CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022271Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Management Review

Date:	January 3, 2013
Reviewer(s):	Joyce Weaver, Pharm.D., Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Cynthia LaCivita, Pharm.D., DRISK
Division Director:	Claudia Manzo, Pharm.D., DRISK
Drug Name(s):	Alogliptin (022271), alogliptin/pioglitazone (022426), and alogliptin/metformin (203414)
Therapeutic Class:	Alogliptin-dipeptidyl peptidase 4 (DPP-4) inhibitor antidiabetic agent
Dosage and Route:	25 mg orally daily
Application Type/Number:	NDA 022426, 022271, 203414
Submissions:	Submissions received July 26, 2012 alogliptin (022271), July 27, 2012 alogliptin/pioglitazone (022426), and November 22, 2011 alogliptin/metformin (203414)
Applicant/sponsor:	Takeda Pharmaceuticals
OSE RCM #:	2012-1928

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION/BACKGROUND

This review by the Division of Risk Management (DRISK) evaluates the need for a risk evaluation and mitigation strategy (REMS) for alogliptin, alogliptin/pioglitazone, and alogliptin/metformin.

Takeda pharmaceuticals submitted an application for alogliptin with the proposed indication for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The combination products have the proposed indication for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes when use of the combination is appropriate.

Serious safety issues for alogliptin necessitating labeling in the *Warnings and Precautions* section of the labeling include:

- Hepatic effects
- Hypersensitivity
- Acute pancreatitis
- Hypoglycemia
- Lack of data on macrovascular outcomes

Three dipeptidyl peptidase 4 (DPP-4) inhibitors are currently approved for use in the United States (U.S.) they include; Januvia (sitagliptin, approved 2006), Onglyza (saxagliptin approved 2009), and Tradjenta(linagliptin, approved 2011). Alogliptin was approved in Japan in April 2012. Januvia labeling includes warnings for acute pancreatitis, acute renal failure, hypoglycemia, hypersensitivity, and lack of data on macrovascular outcomes. Onglyza labeling includes warnings for acute pancreatitis, hypoglycemia, hypersensitivity, and lack of data on macrovascular outcomes. Tradjenta has warnings for hypoglycemia, and lack of data on macrovascular outcomes.

NDAs 022426 and 203414 are alogliptin in combination with either pioglitazone or metformin. Pioglitazone and metformin do not have REMS. Pioglitazone (Actos) previously had a Medication Guide-only REMS to address the risk of bladder cancer. The REMS requirement was removed May 17, 2012.

A complete response letter was issued for alogliptin and alogliptin/pioglitazone on April 25, 2012 because of an unresolved issue of hepatotoxicity. The risk considered in this review for possible mitigation with a REMS for alogliptin-containing products is hepatotoxicity.

2 REGULATORY HISTORY

Two previous actions complete responses (CR) have been issued for NDA 022271 and NDA 022426. The first actions were dated June 26, 2009 for NDA 022271 and September 2, 2009 for NDA 022426. The actions in 2009 were taken because data from a controlled phase 2/3 trial included in NDA 22-271 showed a numerical imbalance in

serious cardiovascular adverse events, not favoring alogliptin therapy. The data had not ruled out an unacceptable increase in cardiovascular risk with alogliptin.

The sponsor submitted complete responses to the NDAs on July 25, 2011 that adequately addressed the deficiencies cited in the 2009 CR letters. However, a new signal for hepatotoxicity emerged in the second review cycle, necessitating second complete response actions for the applications. These complete response actions were taken April 25, 2012. The applications for NDA 022271 and NDA 022426 were resubmitted July 26, 2012, and July 27, 2012, with a goal action date of January 26, 2013.

NDA 203414 (alogliptin + metformin) was filed November 22, 2011. Action has not been taken on this application pending resolution of the hepatotoxicity issue for all three applications.

2.1 PRODUCT LABELING

The proposed labeling for the applications includes a warning for hepatotoxicity. The currently FDA-proposed description of these effects to be included in the highlights of the alogliptin labeling is as follows:

- Hepatic effects: (b) (4) postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. Monitor liver tests prior to and during treatment. If liver injury is detected, promptly interrupt NESINA and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart NESINA if livery injury is confirmed and no alternative etiology can be found.

