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APPLICATION NUMBER:

203414Orig1s000

SUMMARY REVIEW

Division Director's Memo

Date	January 25, 2013
From	Mary H. Parks, M.D.
Subject	Division Director Summary Review
NDA/BLA # Supplement #	NDAs 22-271, 22-426, 203-414
Applicant Name	Takeda
PDUFA Goal Date	January 25, 2013
Proprietary Name / Established (USAN) Name	Alogliptin Alogliptin-pioglitazone FDC Alogliptin-metformin FDC
Dosage Forms / Strength	See below in Introduction
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM
Action/Recommended Action for NME:	Approval

1. Introduction

This memo serves to cover three NDAs:

- NDA 22-271 alogliptin (6.25 mg, 12.5 mg, and 25 mg dosage strengths)
- NDA 203-414 alogliptin/metformin FDC (12.5 mg/500 mg and 12.5 mg/1000 mg dosage strengths)
- NDA 22-426 alogliptin/pioglitazone FDC (12.5 mg/15 mg, 12.5 mg/30 mg, 12.5 mg/45 mg, 25 mg/15 mg, 25 mg/30 mg, and 25 mg/45 mg dosage strengths)

Alogliptin is a dipeptidyl-peptidase-IV (DPP-4) inhibitor being proposed for the control of hyperglycemia in patients with type 2 diabetes mellitus (T2DM). Takeda has also submitted two separate applications for the fixed-dose combinations (FDC) of alogliptin with two other approved anti-diabetic therapies, metformin and pioglitazone.

Separate clinical trials were conducted for each of these NDAs; however, some trials are being relied upon across the three NDAs, especially for safety.

The alogliptin NDA was originally submitted on 27 December 2007 and received a complete response action on 26 June 2009. The primary deficiency in this complete response action was inadequate cardiovascular data for assessment. Takeda addressed this in a resubmission

received on 25 July 2011 for which a second complete response action was issued on 25 April 2012 due to a finding of potential hepatotoxicity. This most recent resubmission on 26 July 2012 is intended to address the liver safety concerns.

For each of the previous two submissions (12/27/07 and 7/25/11), extensive reviews have already been conducted and archived in DARRTS. For my memo covering this most recent submission I will only give a brief regulatory background with the main focus addressing the concerns regarding potential hepatotoxicity resulting in the last complete response action.

2. Background

2.1 Original NDA submission for Alogliptin

After the initial submission of this NDA, FDA issued a Guidance to Industry in December 2008 titled *Diabetes Mellitus – Evaluating CV Risk in New Anti-diabetic Therapies to Treat Type 2 Diabetes*. FDA's review of the original alogliptin NDA supported a conclusion that the drug was effective at lowering HbA1c in different clinical settings; however, it could not conclusively exclude a CV risk margin of 1.8 as discussed in the guidance. Consequently, the applicant, with feedback from the FDA, initiated a cardiovascular outcomes trial (CVOT) titled, EXAMINE (also referred to as Study 402) which is a multicenter, randomized, double-blind, placebo-controlled study evaluating alogliptin with standard of care in patients with T2DM who had a recent acute coronary syndrome (ACS).

2.2 First Resubmission for Alogliptin

The interim results of EXAMINE were submitted and reviewed in the first resubmission. The trial is continuing as a required trial under FDAAA in order to obtain important longer-term CV safety data and to address the FDA requirements to exclude a lower CV risk margin of 1.3. Takeda has provided sufficient evidence from the interim analysis that alogliptin is not associated with an 80% or higher excess CV risk over standard-of-care therapies for T2DM. Consequently, it has been concluded that this application has met the pre-marketing requirements for demonstration of CV safety. More definitive conclusions on CV safety will have to await the completion of EXAMINE. However, as explained below under Section 8.0, an unexpected finding of potential hepatotoxicity was identified in this trial and several postmarketing cases from use of alogliptin in Japan.

2.3 Fixed-Dosed Combination Products

Alogliptin-pioglitazone FDC was submitted on 27 December 2007 and 19 September 2008. Both applications received similar complete response letters as those sent to the alogliptin NDA. Efficacy for the combined use of alogliptin and pioglitazone was demonstrated in the alogliptin NDA and two additional studies in the alogliptin-pioglitazone NDA (Studies 303 and OPI-004). No new efficacy data were reviewed for this FDC in this recent submission.

