CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	January 25, 2013
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # **Supp #**	NDA 22-271 (alogliptin) NDA 20-414 (alogliptin/metformin) NDA 22-426 (alogliptin/pioglitazone)
Applicant Name	Takeda Pharmaceuticals
Proprietary / Established (USAN) Names	Nesina (22-271), Kazano (20-414), Oseni (22-426) alogliptin
Dosage Forms / Strength	Tablets (NDA 22-271) 6.25 mg, 12.5 mg, 25 mg
Proposed Indication(s)	Adjunct to diet and exercise for the treatment of hyperglycemia in adults with T2DM
Action:	*Approval*

Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding alogliptin and the reader should refer to the reviews in the action package for a more detailed discussion and to my two previous reviews for NDA 22-271. Alogliptin is an inhibitor of the serine protease enzyme - dipeptidyl peptidase IV (DPP-4). It is thought that the mechanism of action for this class of drugs is that they enhance the availability of the incretin hormone, glucagon-like peptide-1 (GLP-1). GLP-1, along with glucose-dependent insulinotropic polypeptide (GIP), are short-lived intestinal peptides released in response to food ingestion that have an inhibitory effect on glucagon (which would result in inhibiting hepatic glucose synthesis) and an enhancing effect on insulin secretion when serum glucose is elevated. DPP-4 inhibitors therefore enhance the effect of the incretins by inhibiting their metabolism by the enzyme DPP-4.

The original application for alogliptin was submitted in December 2007, before a public meeting (July, 2008) and subsequent publication of guidance to industry regarding cardiovascular evaluation (December, 2008)[1] of new antidiabetic therapy to treat type 2 diabetes (T2DM) to demonstrate that there is not an unacceptable increase in cardiovascular risk attributable to the drug. All antidiabetic drug applications submitted to treat T2DM that were under review at the time of this policy enactment underwent evaluation in the spirit of this guidance, and alogliptin was found to lack suitable evaluation to rule out unacceptable cardiovascular risk. Therefore, a Complete Response (CR) action letter was sent to the sponsor on June 26, 2009, for NDA 22-271 (alogliptin) identifying this deficiency. All issues identified for NDA 22-271 were also applicable to NDA 22-426 (alogliptin/pioglitazone).

[1] Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, December 2008.

Evidence of acceptable cardiovascular safety was provided with the resubmission received July 25, 2011. This evidence fulfilled the recommendations set forth in guidance[2] and included appropriate trials that demonstrated an upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio of less than 1.8 with an appropriate point estimate. However, a new potential safety signal of hepatotoxicity was identified in that submission leading to a second CR action on April 25, 2012. The submission that is the subject of this review, received July 26, 2012, successfully addresses the hepatotoxicity concern. The successful resolution of the hepatotoxicity concern allows for a recommendation of approval of this application.

Efficacy

In the original NDA, the range of effect of alogliptin on HbA1c reduction was 0.4 to 0.6% relative to placebo, depending on the design of the trial, demonstrating efficacy in treatment of hyperglycemia in adults with T2DM. Increased efficacy has also been demonstrated with use of combinations of alogliptin-metformin as well as alogliptin-pioglitazone compared to the appropriate single ingredients.

Safety

The main issue upon which the approvability of this application rests was the new finding of transaminitis 'shifts' in subjects receiving alogliptin compared to comparators with the updated data received July 25, 2011. There was not a clear case of drug-induced liver disease (DILI) in that database, but an extensive epidemiologic evaluation in the country where alogliptin was marketed (Japan), which when viewed in conjunction with transaminitis shifts in the clinical trial database, may have been suggestive of potential liver toxicity.

With the original application, a potential liver toxicity signal was not identified although there were two subjects exposed to alogliptin with ALT elevations > 10x normal, compared to none in the placebo/comparator group. At the time, this finding was felt to probably be a chance finding which could reasonably occur because of the 4:1 (alogliptin:placebo/comparator) disproportionate randomization making it so that there was not enough exposure in the placebo/comparator group due to projected baseline rates to expect even one event. When there is a small number of events, like in the case with the original application where the disproportionate randomization ratio exceeds the number of events, it can be difficult, depending upon the adverse event of interest, to ascribe the finding to drug exposure. As such, this finding was not identified in the original CR letter.