The expanded description of the hepatic effects, to be included in section 5.1, has not been included in the draft labeling to date. The division has not proposed including a boxed warning regarding the hepatic effects.

3 MATERIALS REVIEWED

3.1 DATA AND INFORMATION SOURCES

We reviewed the sponsor's November 7, 2011 submission of liver findings, the clinical reviews for NDAs 022271 and 022426 (Dr. Valerie Pratt's February 29, 2012 and July 3, 2012 reviews), and the September 2, 2008 biometrics review by Dr. Janice Derr. The final clinical reviews for the current cycle for these NDAs and for NDA 203414 have not been completed.

Additionally, we reviewed the previous action letters for NDAs 022271 and 022426, and the review of hepatic safety of alogliptin, alogliptin/pioglitazone, and alogliptin/metformin conducted by Dr. John Senior and Dr. Leonard Seeff, hepatologists in the Office of Surveillance and Epidemiology, November 8, 2012.

4 RESULTS OF REVIEW

4.1 OVERVIEW OF CLINICAL PROGRAM

The efficacy of alogliptin was confirmed in the September 2, 2008 biometrics review by Dr. Janice Derr. Dr. Derr summarized five phase 3 studies that randomized 2,239

patients. The efficacy studied alogliptin monotherapy and add-on combination therapy with other common oral anti-diabetic drugs (sulfonylurea, metformin or pioglitazone) or insulin. The Phase 3 studies had a treatment period of 26 weeks and three arms: alogliptin 25 mg, alogliptin 12.5 mg and placebo. In the combination therapy trials, the designated background therapy was included in all three arms. The primary efficacy endpoint in all major studies was the change from baseline to study endpoint (week 26) in glycosylated hemoglobin (HbA1c). Fasting plasma glucose was a secondary efficacy endpoint. Dr. Derr concluded that alogliptin produced statistically significant net reductions in HbA1c when compared with placebo as a monotherapy, and when given as an add-on to sulfonylurea, metformin, pioglitazone or insulin.

4.2 SAFETY CONCERNS

The significant safety concern associated with alogliptin important to consideration of a REMS is hepatotoxicity. Although the deficiencies communicated in the first CR letters were adequately addressed with the complete response from Takeda, a signal for drug-induced liver injury (DILI) was identified in the complete response submissions. The data showed numerical imbalances against alogliptin for serum alanine aminiotransferase (ALT) elevations compared to control. In addition, five probable (as categorized by OSE reviewers) cases of alogliptin hepatotoxicity were reported with ~219,000 patient-years of postmarketing experience in Japan.

The following table, excerpted from Dr. Pratt's review and the sponsor's November 7, 2011 submission, shows the imbalance in ALT elevations.

Table 58. Number and percentage of subjects with markedly abnormal ALT values (All completed, controlled phase 2 and 3, studies)

	Number (%) of Subjects With ≥1 Marked Abnormal Result					
	Baseline			During Treatment		
Parameter (Criterion)	All Comparators (a) N=4215	Alogliptin 25 mg N=4829	All Alogliptin (b) N=7187	All Comparators (a) N=4074	Alogliptin 25 mg N=4680	All Alogliptin (b) N=7011
ALT (>20×ULN)	0	0	0	0	1 (<0.1%) [0.0]	2 (<0.1%) [0.1]
ALT (>10×ULN)	2 (<0.1%)	3 (0.1%)	3 (<0.1%)	0	6 (0.1%) [0.2]	8 (0.1%) [0.2]
ALT (>8×ULN)	2 (<0.1%)	3 (0.1%)	3 (<0.1%)	1 (<0.1%) [0.0]	9 (0.2%) [0.4]	11 (0.2%) [0.3]
ALT (>5×ULN)	2 (<0.1%)	4 (0.1%)	6 (0.1%)	6 (0.1%) [0.3]	17 (0.4%) [0.7]	21 (0.3%) [0.6]
ALT (>3×ULN)	10 (0.2%)	23 (0.5%)	30 (0.4%)	39 (1.0%) [1.8]	52 (1.1%) [2.1]	71 (1.0%) [2.1]

Source: November 7, 2011 liver-safety submission Table 8

In the current resubmission, the numerical imbalances in ALT elevations are no longer present with the accumulation of additional data, but, with case reports suggestive of DILI, the concern for hepatotoxicity remains. We note that probable cases of DILI, including fatal cases, have accumulated with only 287,000 patient-years exposure to alogliptin.