Alogliptin-metformin FDC was submitted on 22 November 2011. Efficacy for the combined use of alogliptin and metformin was demonstrated in the alogliptin NDA (Study MET-008)

and alogliptin-pioglitazone NDA (Study OPI-004). A single new trial, MET-302 was submitted to this NDA and reviewed by Dr. Janice Derr for efficacy and Dr. Valerie Pratt for safety.

3. CMC/Device

Office of Compliance has completed its inspection of manufacturing facilities for all three NDAs and issued an acceptable recommendation for alogliptin and the FDC of alogliptin and metformin. The final recommendation for the FDC of alogliptin and pioglitazone is still pending at present.

4. Nonclinical Pharmacology/Toxicology

No new review issues with this resubmission.

5. Clinical Pharmacology/Biopharmaceutics

No new review issues with this resubmission.

6. Clinical Microbiology

Not applicable.

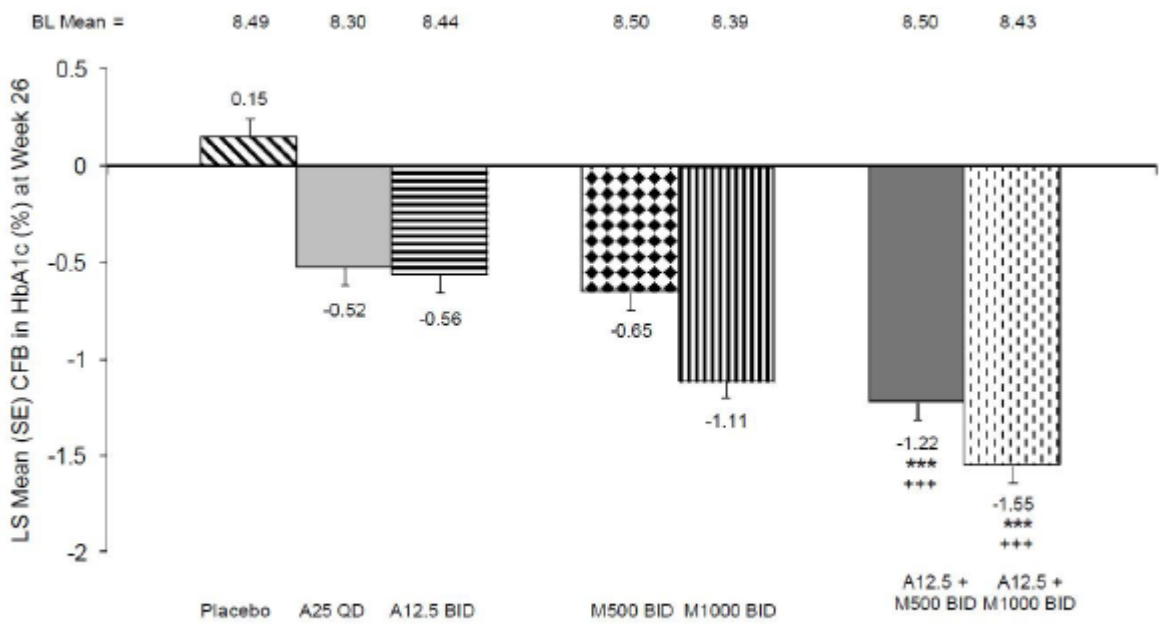
7. Clinical/Statistical-Efficacy

The only new clinical trial presenting efficacy data for labeling consideration was from Study MET-302 submitted in support of the fixed-dose combination of alogliptin and metformin. Please see Dr. Janice Derr's review dated 17 July 2012 for details.

This was a 26-week factorial design trial evaluating alogliptin co-administered with metformin to each of the individual components. Patients with T2DM inadequately treated with diet and exercise with a HbA1c between 7.5 and 10% were randomized to one of 7 treatment groups: (1) placebo; (2) metformin 500 mg bid; (3) metformin 1000 mg bid; (4) alogliptin 12.5 mg bid; (5) alogliptin 25 mg qd; (6) alogliptin 12.5 mg bid + metformin 500 mg bid; (7) alogliptin 12.5 mg bid + metformin 1000 mg bid.

The study showed superior HbA1c reduction with the combination treatment over the individual components best summarized in the following figure from Dr. Derr's review.

