CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	May 2, 2011
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	NDA 20-280
Applicant Name	Boehringer Ingelheim Pharmaceuticals, Inc.
Proprietary / Established (USAN) Names	Tradjenta Linagliptin
Dosage Forms / Strength	Tablet 5 mg
Proposed Indication(s)	To improve glycemic control in adults with T2DM as an adjunct to diet and exercise
Action:	*Approval*

Introduction

This review will be a brief summary of the basis for the regulatory action regarding linagliptin and the reader should refer to the reviews in the action package for a more detailed discussion. Linagliptin is an inhibitor of the serine protease enzyme - dipeptidyl peptidase IV (DPP-4) which is responsible for the rapid degradation of the incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP are short-lived intestinal peptides released in response to food ingestion that have an inhibitory effect on glucagon (which would result on 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 increasing their circulating half-life. While this is a relatively new class of anti-diabetic therapy, we have had several applications that have provided us with experience regarding this drug category. We also have approved two other DPP-4 inhibitors, Januvia (saxagliptin) and Onglyza (sitagliptin) which provides us with marketing safety information.

There have been safety concerns with anti-diabetic drugs in general, and some specific issues for the DPP-4 drugs, which require attention. From a general safety standpoint common to all anti-diabetic drugs, there have been concerns regarding the cardiovascular safety of certain diabetic drugs. This has led to requiring evidence that new anti-diabetes drugs are not associated with increased cardiovascular risks. Guidance[1] has been issued that allows for a two-step, 'step-wise' assessment of potential cardiovascular risk during drug development. The first step, 'step-one', is to make a determination that the investigational agent has an upper bound of a two-sided 95 percent confidence interval for the estimated risk ratio of less than 1.8 compared to a control group (with a point estimate near unity). For this first step, we have not

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

specified what the control group will be, but we have allowed most of the companies that were in late Phase 3 development to use a pooling of comparators. Assuring that there is not an eighty percent increase in risk would allow marketing while a longer and larger outcome study, which would assure even less risk, is conducted. The boundary of 1.8 was chosen because a more conservative 'goal-post' to pre-approval testing would be too burdensome/prohibitive to drug develop, but this level of assurance (1.8) would be feasible and would provide some assurances while further testing was underway. The 'step-two' testing would be accomplished by a larger outcome study that must demonstrate that the investigational agent has an upper bound of a two-sided 95 percent confidence interval for the estimated risk ratio of less than 1.3 compared to a control group in order for marketing to continue and a point estimate near unity. While not explicitly stated in guidance, the control group should be chosen such that is known to itself not have a cardiovascular risk (placebo comparator add-on to balanced background therapy with rescue as needed). Linagliptin does fulfill the criteria that would allow marketing with a post-marketing requirement for a definitive trial.

There has been concern with the DPP-4 inhibitors in regard to their potential adverse event profile based on whether they have promiscuity toward other DPP enzymes, in particular DPP-8/9. During development of a different DPP-4 agent, it was noted that monkeys developed dose and duration dependent cutaneous lesions that ranged from some flaking and blistering to frank ulceration and necrosis requiring euthanasia of the animals. These findings prevented the marketing of this other DPP-4 agent. Both saxagliptin and sitagliptin were very specific for DPP-4 (as is linagliptin) and did not have a preclinical signal which allowed for their approval for marketing. The nonclinical data for linagliptin also indicates specificity for DPP-4 and did not demonstrate a signal of concern.

There have been postmarketing reports of pancreatitis in association with drugs working through the incretin system. The nonclinical evaluations of incretin drugs performed by the sponsors have been negative for this concern, but there is published literature of animal studies that conflicts. Additionally, there have been epidemiologic studies that are also conflicting, some showing potential risk while others do not. With that in mind, we look closely for this potential with drugs whose mechanism of action is through the incretin system. Linagliptin's package does not contain evidence of this potential that stands out from other DPP-4 agents with which we have experience.

The clinical development program for linagliptin is typical of most anti-diabetics and has clearly demonstrated efficacy. There has not been any safety signals identified not associated with the other marketed DPP-4 drugs. As such, the Division and I agree that linagliptin may be approved for marketing as long as appropriate labeling can be agreed upon.

