0.44)
Dula-Met (95% CI) MMRM Wk 26 assessment ANCOVA-LOCF	-0.10 (-0.25, 0.05) -0.06 (-0.21, 0.08) -0.12 (-0.26, 0.02)	-0.21 (-0.36, -0.05) -0.16 (-0.30, -0.01) -0.19 (-0.33, -0.05)	--

(b) (4)

Dulaglutide versus Exenatide

Study GBDA was pre-specified to test the non-inferiority and superiority of dulaglutide 0.75 and 1.5 mg to exenatide titrated to 10 mcg twice daily at both Week 26 (primary) and Week 52 (secondary). Note that this trial included a placebo group and the comparison to placebo has been discussed above. Patients randomized to the exenatide arm were not blinded to therapy.

Both doses of dulaglutide were non-inferior and superior to exenatide with regard to change in HbA1c from baseline at Weeks 26 and 52. Additional analyses to assess the impact of missing data/rescue medication on efficacy supported these conclusions. The following table adapted from Table 19 of Dr. McEvoy's review summarizes the efficacy findings at Week 26 comparing dulaglutide to exenatide.

	Dula 0.75	Dula 1.5 mg	Exenatide
Adj. Mean Chg (95% CI) Wk 26 Wk 52	-1.30 (-1.42, -1.18) -1.07 (-1.22, -0.92)	-1.51 (-1.63, -1.40) -1.35 (-1.51, -1.21)	-0.99 (-1.11, -0.87) -0.80 (-0.94, -0.65)
Supportive Analyses, dula-exenatide (95% CI) MMRM Wk 26 assessment ANCOVA w/ LOCF	-0.29 (-0.43, -0.16) -0.28 (-0.42, -0.14) -0.30 (-0.44, -0.16)	-0.52 (-0.65, -0.38) -0.51 (-0.65, -0.36) -0.50 (-0.64, -0.36)	---

Dulaglutide versus Insulin Glargine

The applicant compared dulaglutide to glargine in two separate trials. Study GBDB used glargine as add-on to maximally tolerated use of metformin and sulfonylurea whereas Study GBDD used glargine as the basal component in basal-bolus therapy with lispro serving as the bolus (or prandial) insulin. Both of these trials pre-specified testing dulaglutide 0.75 and 1.5 mg for non-inferiority and superiority to glargine and employed tree-gatekeeping test strategy for multiple hypotheses tested. Both trials were also open-label (dulaglutide groups were blinded to dose) as maintaining blind in insulin trials is very challenging.

In GBDB, the primary endpoint was change in HbA1c from baseline at Week 52. Both doses were first sequentially tested for non-inferiority and if established were sequentially tested for

superiority to glargine (See Table 21 from Dr. McEvoy’s review). Dulaglutide 0.75 mg was non-inferior to glargine but failed to demonstrate superiority. The treatment difference and its corresponding 95% CI between dulaglutide 1.5 mg and glargine excluded the NI margin and zero and therefore met the criteria for non-inferiority and superiority at Week 52.

Additional analyses to assess effect of missing data/rescue medication supported the non-inferiority findings of dulaglutide 0.75 mg and superiority findings of dulaglutide 1.5 mg compared to glargine.

In GBDD, the primary endpoint was change in HbA1c from baseline at Week 26. Similar pre-specified, sequential testing for non-inferiority and superiority as performed in GBDB were conducted. Dulaglutide 0.75 mg and 1.5 mg were found to be both non-inferior and superior to glargine at Week 26 and Week 52 (secondary).

Additional analyses to assess effect of missing data/rescue medication challenged the finding of superiority in the dulaglutide 0.75 mg dose group but supported this finding at the 1.5 mg dose group.

(b) (4)

Insulin has no maximal dose that will limit efficacy. The main limitation to efficacy of injectable insulin is the risk of developing hypoglycemia, which is a consequence of its effectiveness. In considering whether dulaglutide 1.5 mg is superior to glargine, one must first consider if the use of glargine was reasonably maximized. Defining reasonable maximal dosing is difficult to establish but one could first consider protocol dosing algorithms and whether investigators fully followed these algorithms. In GBDD, where dulaglutide and glargine were compared as add-on to lispro, we also have to consider whether lispro dosing affected efficacy.

In reviewing Dr. Balakrishnan’s review, I am finding it difficult to tease out the effect of dulaglutide on efficacy in GBDD as doses of lispro were being up-titrated throughout the trial. In Table 20 of Dr. Balakrishnan’s review, she summarizes total daily insulin dose by components (glargine and lispro) in the three treatment groups in GBDD. Total daily insulin dose is always higher in the glargine group because of the basal insulin; however, it is interesting that the prandial insulin (lispro) dose steadily increased in all three treatment groups throughout the trial and the doses were always higher in the dulaglutide groups compared to the glargine group. I have created the following table with data excerpted from Table 20 from Dr. Balakrishnan’s review. From Week 2 to 8 to 26 there are increasing lispro requirements but doses were always higher in dulaglutide groups.