Figure 3 Study 302; HbA1c change from baseline at week 26 (FAS/LOCF; analysis 1a)



Note: All analyses are based on the FAS analysis set with LOCF imputation for dropouts and for rescues (Applicant's analysis 1a)

Sources: Study 301 clinical report, Table 11.h and Figure 11.i

8. Safety

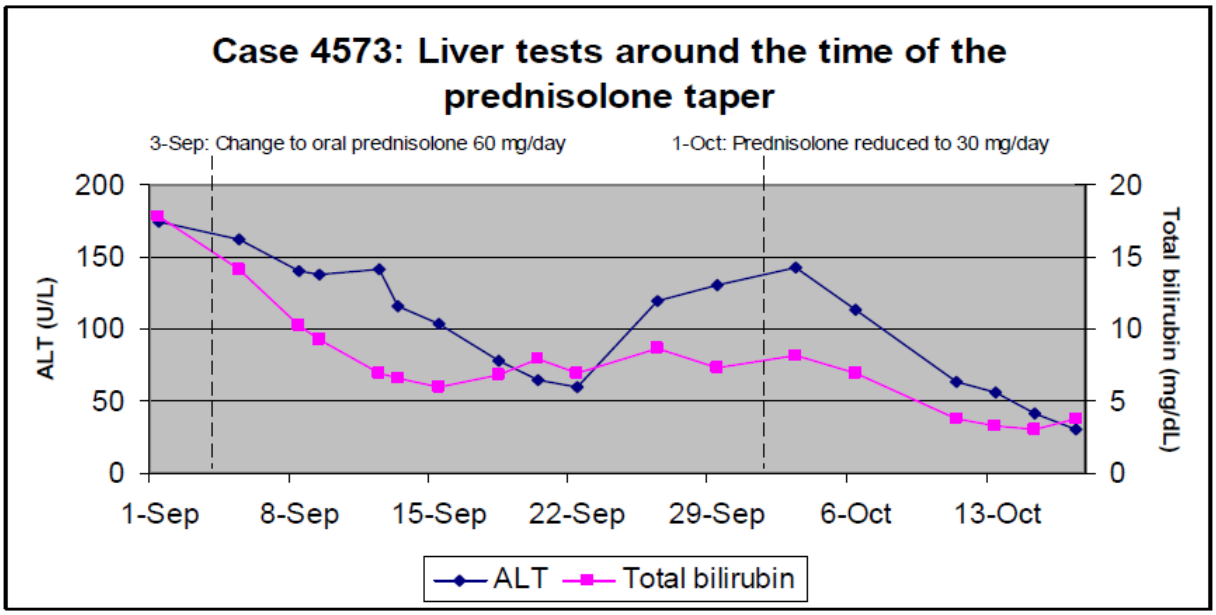
This NDA received its 2nd complete response as a result of a liver safety concern identified after the first resubmission. Three consults from FDA hepatologist, Dr. Leonard Seeff, have been completed and the reader is referred to the following dated documents in DARRTS under NDA 22-271 for details of his consult: February 22, May 8, and November 10, 2012. Below I only highlight the concerning findings resulting in the 2nd CR and new information submitted with the subsequent resubmission.

Index Case TCI2011A04573

FDA's concerns over liver safety arose after receipt of a postmarketing case of a 77-year old woman who had a history of Hashimoto's thyroiditis and T2DM and was previously treated with voglibose and glimepiride. On June 1 and July 17, 2011, she was initiated on levothyroxine and alogliptin 25 mg, respectively. Baseline transaminases and serum bilirubin were normal and alkaline phosphatase was 290 IU/L. Thirteen days after initiating alogliptin treatment her transaminase levels increased and worsened over the course of the month with development of jaundice, elevated ammonia levels and coagulation parameters, resulting in drug discontinuation 39 days after initiation. Corticosteroids were initiated for presumptive autoimmune hepatitis; however, the patient's clinical condition did not improve. She became febrile, developed pneumonia and expired on (b) (6) Work-up was notable for negative serology for hepatitis A, B, and C, EBV and CMV and autoimmune markers.

The patient died of fulminant hepatic failure and its complications and was deemed ***probable to highly likely*** by Dr. Seeff. At the time that this case was being discussed, Takeda had employed two outside liver experts – (b) (4) Neither of them agreed with Dr. Seeff's assessment and considered autoimmune hepatitis (AIH) a possible etiology resulting in their lower grading of attribution of possible and unlikely, respectively. During a telephone conference with Drs. (b) (4), they noted the transaminase response to glucocorticoid therapy as evidence for AIH but upon request of laboratory data, Dr. John Senior from the FDA plotted the time course of these laboratory values and it was not evident that biochemical tests improved and remained so as a result of steroid therapy. Furthermore, the patient's transaminases had begun to decrease with discontinuation of alogliptin (August 9) two weeks before steroid therapy was initiated (August 23).