In their November 2012 review, Dr. John Senior and Dr. Leonard Seeff reviewed 19 cases of increased serum aminotransferases occurring during the conduct of clinical trials

for alogliptin, and two postmarketing cases from Japan. Although many of the cases had other possible causative explanation, there remain cases for which no alternative causative diagnosis other than alogliptin-induced liver injury is apparent. Dr. Senior and Dr. Seeff concluded in the review that, should alogliptin be approved, liver monitoring should be instituted comprising two sets of liver tests before starting alogliptin therapy, and then monthly liver testing for at least the first six months of alogliptin therapy.

4.3 APPLICANT'S PROPOSAL FOR RISK MANAGEMENT

The applicant did not propose a REMS or RMP for alogliptin or alogliptin/metformin. (b) (4), but the applicant has subsequently indicated that, because the Medication Guide-only REMS for pioglitazone has been eliminated, they believe no REMS is needed for alogliptin/pioglitazone.

5 DISCUSSION

As noted above, Dr. Senior and Dr. Seeff recommend that liver monitoring should be instituted comprising two sets of liver tests before starting alogliptin therapy, to first screen prospective patients for pre-existing liver injury, and then monthly liver testing for at least the first six months to monitor for alogliptin-induced liver injury. Alogliptin is a new molecular entity (NME), and prescribing practices have not been established in the U.S. Based on what is known to date about hepatotoxicity, it would be appropriate to maximize labeling with prominent warnings about the risk or hepatotoxicity and recommendations for monitoring for liver toxicity.

If new safety information becomes available the need for a REMS that requires elements to assure safe use that includes prescribing by specially certified prescribers, dispensing by specially certified pharmacies, and/or dispensing to enrolled patients with evidence of safe-use conditions can be re-evaluated.

6 CONCLUSION

At this time, DRISK does not recommend a REMS for the alogliptin-containing products. Should the alogliptin applications be approved, we recommend that labeling be maximized to convey recommendations for liver monitoring and hepatotoxicity. If new safety information becomes available this decision can be re-evaluated.

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

/s/

JOYCE P WEAVER
01/03/2013

CLAUDIA B MANZO
01/03/2013
concur

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Date: March 28, 2012

To: Mary Parks, MD, Director
Division of Metabolic and Endocrinology Products (DMEP)

Through: Claudia B. Karwoski, PharmD, Director
Division of Risk Management (DRISK)

From: Mary Dempsey, BS, Risk Management Programs Coordinator, DRISK
Cynthia LaCivita, Pharm.D., Senior Drug Risk Management Analyst, TL, DRISK
Joyce Weaver, Pharm.D., BCPS, Senior Drug Risk Management Analyst, DRISK

Subject: Original Risk Management Plan Review

Drug Name: Alogliptin

Application Type/ Number: NDA 022271

Applicant/Sponsor: Takeda Global Research and Development Center, Inc. (TGRD)

OSE RCM #: 2011-2666

1 Background

The Division of Metabolic and Endocrinology Products (DMEP) requested the Division of Risk Management (DRISK) review the Alogliptin proposed risk management program for New Drug Application (NDA) 022271 submitted by Takeda Global Research and Development Center, Inc. (TGRD) as a complete response (CR) July 25, 2011.

Alogliptin is an oral antihyperglycemic agent that is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4). The proposed indication is as adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes mellitus (T2DM). The proposed dosing is 25 mg daily for use in patients with normal renal function and 12.5 mg and 6.25 mg for patients with moderate and severe renal impairment, respectively.