Efficacy

This has been thoroughly discussed in Drs. Parks, Irony, Dunn and Liu reviews and I agree with their conclusions. Appropriate dose ranging was performed, and as outlined in the other reviews, I agree with the dose selected. Seven Phase 3 trials were performed to demonstrate efficacy. The primary efficacy endpoint in all trials was percent change in HbA1c from

baseline. Trials 1218.16 and 1218.50 were performed to evaluate monotherapy and the results are presented below from Dr. Parks's review (page 12).

Table 5. Study 1218.16 Primary Efficacy Results

	Placebo	Linagliptin 5 mg
Sponsor's Analysis*		
Number of patients	163	333
Baseline mean HbA1c	8%	8%
Adjusted mean chg from baseline (SE)	+0.25 (0.07)	-0.44 (0.05)
Adjusted mean treatment difference (linagliptin-pbo) 95% CI		-0.69 (-0.85,-0.53)
FDA's Analysis**		
Number of patients	167	336
Baseline mean HbA1c	8%	8%
Adjusted mean chg from baseline (SE)	+0.26 (0.08)	-0.45 (0.05)
Adjusted mean treatment difference (linagliptin-pbo) 95% CI		-0.71 (-0.89,-0.53)

*Analysis of covariance method w/ treatment and prior anti-DM as fixed effects and baseline HbA1c as linear covariate on full analysis set
**mixed model repeated measures method with visit week as an additional fixed effect on the observed completers population

Table 6. Study 1218.50 Primary Efficacy Results (FDA analysis)

	Placebo	Linagliptin 5 mg
Number of patients	76	155
Baseline mean HbA1c	8.09%	8.12%
Adjusted mean chg from baseline (SE)	+0.25 (0.13)	-0.33 (0.09)
Adjusted mean treatment difference (linagliptin-pbo) 95% CI		-0.57 (-0.89,-0.26)

Both of these trials confirm the effectiveness of linagliptin 5 mg daily as monotherapy. Dr. Parks notes that Phase 2 trials indicate that metformin and glimepiride provide greater glycemic control (data not presented here) and that is a fair assessment as well.

Five Phase 3 trials evaluated the addition of linagliptin to other anti-diabetic therapies. Four of these trials compared linagliptin add-on to placebo add-on in patients who had not achieved adequate glycemic control on other anti-diabetic therapies and are presented in the table below from Dr. Parks's review (page 13-14).

Table 7. Glycemic Control Efficacy Results in Linagliptin Add-on, Placebo-controlled Trials

	Placebo	**Linagliptin**

Study 1218.15 (24 wks)			
Compared lina+pio to pbo+pio in drug-naïve or patients wash-out of current anti-DM therapies 24-wk trial	N	130	259
	Mean baseline HbA1c (SE)	8.6 (0.08)	8.6 (0.05)
	Adjusted mean chg from baseline (SE)	-0.85 (0.09)	-1.30 (0.06)
	Adjusted mean treatment diff (95% CI)		-0.46 (-0.67, -0.24)
Study 1218.17 (24 wks)			
Compared lina+metformin to pbo+metformin in patient inadequately controlled on metformin	N	177	523
	Mean baseline HbA1c (SE)	8.0 (0.07)	8.1 (0.04)
	Adjusted mean chg from baseline (SE)	0.08 (0.07)	-0.58 (0.04)
	Adjusted mean treatment diff (95% CI)		-0.66 (-0.82,-0.50)
Study 1218.18 (24 wks)			
Compared lina + met/su to pbo + met/su in patients inadequately controlled on met/su	N	263	792
	Mean baseline HbA1c (SE)	8.1 (0.05)	8.2 (0.03)
	Adjusted mean chg from baseline (SE)	-0.11 (0.05)	-0.72 (0.03)
	Adjusted mean treatment diff (95% CI)		-0.61 (-0.73, -0.49)
Study 1218.35 (18 wks)			
Compared lina+SU to pbo+SU in patients inadequately controlled on SU	N	84	161
	Mean baseline HbA1c (SE)	8.6 (0.08)	8.6 (0.07)
	Adjusted mean chg from baseline (SE)	-0.13 (0.10)	-0.60 (0.07)
	Adjusted mean treatment diff (95% CI)		-0.47 (-0.71,-0.22)

These trials confirm the effectiveness of linagliptin 5 mg daily as add-on therapy.