Figure 8.1. Time course of response to corticosteroid therapy for Patient TCI2011A04573



This case prompted FDA to request information on the clinical trial database and postmarketing experience for alogliptin. Please see reviews by Drs. Pratt, Joffe and myself from the 1st resubmission as all these cases have been summarized repeatedly by the clinical review staff and consultants. In total, there were 5 cases from the post-marketing experience adjudicated as probable by Dr. Seeff and these are all summarized in Table 8.1 below. Preceding the table is the narrative of a 2nd concerning case that was associated with hyperbilirubinemia.

TC201A06837 (transaminase elevations with hyperbilirubinemia)

This was a 66-year old man who was previously treated with pioglitazone and glimepiride for his T2DM and was switched to pioglitazone and sitagliptin on 13 October 2011. Due to lack of efficacy, sitagliptin was replaced with alogliptin 25 mg (b) (6) Baseline transaminases were normal (ALT 27 IU/L and AST 36 IU/L). Alk phos and bilirubin levels were not provided. One month (b) (6) after alogliptin was initiated a routine labwork

found his ALT markedly elevated at 1512 IU/L and AST 2188 IU/L with a serum bilirubin of 3.9 mg/dL and alk phose of 313 IU/L. Although the patient initially reported no symptoms, in retrospect he stated he may have had mild malaise. The patient was hospitalized; alogliptin was discontinued but all other meds, including glimepiride, were continued. Tests for hepatitis B and C were negative. Transaminases declined rapidly with ALT 425 and total bili 1.3 (b) (6) ; ALT 27 on (b) (6); normalized by (b) (6) There was no reported history of alcohol abuse and serologies for hepatitis E came back negative on 9 February 2012 resulting in the upgrading of the case to probable by the two hepatology consultants for Takeda. This case had already been adjudicated as ***probable*** by Dr. Seeff.

Table 8.1 Postmarketing Cases of Notable Concern Reviewed in First Re-Submission

	Biochemical Hy's Law	Onset from Drug Initiation	Liver Tests	Outcome	Expert Assessment		
					(b) (4)	(b) (4)	Seeff
TCI2011A03640	No	immediate N/V, darkening or urine about 4 days, abnl labs 3wks	mixed hepatocellular/cholestatic injury w/ cholestatic pattern predominating ALT869,AST625, AP1169 bilirubin normal No viral hepatitis reports	not life-threatening	possible	possible	probable
TCI2010A05612	no	2 months	mixed hepatocelluar/cholestatic pattern ALT230, AST108, AP1260, bili 0.9 u/s shows steatosis Hep A/B/C negative	recovering	possible	possible	probable
TCI2011A04039	no	3 days	ALT106,AST125, AP336, bili0.3	recovering	possible	possible	possible/probable
TCI2011A04573	yes	13 days-1 month	@ 1month ALT 1178, AST1070, AP905, bili 6.3 increase ammonia and coags, febrile	death	unlikely	possible	probable to highly likely
TCI2011A06837	yes	1 month	ALT 1512,AST 2188,bili3.9,AP313	recovered	probable	probable	probable to highly likely

Transaminase Elevations

In addition to the aforementioned postmarketing cases, there were imbalances in marked transaminase elevations with the 1st resubmission. The interim results of the ongoing CVOT were provided with the first resubmission to meet the 2008 FDA guidance requiring that a pre-market threshold for CV risk of 80% be excluded for new anti-diabetics. Takeda was able to meet this requirement; however, this single trial also revealed imbalances in transaminase levels. The table below is from the single trial, Study 402, with a data cutoff date of 11 September 2011.

Table 7 Number and Percentage of Subjects With Markedly Abnormal ALT Values (Study 402)

	Number (%) of Subjects With ≥1 Marked Abnormal Result			
	Baseline		Post-Baseline	
Parameter (Criterion)	Placebo N=1466	Alogliptin N=1467	Placebo N=1372	Alogliptin N=1387
ALT (>20×ULN)	0	0	0	0
ALT (>10×ULN)	1 (0.1%)	2 (0.1%)	0	5 (0.4%)
ALT (>8×ULN)	1 (0.1%)	2 (0.1%)	0	6 (0.4%)
ALT (>5×ULN)	2 (0.1%)	5 (0.3%)	1 (0.1%)	10 (0.7%)
ALT (>3×ULN)	13 (0.9%)	18 (1.2%)	5 (0.4%)	17 (1.2%)
>3×ULN and total bilirubin >2.0 mg/dL	0	0	0	0
>3×ULN and total bilirubin >2×ULN	0	0	0	0

Source: Appendix 8, Table 4.
Note: The Baseline visit window includes all results obtained on or before the date of randomization.

