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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

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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.

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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

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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**

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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,*

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