The final Phase 3 trial (Study 1218.20) was an active-control trial comparing linagliptin 5 mg daily to glimepiride. This trial was designed to be a 104-wk (2-yr) trial with only the interim results presented (52 wk data). The primary hypothesis is that linagliptin is non-inferior to glimepiride. It is important to note that this trial was the longest in duration, and provides the bulk of the CV safety data used in the meta-analysis. The results from Dr. Parks review (page 14) are below.

> *After 52 weeks of treatment, the mean treatment difference in HbA1c from baseline of linagliptin compared to glimepiride was 0.20% (97.5% CI: 0.11, 0.30) based on the FDA analysis (note that Table 3.1.10 in Dr. Liu's review has the treatment difference reversed wherein negative values should be positive and the 97.5% boundaries are presented in reverse order – upper to lower bound).*
>
> *Linaglipin 5 mg daily dosing yielded lower glycemic control than glimepiride 1 to 4 mg with the loss in efficacy potentially being as higher as 0.30%. Although the upper bound of the 97.5% CI is still below the pre-specified NI margin of 0.35%, it should also be noted that the lower bound excludes zero,*

indicating that linagliptin is both statistically non-inferior and inferior to glimepiride.

I agree that the non-inferiority confidence interval does not cross zero, and for all intents and purposes linagliptin is less effective than glimepiride. I also note that the glimepiride dose was limited to 4 mg per day, while the label indicates the highest dose is 8 mg per day. This indicates that the differences of effect may have been even larger if the maximal dose of glimepiride had been used. It is not surprising, based upon the results of the Phase 2 trials, that linagliptin yielded lower glycemic control than glimepiride.

I believe the totality of the data indicate that linagliptin is an effective anti-diabetic agent, but may not be as effective as other anti-diabetic agents of different classes.

Safety

As noted above, we now require assessment of potential cardiovascular risk of anti-diabetic medications during development. This clinical development program was in Phase 3 development at the time of our Guidance issuance. As with previous anti-diabetic drug applications that were in late phase development during our policy change regarding cardiovascular assessment, a meta-analysis of Phase 2 and 3 trials was conducted. It should be noted that the analysis in this application was not prospectively designed as future programs are required to do because of the late stage of development. Below are summary tables from Dr. Parks' review (page 16-19) of the trials included, number of events per trial and results.

Table 8. Trials Included in CV Meta-analysis

	Description of trials/design considered in MA	**Linagliptin**	**Placebo**	**Active Comparators**
Study 1218.15 Study 1218.16 Study 1218.17 Study 1218.18	24-wks, placebo-controlled	259 336 524 793	130 167 177 265	- - - -
Study 1218.20*	52-wks, active-control (glimepiride)	779	-	781
Study 1218.23**	12-wk, placebo-controlled 26-wk, active-controlled (voglibose)	319	80	162
Study 1218.35	18-wks, placebo-	161	84	-

Study 1218.50***	controlled	151	76	-
Number of patients		3322	979	943 -781 glimepiride -162 voglibose

*Trial is 104-wk long but only 52-wk interim data reviewed
**Trial has 4 treatment arms with different objectives: 12-wk comparison to pbo and 26-wk comparison to voglibose
***Trial has 2nd phase, double-blind, active control using glimepiride. Only 18wk data reviewed

Table 10. Summary of Events of Primary Composite Endpoint by Study and Treatment Group (Safety Population) – Table obtained from FDA statistical review

Study	Arms	Sample Size	Primary Composite Endpoint n (%)	CV Death n (%)	Non-fatal MI n (%)	Non-fatal Stroke n (%)	UA with Hosp* n (%)
1218.15	linagliptin	259	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
	placebo	130	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.16	linagliptin	336	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	placebo	167	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.17	linagliptin	523	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
	placebo	177	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
1218.18	linagliptin	792	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
	placebo	263	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
1218.20	linagliptin	778	3 (0.4)	1 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)
	glimepiride	781	20 (2.6)	2 (0.3)	6 (0.8)	10 (1.3)	2 (0.3)
1218.23	linagliptin	319	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
	placebo/ ***voglibose***	242	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.35	linagliptin	161	2 (1.2)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)
	placebo	84	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.50	linagliptin	151	2 (1.3)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)
	placebo	76	1 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)

* UA with Hosp – Hospitalization due to unstable angina

Source: Created by reviewer.