Upon receipt of the information in the above table, FDA requested the company to calculate the incidence of ALT/AST elevations with the pooled Phase 2/3 trials. The table below is for Phase 2/3 trials, combined from the October 2011 FDA request.

Table 3.a Number (%) of Subjects With Markedly Abnormal ALT Values (Controlled Phase 2 and 3 Studies) – October 2011 FDA Request

	Number (%) of Subjects With Markedly Abnormal Result			
	Baseline (a)		During Treatment (b)	
Parameter	All Comparators (c) N=4215	All Alogliptin (d) N=7187	All Comparators N=4074	All Alogliptin N=7011
ALT >20×ULN	0	0	0	2 (<0.1) [0.1]
ALT >10×ULN	2 (<0.1)	3 (<0.1)	0	8 (0.1) [0.2]
ALT >5×ULN	2 (<0.1)	6 (<0.1)	6 (0.1) [0.3]	21 (0.3) [0.6]
ALT >3×ULN	10 (0.2)	30 (0.4)	39 (1.0) [1.8]	71 (1.0) [2.1]

Source: Appendix 8, Table 5 (Response to 24 October 2011 FDA Request).
Note: This table includes subjects with a baseline and/or a post-baseline value.
(a) Baseline was defined as the last value collected on or prior to the date of first dose of study medication.
(b) The number of subjects with marked abnormalities per 100 subject-years of exposure is presented in brackets.
(c) The All Comparators Grouping combines placebo and active comparator dose groups.
(d) The All Alogliptin Grouping combines the 6.25, 12.5, 25, 50, and 100 mg dose groups.

The incidence in marked ALT elevations (>5 and 10xULN) in Study 402 during treatment was only noted in alogliptin-treated patients and was not diminished when data from other Phase 2/3 trials were added. Instead, additional imbalances were noted with ALT increased exceeding 20xULN. The individual cases for these marked lab abnormalities were reviewed and summarized by Dr. Seeff in his consults. No serious sequelae resulted from any of these cases; the majority had other causes to attribute enzyme elevations; and resolved with discontinuation of alogliptin. However, this imbalance in a controlled clinical trial database, alongside the 2 concerning postmarketing cases, was sufficient to give FDA pause in approving alogliptin at that time.

With this 2nd resubmission, Takeda has now provided additional exposure data for both alogliptin and comparators. Whereas in the July 2011 submission data from 12 controlled Phase 2/3 trials comprised the pool for hepatic safety, the 2012 resubmission included 8 additional studies. From Table 1.a below provided by the applicant, one can compare the difference in the two databases. The 8 new studies included 5 new studied conducted in Japan only (CCT studies) and Study 308, which was conducted in China, Taiwan, and Hong Kong in support of a registration dossier in China. Studies MET-302 and 305 were conducted as part of the development program for the fixed-dose combination of alogliptin and metformin. In addition, one additional year of data from the ongoing CVOT 402 was provided with this recent resubmission.

Table 1.a Studies in the Controlled Phase 2 and 3 Study Pool

Studies in 2011 Resubmission	Studies in 2012 Resubmission
003, 007, 008, 009, 010, 011, 303, 301, 402 (a), 322OPI-004, 322OPI-001, 322OPI-002	003, 007, 008, 009, 010, 011, 303, 301, 402 (b), 322OPI-004, 322OPI-001, 322OPI-002, CCT-001, CCT-003, CCT-004, CCT-005, CCT-006, MET-302, 308, and 305 (c) Updated to add 8 studies.

(a) Interim data (as of 29 April 2011) from Study 402.
(b) Interim data (as of 18 April 2012 from Study 402.
(c) Interim data (as of 24 April 2012) from Study 305.

The following table provides the breakdown of exposure by treatment group and shows the increasing alogliptin exposure data with each submission and information request.