2 Materials Reviewed

- July 25, 2011 proposed risk management program submitted as complete response (CR)
- February 13, 2012 review of cases of liver injury in association with alogliptin by Leonard Seeff, M.D., Hepatologist, Office of Pharmacovigilance 1

3 Safety Profile

Adverse events of special interest (AESIs) were predefined based on known or suspected effects of the drug class, observations made during the clinical program, and conditions in the T2DM patient population. These AESIs include hypersensitivity reactions, pancreatitis, and malignancies. Enhanced pharmacovigilance activities are proposed for serious hypersensitivity reactions, serious pancreatitis, and malignancies. Also, the cardiovascular safety of alogliptin is being evaluated in an ongoing cardiovascular outcomes trial.

4 Proposed Risk Management Plan

Several classes of drugs can be used either alone or in combination to manage T2DM, including insulin and insulin analogues, sulfonylureas, metformin, meglitinides, thiazolidinediones, inhibitors of glucosidase, analogues of glucagon-like peptide-1 (GLP-1), and synthetic analogues of human amylin. Three DPP-4 inhibitors have been approved by the Food and Drug Administration (FDA): sitagliptin, saxagliptin, and linagliptin.

Alogliptin is an orally available, highly selective and highly potent inhibitor of DPP-4 that does not inhibit the activity of other closely related enzymes such as DPP-8 and DPP-9. The overarching goal of this risk management plan is to monitor, evaluate, and manage the risks associated with the use of alogliptin on an ongoing basis.

5 Discussion and Conclusion

The Medical Officer, Valerie Pratt, provided her review results at the Wrap-Up meeting held February 28, 2012. Dr. Pratt noted the safety risks of hypersensitivity, skin lesions, pancreatitis, infection, and hypoglycemia were consistent with other DPP-4 inhibitors and

not an approvability issue, but would need to be adequately labeled for approval. The incidence of AEs involving malignancy, including bladder, thyroid and pancreatic cancer, was similar in the alogliptin-treated subjects and the comparator groups.

Dr. Pratt described an imbalance in the clinical trails in the number and percentage of subjects with markedly abnormal ALT values, including ALT>10x and 20x ULN. Referencing the July 2009 Guidance, *Drug-Induced Liver Injury: Premarketing Clinical Evaluation,* ALT is generally considered more liver-specific than AST. The finding of a higher rate of ALT elevation in drug-treated subjects than in the control group is a sensitive signal of the potential for drug induced liver injury (DILI). Data on Japan's two postmarketing Hy's law cases describe moderate to severe liver injury and a probable or highly likely association to alogliptin. Therefore, there is concern of more cases of alogliptin-associated liver toxicity if the drug is used more widely.

A previous review by OSE's Division of Pharmacovigilance 1 (DPV 1) of 50 cases of liver-related test abnormalities in patients exposed to alogliptin determined that the majority liver-related test abnormalities were not attributed to alogliptin. Dr. Seeff's review focuses on an additional 13 cases of liver injury. Six of the cases were scored as possible alogliptin drug-induced liver injury and two cases with more a compelling association were scored as probable drug-induced liver injury. Both probable cases presented with jaundice and severe hepatocellular injury. Dr. Seeff concludes by suggesting that additional study regarding drug-induced liver injury is warranted. In addition, there is a pending consult with OSE's Division of Pharmacovigilance (DPV) to further investigate if there is similar propensity for liver injury with other DPP-4 inhibitors. The results of that review are pending.

If the OSE review results do not find similar liver injury with already marketed DPP-4 inhibitors then, Dr. Pratt is inclined to recommend a complete response (CR) and require the applicant to clearly demonstrate the liver safety of alogliptin.

6 Recommendation to DMEP

Because the liver safety profile is not well characterized, DRISK does not believe that additional risk mitigation measures are warranted at this time to address the potential risk of liver toxicity associated with alogliptin. Please consult DRISK in the future if new safety information becomes available.

The applicant submitted a proposal for a Patient Package Insert (PPI) which is being reviewed by the Division of Medical Policy Programs (DMPP).

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

/s/

MARY J DEMPSEY
03/28/2012

CLAUDIA B MANZO
03/28/2012
concur