Table 11. Analyses of Incidence of Primary CV Composite Endpoint in Meta-Analysis (adapted from review by Drs. Ding and Soukup)

	Linagliptin	Comparator
Overall Results		
Incidence of Events	11/3319 (0.33%)	23/1920 (1.2%)
MH Risk Difference (95% CI) MH Relative Risk Ratio (95% CI) Exact Stratified OR (95% CI)	-0.69% (-1.17, -0.21%) 0.34 (0.15, 0.74) 0.36 (0.16, 0.78)	
Excluding Study 1218.20		
Incidence of Events	8/2541 (0.31%)	3/1139 (0.26%)
MH Risk Difference (95% CI) MH Relative Risk Ratio (95% CI) Exact Stratified OR (95% CI)	0.06% (-0.34, 0.46%) 1.21 (0.35, 4.26) 1.23 (0.29, 7.27)	
Linagliptin vs Placebo Controls Only		
Incidence of Events	6/2541 (0.24%)	3/977 (0.31%)
MH Risk Difference (95% CI) MH Relative Risk Ratio (95% CI) Exact Stratified OR (95% CI)	-0.04% (-0.45, 0.37%) 0.86 (0.23, 3.26) 0.85 (0.18, 5.32)	

These results demonstrate that overall, linagliptin had a point estimate less than 1 and an upper confidence interval less than 1.8. This fulfills criteria for marketing approval, but must be viewed with great caution because this was an unplanned analysis, evaluated low risk subjects, there were imbalances in Framingham risk score in groups with higher risk in the groups compared to linagliptin, there were few events, and one trial (1218.20) drove the analysis. Trial 1218.20 compared linagliptin to an active comparator (glimepiride) and not against placebo. While the results compared to glimepiride may seem to indicate that linagliptin does not have a cardiovascular risk or may even look favorable, this interpretation is not supportable at this time. We do not know whether linagliptin has an intrinsic risk or not, because we do not know the cardiovascular risk status of glimepiride (in addition to the issues I mention above). The most that can be said is that there does not seem to be any greater risk than with an already marketed drug, recognizing that we do not know what the risk associated with glimepiride may be. A definitive cardiovascular safety trial comparing linagliptin to a comparator that is known to not have a cardiovascular risk (likely placebo on balanced background therapy as all the others have done) will be necessary for accurate assessment.

Hypoglycemia, as noted for all the DPP-4 inhibitor drugs when co-administered with other anti-diabetic drugs (insulin secretagogues), was noted. The rate seems comparable to other agents in this class.

Hypersensitivity and exfoliative reactions have been noted with other DPP-4 agents. There was a slight imbalance not favoring linagliptin, but this is based on a limited number of events, so is fragile at best. However, as this does seem to be a class effect, we should expect that there will be events with marketing approval, and labeling should reflect the potential of this type of reaction.

Pancreatitis has been reported in spontaneous postmarketing reports for exenatide and sitagliptin. It is unknown what role incretin agents may have in pancreatitis. Patients with diabetes may have up to a 3-fold[2] increased rate compared to matched controls making this a common event which makes post-marketing reporting even more difficult to interpret (compared to assessment of rare events). Also confusing the safety issue is that healthclaims databases and animal studies have conflicting results regarding incretins possible association with pancreatitis. There were numerical imbalances of pancreatitis in this database (which may not be exist when time-exposure is considered) not favoring linagliptin, but there was a small number of events making the data too fragile upon which to draw conclusions. As with the other agents in this class, labeling should reflect this concern and the sponsor will be conducting required post-marketing evaluation.