Table 8.2 Exposure Summary for Resubmission

	Placebo N=3647	Active comparator N=2340	All comparator N=5987	Alogliptin 12.5 mg N=2944	Alogliptin 25 mg N=6626	All alogliptin N=9857*
Duration of exposure, days Mean (SD)	239.1 (186.3)	309.7 (219.2)	266.7 (202.7)	252.5 (216.5)	266.8 (197.5)	256.9 (203.2)
>365 days, n (%)	895 (24.5%)	790 (33.8%)	1685 (28.1%)	642 (21.8%)	1779 (26.8%)	2421 (24.6%)
	Alogliptin total subject numbers			**Alogliptin cumulative exposure (subject-yrs)**		
July 2011	5232			2498		
Nov 2011	7229			3378		
July 2012	9857			6934		

*lower doses of alogliptin were also studied and comprised 287 of the total N for all alogliptin

With an impressive increase in patient exposure, Takeda was able to provide an update on incidence of transaminase elevations in its *combined* controlled Phase 2/3 trials. Imbalances in transaminase elevations are no longer evident.

Table 3.b Number and Percentage of Subjects With Markedly Abnormal Values for Hepatic Function Test Parameters (Controlled Phase 2 and 3 Study Group)

	Number (%) of Subjects With Markedly Abnormal Result					
	Baseline (a)		During Treatment (b)		Last Assessment (c)	
Parameter	All Comparators (d) N=5786	All Alogliptin (e) N=9608	All Comparators N=5786	All Alogliptin N=9608	All Comparators N=5699	All Alogliptin N=9495
ALT (>3×ULN) and total bilirubin >2×ULN	0	0	3 (0.05) [0.07]	2 (0.02) [0.03]	2 (0.04)	1 (0.01)
ALT (>20×ULN)	0	0	3 (0.05) [0.07]	3 (0.03) [0.04]	2 (0.04)	2 (0.02)
ALT (>10×ULN)	1 (0.02)	3 (0.03)	5 (0.09) [0.11]	12 (0.12) [0.17]	3 (0.05)	4 (0.04)
ALT (>5×ULN)	2 (0.03)	6 (0.06)	17 (0.29) [0.39]	34 (0.35) [0.49]	7 (0.12)	11 (0.12)
ALT (>3×ULN)	16 (0.28)	41 (0.43)	89 (1.54) [2.04]	126 (1.31) [1.82]	30 (0.53)	32 (0.34)
ALP (>3×ULN)	3 (0.05)	3 (0.03)	9 (0.16) [0.21]	18 (0.19) [0.26]	5 (0.09)	8 (0.08)
Bilirubin, total (>2.0 mg/dL)	11 (0.19)	19 (0.20)	42 (0.73) [0.96]	55 (0.57) [0.79]	22 (0.39)	24 (0.25)

Source: IAS Table 5.1.1, 5.1.2, 5.6.1, and 5.6.2.
Note: This table includes only subjects with both a baseline and a post-baseline value.
(a) Baseline is defined as the last value collected on or prior to the date of first dose of study medication.
(b) The number of subjects with marked abnormalities per 100 subject-years of exposure is presented in brackets.
(c) Last assessment is the last assessment of ALT on or before the last dose of study medication.
(d) The All Comparators grouping combines placebo and active comparator dose groups.
(e) The All Alogliptin grouping combines the 6.25, 12.5, 25, 50, and 100 mg dose groups.

Because the original signal for transaminase imbalance that led FDA to request more data came from the CVOT, EXAMINE, an update of transaminase elevations from this trial was also requested. Based on the table below for which the data cutoff date was 6 November 2012, there is no imbalance in incidence of ALT > 3xULN and total bili > 2xULN. While the incidence of ALT > 5 and 10xULN are still higher in alogliptin versus placebo, the difference between treatment groups is diminished than those observed in Table 7 above, owing to the finding of more events in placebo.

Table 8.3. Updated Incidence for Transaminase Elevations in EXAMINE (data cut-off 6 Nov 2012)

	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline (a)		During Treatment		Endpoint (b)	
Parameter	Placebo N=2372	Alogliptin N=2389	Placebo N=2372	Alogliptin N=2389	Placebo N=2372	Alogliptin N=2389
ALT >3×ULN and total bilirubin >2×ULN	0	0	1 (0.04)	1 (0.04)	0	1 (0.04)
ALT >20×ULN	0	0	1 (0.04)	0	0	0
ALT >10×ULN	1 (0.04)	2 (0.08)	2 (0.08)	4 (0.17)	0	1 (0.04)
ALT >5×ULN	2 (0.08)	2 (0.08)	12 (0.51)	19 (0.80)	2 (0.08)	5 (0.21)
ALT >3×ULN	10 (0.42)	14 (0.59)	32 (1.35)	44 (1.84)	8 (0.34)	12 (0.50)