The resubmission of July 25, 2011, to address the CV issue, contained a greatly expanded database where it is noted that a greater number of alogliptin-treated subjects experienced marked ALT elevations over comparators, probably more than should be ascribed to simply a chance finding. Even more concerning was the finding of two subjects that had ALT elevations > 20x normal as noted in the table below (from my previous review).

[2] Guidance for Industry. Diabetes mellitus-Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf

Table 8.3 ALT Elevations in Original NDA and Resubmission (Phase 2/3 Clinical Trials)

	Placebo/Comparator	All Alogliptin
Original NDA	**N=534**	**N=1961**
ALT > 3 xULN	6 (1.1%)	23 (1.2%)
ALT > 5x ULN	1 (0.2%)	7 (0.4%)
ALT > 10x ULN	0	2 (0.1%)
Resubmission	**N=4074**	**N=7011**
ALT > 3 xULN	39 (1%)	71 (1%)
ALT > 5x ULN	6 (0.1%)	21 (0.3%)
ALT > 10x ULN	0	8 (0.1%)
ALT > 20x ULN	0	2 (<0.1%)

Interim analysis of a large CV outcome trial (Study 402-included in the overall results above) also demonstrated similar findings.

Study 402: Number (%) Subjects with >/=1 Marked Abnormal Result				
	Baseline		Post-Baseline	
Parameter	Placebo N=1466	Alogliptin N1467	Placebo N=1372	Alogliptin N=1387
ALT >20x ULN	0	0	0	0
ALT>10x ULN	1 (0.1%)	2 (0.1%)	0	5 (0.4%)
ALT>8x ULN	1 (0.1%)	2 (0.1%)	0	6 (0.4%)
ALT>5x ULN	2 (0.1%)	5 (0.3%)	1 (0.1%)	10 (0.7%)
ALT>3x ULN	13 (0.9%)	18 (1.2%)	5 (0.4%)	17 (1.2%)

Additionally, postmarketing reports from Japan, the only country where alogliptin was approved and marketed, included cases that may represent DILI, although in some cases alternative explanations may exist. It should be noted that information, as is typical of post-marketing reporting, was very scant.

The expanded database that we received with the second submission also had disproportionate randomization between the alogliptin and placebo/comparator groups, however there were not any cases of ALT elevation > than 10x ULN in the placebo/comparator group even though with the expansion of data some elevations would have been expected if this observation was due to chance. Each subject case of ALT>10x ULN was reviewed and adjudicated by our internal hepatologists as well as the sponsor's external hepatologists, and none of these cases were definitively identified as DILI. However, although an infrequent event, there still was an imbalance of ALT elevation between groups. It is always difficult to know what to do when confronted with a limited number of events of a safety issue but the combination of transaminitis with findings of possible DILI from post-marketing data, and no unique advantage of alogliptin that would change the balance of risk:benefit considerations should a true liver toxicity exist, led us to take a second CR action.

To summarize, in the resubmission of July 25, 2011, we received additional clinical trial data in response to a deficiency regarding cardiac safety assessment. This additional randomized, data generated in a blinded fashion demonstrated transaminitis shifts associated with alogliptin use compared to placebo/comparator. These shifts included higher, concerning levels of ALT elevation not demonstrated by placebo/comparator. There were no cases of Hy's law in the controlled phase 2/3 clinical trial data with 5232 patients (2498 patient-year) exposed to any dose and 3,500 (1773 patient-year) exposed to the highest therapeutic dose of alogliptin (25 mg). Further data examining postmarking experience in Japan identified cases of liver injury that were internally evaluated as being probably to highly likely as DILI.