Excerpted data from Table 20 in Dr. Balakrishnan’s review

Study Visit	Treatment Group	Lispro dose (units)
Week 2	Glargine	35.89 (±20.63)
	Dula 0.75 mg	45.66 (±26.86)
	Dula 1.5 mg	41.26 (±28.13)
Week 8	Glargine	59.62 (±34.6)

	Dula 0.75 mg Dula 1.5 mg	82.92 (\pm 45.77) 74.72 (\pm 45.07)
Week 26	Glargine Dula 0.75 mg Dula 1.5 mg	67.79 (\pm 44.59) 96.69 (\pm 62.13) 93.24 (\pm 78.02)

In GBDB, glargine doses were being titrated to a pre-specified fasting plasma glucose level and mean doses did increase over the duration of the trial. However, the percentage of patients achieving the targeted FPG was only about 24% at the primary efficacy endpoint of Week 52. This observation leaves me to question whether glargine was adequately dosed. In fact, the mean reduction in HbA1c from baseline in the glargine arm was 0.63. This is in contrast to efficacy observed with glargine similarly added on to metformin/SU in other GLP-1 agonist trials where reductions ranged from 0.8 to 1.1%.¹

The applicant acknowledges the less than expected efficacy with glargine but postulated that the dosing may have been limited by concerns over increased risk of hypoglycemia. From Table 33 in Dr. McEvoy's review, the risk of documented symptomatic hypoglycemia was lower in the dulaglutide; however, severe cases were rare with only 1 case reported in dulaglutide 1.5 mg group and 2 cases in glargine group.

In both these trials the treatment difference between dulaglutide 1.5 mg and glargine that met the statistical criteria for superiority was -0.22 (GBDD) and -0.45 (GBDB). These are modest gains in efficacy that could be over-turned if the confounders of inadequate insulin dosing or imbalanced dosing between treatments can be accounted for. (b) (4)

(b) (4)

These two studies (b) (4), I do believe the results of the trials can be conveyed in labeling (b) (4).

Clinical Safety

As noted in Dr. William Chong's CDTL memo, the safety reviews also focused on adverse events of special interest that have been observed with other GLP-1 analogues, either in their clinical development program or from post-marketing adverse event reports. These AEs included: pancreatitis, renal impairment, hypersensitivity reactions, thyroid C-cell tumors, pancreatic cancer, GI intolerance, injection site reactions, and hypoglycemia (especially in combination with insulin or insulin secretagogues). Drs. Balikrishnan and Chong have thoroughly reviewed and summarized the safety findings from this program. I agree that no new safety concern was identified to alter the benefit-risk assessment against approval.

As noted above, the applicant conducted a prospective meta-analysis of 9 completed Phase 2 and 3 trials to assess pre-marketing CV safety of dulaglutide. The objective was to exclude an

¹ See product labels for Victoza and Tanzeum.

80% excess risk in CV events. Their plan included the possibility of two meta-analyses should the first one fail to exclude a 1.8 risk margin; however, the first meta-analysis met its objective and those results will be highlighted below. Please see Dr. Janelle Charles statistical review of the meta-analysis for details of the statistical analysis plan, patient population, execution of the analysis, and the results.

The pre-specified endpoint was a composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization due to unstable angina (UA), hereafter referred to as MACE+. A secondary endpoint for just MACE, a composite of CV death, nonfatal MI and nonfatal stroke was also evaluated in the meta-analysis. In addition to the 5 clinical trials reviewed for glyceic efficacy (see Table 2 above on page 3), this meta-analysis included 4 additional placebo-controlled studies that were 12 to 26 weeks in duration. A total of 6010 patients (3885 dulaglutide and 2125 comparator) comprised the CV safety population.

The overall result for MACE+ was 0.57 (0.3, 1.1) and for MACE was 0.6 (0.3, 1.21).² Both analyses excluded the 1.8 risk margin, necessary for consideration of approval. As expected, given the relatively low-risk population, overall results were based on few events (51 MACE+ and 44 MACE). The applicant has initiated a dedicated CV outcomes trial with the objectives of excluding a more conservative risk margin (1.3). This trial, known as REWIND, will be subject of a PMR.

Conclusion

In conclusion, the applicant has submitted all necessary data from their development program to support the proposed indication for improving glyceic control in adults with T2DM. Across multiple disciplines within CDER and CDRH, reviewers have not identified deficiencies precluding approval.

Pending the final negotiations of product labeling, I recommend approval of this BLA.

² 98.02% CI used to assess the 1.8 risk margin

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/s/

MARY H PARKS
09/18/2014