FDA requested the narratives for all patients with ALT > 10xULN and ALT>3xULN with total bili >2xULN. The majority of these narratives have already been reviewed from a prior information request on 24 September 2012 and none of the cases were considered DILI (see previous consults by Dr. Seeff). However, there is one case of ALT>3xULN with total bili

>2xULN that was discussed in the 10 November 2012 consult from Dr. Seeff that requires an update due to recent information submitted. The case is summarized below.

Patient 8413-006/402

This case involves a 57-year old male enrolled in the cardiovascular outcomes trial, EXAMINE. Past medical history included T2DM, coronary artery disease and congestive heart failure. The patient also had dyslipidemia and hypertension with notable concomitant medications including atorvastatin, clopidogrel, metoprolol, perindopril, and glibenclamide.

The patient was started on alogliptin 25 mg daily on November 16, 2011. Baseline transaminases and bilirubin levels were within normal ranges and were again normal at study visit Day 85. During a regularly schedule study visit on Day 181, ALT and AST values were elevated to > 5x ULN (176 and 142 U/L, respectively), alk phos was elevated at 109 U/L (normal 32-72), and total bilirubin was WNL at 0.82 mg/dL. The patient reported drinking ~200 mL of vodka 2 days prior to this study visit. On Day 187, the subject reported to be subicteric prompting an unscheduled study visit on Day 203 where ALT was elevated to 1410 U/L, AST 1390 U/L (both > 10xULN) and total bilirubin was 3.03 mg/dL (> 2xULN). Alk phos remained elevated at 125 U/L. Study site reported no change in CV status to suggest contribution from his underlying heart failure condition.

Both alogliptin and atorvastain were discontinued on Day 207 and labs drawn on that day revealed declining transaminase and total bilirubin levels with ALT 516 U/L, AST 79 U/L, and tbili 1.96 mg/dL. However, alk phos remained elevated at 200 U/L and GGT was also elevated at 2090 U/L (normal 5-66). Liver scintigraphy and abdominal ultrasound showed nonspecific liver findings. Labs on study Day 212 showed continued decline in transaminase and total bilirubin levels and on Day 253, values including alk phos had returned to normal.

Initial work-up excluded hepatitis A, B, and C and Dr. Seeff's assessment was 'at least possible, verging on probable' for alogliptin-induced DILI due to the absence of data to rule-out acute hepatitis E. As a result, FDA sent specific requests to Takeda including a request to bring the patient back to the study site to obtain recent serum samples. On December 18, FDA received the responses to this information request and the possibility of acute hepatitis E was excluded based on negative results for HEV IgM and IgG from both stored and recent serum samples. As a result of this updated information four original hepatology experts hired by Takeda upgraded their original assessment from possible DILI to probable DILI. Dr. Seeff's assessment of the case is probable DILI.

This one case has resulted in numerous information requests from FDA including the updated table for the EXAMINE trial. On 7 January 2013, Takeda informed FDA that it had uncovered a treatment code error for Subject 8413-006/402 and that this patient was **actually assigned to placebo**.

In consultation with the Office of Scientific Investigations (OSI), FDA has reviewed case report forms, medication accountability forms, and SAS datasets submitted in July 2012, and all these other sources confirm that this patient was on placebo and NOT alogliptin as

previously reported. I have shared this new information with Dr. Seeff and we both agree that probable DILI can no longer be attributed to alogliptin exposure. However, this patient still had evidence of serious liver injury for which no cause has been identified, including hepatitis A, B, C, and E. A recommendation will be made to Takeda to make further inquiries on use of over-the-counter supplements, including herbal/dietary supplements. If there was use of such agents around the time of this event it would be imperative to warn the patient to avoid using those products again.