With the second CR action, I had opined:

> It should also be recognized that either transaminitis shifts alone, or some post-marketing reports alone, may not cause the level of concern (suspicion) that the combination together causes. In that regard, none of the other DPP4-inhibitors have demonstrated transaminitis imbalances in the NDA application and therefore post-marketing reports associated with their use may be viewed with less suspicion.
>
> The evidence of this potential adverse event is in way of the combination of transaminitis imbalances (ALT>10x ULN) between alogliptin compared to placebo/comparator and concerning post-marketing case reports from Japan. Neither of these findings by themselves may have caused us enough concern to take a CR action, but the combination is unique for alogliptin compared to the other DPP4 inhibitors. There are not any Hy's law cases in the NDA database, which may give some indication that DILI associated with alogliptin use, if real, is rare. While there does not seem to be a 'clean' case that clearly implicates alogliptin, there is strong circumstantial evidence with the combination of the database transaminitis imbalances and the post-marketing experience. This is equivalent to 'a lot of smoke, but no fire'. So is the smoke that is being expressed just 'steam' from some innocuous source, or a small fire that could cause tremendous damage, if even rarely? It is difficult to tell based on the data (incomplete in some cases) that we have to date. Yet, a decision must be made based on the totality of what we presently have to review. Such are the complexities of trying to make decisions with incomplete data on what are possibly rare events. I believe that the reports that we have from Japan and the transaminitis shifts that are in the clinical database stand alogliptin texturally apart from the other DPP4 inhibitors, and that we should take a Complete Response action until further data become available to assuage our concern.
>
> The question will then become what data are necessary to either allow marketing or confirm our suspicion? This is a difficult question as we have very imprecise measures of what the true event rate may be should alogliptin really cause liver injury. As I have stated above, the rate may be less than 1:17,000 or less than 1:50,000 based on extrapolations from the lack of Hy's

law cases in the trial database. One approach may be to collect further data from Study 402 which will add anywhere from 5400 to 7400 patient-years of exposure to the existing trial database. This could provide anywhere from 7100 patient-years to 9900 patient-years depending upon when another evaluation is taken and what limitations we use for the evaluation (further interim data from Study 402, all data from the NDA or only data from the 25 mg dose etc.). If a Hy's Law or DILI case does not occur, we should feel comfortable that the risk of liver induced injury with alogliptin use may not be real, or at least that the rate would be so low as to not be detectable. This may allow marketing as this data would be from clinical trials and provide a more secure estimate than the post-marketing data.

Along with the above thinking, if more data were provided such that the transaminitis shift was no longer apparent, and no cases of DILI were noted, this would also allow for marketing.

With this new resubmission, Takeda has provided additional exposure data including 8 additional studies. This has substantially increased the exposure time of subjects to alogliptin as noted in the table below from Dr. Parks' review (Page 8).

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 this increase in patient exposure, the imbalances in transaminase elevations are no longer evident as noted in the table below from Dr. Parks' review (Page 9).

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.

As I noted above, our original concern was also based on an imbalance noted in Study 402. Below is an update of this trial where transaminase elevations appear balanced (Dr. Parks' review, page 9)

Table 8.3. Updated Incidence for Transaminase Elevations in Study 402 (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)

As Dr. Parks' discusses in detail, there was on case that appeared to represent DILI (8413-006/402). However, upon further exploration, this subject was actually assigned to placebo. This case has been investigated by our Office of Scientific Investigations (OSI) as well as re-review of our SAS datasets and all these sources confirm that this patient was assigned to placebo and not alogliptin.

In our CR letter to the sponsor from April 25, 2012, we had advised that additional clinical trial data would be necessary to provide reassurance that alogliptin hepatotoxicity was of limited clinical significance. We instructed that if imbalances in serum ALT elevations

became less apparent and there were not any Hy's Law cases, there may be sufficient reassurance that alogliptin had an acceptable hepatic profile. This resubmission has provided a doubling in pt-yr exposure that has demonstrated resolution of ALT elevation imbalances and no cases of DILI thus providing us with reassurance.

Advisory committee meeting

An advisory committee was not held for this NME as this drug is not a first in its class and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

Conclusions and Recommendations

Alogliptin is a DPP4-Inhibitor that has demonstrated efficacy by placebo-corrected reductions in HbA1c of 0.4 to 0.6% in a range of different populations. All deficiencies identified in the original CR letter have been successfully remediated as well as the deficiency noted in the second CR letter. Therefore this application should receive an Approval action if labeling can be agreed upon. The sponsor continues on with what will be a required CVOT.

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/s/

CURTIS J ROSEBRAUGH
01/25/2013