Advisory Committee

This application was not discussed before a public advisory committee for the following reasons:

- it is not a first-in-class anti-diabetic therapy

[2] Noel RA, Braun DK, Patterson RE, Bloomgren GL. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. Diabetes Care. 2009 May; 32(5):834-8

- the indication sought is based on a well-established efficacy endpoint used in the approval of 11 different classes of anti-diabetic therapies
- clinical trials assessing efficacy and safety are typical of diabetes programs for approval of anti-diabetic therapies
- no unexpected nonclinical or clinical safety concerns were identified

Conclusions and Recommendations

The data submitted support that there is an appropriate risk-benefit to allow marketing of linagliptin. Thus, I recommend approval with appropriate labeling and PMR commitments as outlined in Dr. Parks' review. The sponsor must conduct a Post Marketing Requirement (PMR) to further evaluate any potential cardiovascular effects, and as part of that trial obtain further data regarding potential pancreatitis.

Regarding the cardiovascular safety PMR, the sponsor has already begun an active-control trial comparing linagliptin to glimepiride in the Cardiovascular Safety of Linagliptin vs Glimepiride in Patients with T2DM at High CV Risk (CAROLINA). This proposal is unique compared to the other outcome trials we have required as it would compare linagliptin to an active control (upon balanced baseline therapy) instead of placebo. It is important to recognize that many currently market drugs do not have assessment of their cardiovascular risk, and any information on their risk would be valuable. The proposed trial design could give us a relative comparison of two drugs. However, this trial design does not answer whether there is any cardiovascular risk that is intrinsic to linagliptin itself as we do not know if glimepiride has a risk and there is not a control arm (placebo) upon which to make comparisons. Therefore, the cardiovascular risk of linagliptin can only be answered in a placebo control trial. Trying to draw conclusions based on CAROLINA could lead us to make erroneous assumptions. As an example, suppose, as an academic exercise, that glimepiride has a 2.5-fold increase in cardiovascular events compared to placebo. With the current trial design, linagliptin could have a 2-fold increase in cardiovascular events, be determined to be 'superior' regarding cardiovascular risk to glimepiride, but still carry an excess risk that we would not know about because of the lack of a placebo control. This may draw clinicians to the false assumption that linagliptin was free of cardiovascular events (although in this premise it would have less toxicity than glimepiride), when in fact it is not. Carrying this exercise even further, if those drugs that are comparing themselves to placebo are found not to have a risk, they may still be considered less desirable than linagliptin in our above example because linagliptin would have demonstrated an advantage to glimepiride, while in fact it may still have a risk greater than placebo and the drugs demonstrating non-inferiority or superiority to placebo (on background therapy). Even worse, carrying our hypothetical example above further, consider if linagliptin was considered non-inferior to glimepiride. Then both marketed drugs would have a 2.5-fold increase, and we would not know it. Therefore, while it may tempt some to consider that a risk similar to a marketed drug is appropriate (or this comparison tempting as it may define the risk of marketed drugs), lack of knowledge regarding marketed drugs should not influence us to allow approval and marketing of new anti-diabetic drugs with potentially equally adverse cardiovascular effects. This would defeat the purpose of our initiative to not allow marketing of anti-diabetic drugs with cardiovascular risk.

What would be the most useful is to add a placebo arm to CAROLINA. Although I don't think we could require the sponsor to include an active control (glimepiride) in a cardiovascular safety trial, the information would be very valuable to the medical profession. As stated though, I do not think, under our current regulatory authority, that we can require more than a placebo trial, and CAROLINA will have to be altered to have a placebo control for the primary analysis or the sponsor will have to conduct an independent placebo control cardiovascular safety trial. However, if the sponsor would care to go to the added expense of having an active control, it would be an important question to answer (cardiovascular risks associated with a drug in the sulfonylurea class), and something the medical community would greatly appreciate. From the sponsor's standpoint, should they demonstrate convincing evidence of greater cardiovascular safety compared to glimepiride, this could potentially lead to labeling (depending on the comparison to placebo).

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/s/

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