Conclusions on Hepatic Safety
In FDA's 25 April 2012 Complete Response letter, we informed Takeda of the following:

> You will need to provide additional postmarketing data from countries where alogliptin is approved as well as additional clinical trial data to provide reassurance that alogliptin hepatotoxicity is of limited clinical significance. The additional clinical trial data may come from your ongoing EXAMINE trial as well as other available clinical trials, such as Study 305. If the imbalances in serum ALT elevations in your controlled clinical trial database become less apparent with additional patient exposures and a true Hy's Law case is still not seen, we may have sufficient reassurance that alogliptin has an acceptable hepatic profile, particularly if additional postmarketing data do not identify further reports of severe drug-induced liver injury (e.g., leading to death or liver transplantation).
>
> We strongly encourage you to perform enhanced pharmacovigilance (e.g., real-time follow-up to rule out alternative etiologies) for all potential cases of drug-induced liver injury reported with alogliptin to ensure that as much information as possible is obtained for these cases.
>
> When presenting serum ALT elevations >3X, >5X, >10X and >20X ULN for your controlled phase 2/3 database in your resubmission, show baseline data only for those patients who received at least one dose of study medication and who have at least one post-baseline serum ALT value.

This resubmission has provided a doubling in pt-yrs exposure to alogliptin (6934 pt-yrs) from the last submission (3378 pt-yrs in July 2011) in the clinical trials database. In addition, the most recent PSUR (4th), covering period from 16 October 2011 to 15 April 2012, has also provided an increase in postmarketing exposure from ~219,000 to ~290,000 pt-yrs since the previous submission (alogliptin and its FDC products remain approved only in Japan). Individual hepatic cases in both the clinical trial and postmarketing setting were reviewed by an independent Liver Safety Evaluation Committee (LSEC) comprised of 5 hepatologists who adjudicated each case and assessed causality in accordance with the Drug-Induced Livery Injury Network (DILIN). The LSEC reviewed all cases meeting any one of these criteria:

- Serious liver-related adverse events reported from the clinical database
- Serious and nonserious postmarketing liver-related cases
- Potential biochemical Hy's Law cases in the clinical database
- Potential biochemical Hy's Law cases from postmarketing reports
- All cases of ALT > 5x ULN from clinical studies

Similarly, FDA's Drs. Leonard Seeff and John Senior were forwarded cases of concern (ALT > 10x ULN and biochemical Hy's Law) from both the clinical trial and postmarketing setting

to review and adjudicate. There were a total of 15 pre-marketing and 2 post-marketing cases. Please see their consult dated 10 November 2012. Many of these cases had limited information and some were readily attributed to another cause. There was only one case identified as possible/probably which I have already summarized above as erroneously classified as an alogliptin case when the patient actually received placebo.

In summary, with the increased exposure in both pre- and post-marketing, the imbalance in ALT elevations in the controlled clinical trial database has become less apparent and no cases of Hy's Law were identified in either pre- or post-marketing with this updated database. I believe this updated database provides reassurance that if a potential for alogliptin-induced liver injury exists, it is at a very low rate. I can not dismiss the possibility that such a risk does exist since there were cases of notable transaminase elevations and while no serious sequelae resulted or laboratory abnormalities resolved with drug discontinuation, labeling should still make note of the potential for liver injury under the Warnings and Precautions with specific recommendation for monitoring at baseline and periodically while on therapy.

In our 25 April 2012 Complete Response letter, we also advise the company to consider (b) (4) This was deemed acceptable by FDA statisticians.

9. Advisory Committee Meeting

No advisory committee meeting was held as this is not a first-in-class anti-diabetic therapy and the efficacy and safety issues related to the application do not present novel regulatory or scientific challenges.

10. Pediatrics

Please see Dr. Pratt's summary of pediatric PMRs to be included in the action letter.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

All three drug products will have a non-REMS medication guide to convey safety concerns over hypersensitivity reactions, potential liver toxicity, and pancreatitis.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

The applicant has provided sufficient and consistent evidence for effectiveness as an anti-diabetic for all three products that is comparable to other drug products approved in this class. Previous deficiencies surrounding inadequate CV risk assessment and potential liver toxicity have been adequately addressed with resubmitted data. Areas of uncertainty are not of such magnitude to outweigh the benefits of improved glycemic control with these agents and can be adequately addressed in labeling.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

No REMS is recommended at this time.

- Recommendation for other Postmarketing Requirements and Commitments

The ongoing CVOT, EXAMINE, is a postmarketing required trial for the alogliptin NDA. The event rates for this trial have been higher than anticipated and the second interim analysis to determine if the 1.3 margin is excluded may occur within this year.

Other PMRs include enhanced pharmacovigilance to assess and analyze spontaneous reports of hepatic abnormalities, fatal pancreatitis, and hemorrhagic/necrotizing pancreatitis, and PREA-related studies.

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/s/

MARY H PARKS
01/24/2013