

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

April 1, 2009

Saxagliptin (Onglyza) – Bristol Myers Squibb

April 2, 2009

Liraglutide (Victoza) – Novo Nordisk

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Overview of Presentation

- Objectives and agenda
- Glucagon-like peptide (GLP)-1-based therapies
- July 2008 advisory committee meeting
- Final diabetes cardiovascular guidance
- Saxagliptin and liraglutide new drug applications
 - Overview of FDA cardiovascular analyses
 - Important considerations
 - Discussion points and voting questions
- Conclusions

Advisory Committee Meeting Objectives

Saxagliptin

- To discuss whether there is adequate evidence of cardiovascular safety to support marketing

Advisory Committee Meeting Objectives

Liraglutide

- To discuss whether there is adequate evidence of cardiovascular safety to support marketing
- To discuss the human relevance of thyroid C-cell tumors that occur at clinically relevant exposures in rats and mice
- To discuss the significance of several cases of papillary thyroid cancer in the phase 2/3 program

Agenda for Both Days

- FDA introduction (Day 1 only; applicable to both days)
- Applicant presentation(s)
- Questions from the advisory panel to the applicant
- FDA presentation(s)
- Questions from the advisory panel to FDA
- Open public hearing (requests only received for Day 1)
- Questions from the panel to the applicant and FDA
- Panel discussion and voting

Glucagon-Like Peptide (GLP)-1-Based Therapies for Type 2 Diabetes

- Glucagon-like peptide(GLP)-1 is released from the small intestine during meals
- GLP-1 stimulates glucose-dependent insulin release from the pancreas, minimizing hypoglycemia
- GLP-1 also slows gastric emptying and reduces inappropriate post-meal glucagon release
- Patients with type 2 diabetes have a reduced GLP-1 response to meals but a preserved insulin response to GLP-1

Glucagon-Like Peptide (GLP)-1-Based Therapies for Type 2 Diabetes

- GLP-1 has a <2-minute half-life because of rapid degradation by dipeptidyl peptidase (DPP)-4
- Currently, there are two approaches to GLP-1-based therapies for type 2 diabetes
 - Slow endogenous GLP-1 degradation using a DPP-4 inhibitor (e.g., saxagliptin)
 - Administer pharmacologic GLP-1 that is resistant to DPP-4 degradation (e.g., liraglutide)

Dipeptidyl Peptidase (DPP)-4 Inhibitors

- **Saxagliptin**
 - DPP-4 inhibitor
 - Administered orally
 - Dosed once daily
- **Januvia (sitagliptin)**
 - The only FDA-approved DPP-4 inhibitor
 - Administered orally
 - Dosed once daily
- There are other DPP-4 inhibitors under development

Glucagon-Like Peptide (GLP)-1 Agonists

- **Liraglutide**
 - Glucagon-like peptide (GLP)-1 agonist
 - Administered subcutaneously
 - Dosed once daily
- **Byetta (exenatide)**
 - The only FDA-approved GLP-1 agonist
 - Administered subcutaneously
 - Dosed twice daily
- There are other GLP-1 agonists, including longer-acting formulations, under development

July 2008 Advisory Committee Meeting

- Discussed cardiovascular assessment in the pre- and post-approval settings for drugs and biologics developed to treat type 2 diabetes
- Presentations by experts in endocrinology and cardiology
- Panel included endocrinologists, diabetologists, cardiologists, statisticians, and drug safety experts

Transcript at www.fda.gov/ohrms/dockets/ac/cder08.html#EndocrinologicMetabolic

July 2008 Advisory Committee Meeting

“It should be assumed that an anti-diabetic therapy with a concerning CV [cardiovascular] safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial, or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk?”

14 “Yes” votes

2 “No” votes

Transcript at www.fda.gov/ohrms/dockets/ac/cder08.html#EndocrinologicMetabolic

Diabetes Cardiovascular Guidance

- A Guidance describes FDA's current thinking on a topic and provides recommendations
- *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*
- Finalized December 2008 after FDA considered the July 2008 advisory panel discussion and other data

<http://www.fda.gov/cder/guidance/8576f1.htm>

Diabetes Cardiovascular Guidance

- Reaffirms HbA1c as the primary efficacy endpoint for glucose reduction but notes vulnerability of patients with diabetes to cardiovascular disease
- Asks sponsors to demonstrate that new therapies for type 2 diabetes do not unacceptably increase cardiovascular risk
- FDA also requests evidence of cardiovascular safety for unapproved therapies that had completed or ongoing programs at the time the guidance was issued
- Cardiovascular assessment of already approved treatments to be addressed separately in the near future

Diabetes Cardiovascular Guidance

Recommendations:

- Independent committee should prospectively and blindly adjudicate major cardiovascular events
- Phase 2/3 design should permit a pre-specified meta-analysis of major cardiovascular events
- Trials should include patients at increased risk for cardiovascular disease
- Trial duration(s) should be longer than 3-6 months to obtain enough events and provide long-term data

Diabetes Cardiovascular Guidance: Comparing Risk of Investigational Drug to Comparator

- Is the estimated increase risk of cardiovascular events with the investigational drug no worse than 1.3 or 1.8 times the risk with the comparator?
- Compute the point estimate of the risk ratio and its 95% confidence interval
- Compare the upper bound of the 95% confidence interval to the criterion levels of 1.3 and 1.8
- The upper bound of the 95% confidence interval represents the “worst case” potential for increased risk, based on the combined analysis across studies

Diabetes Cardiovascular Guidance

Upper Bound of 95% CI for Risk Ratio	Conclusion
>1.8	Inadequate to support approvability
>1.3 but <1.8*	Postmarketing trial(s) needed to show definitively <1.3
<1.3*	Postmarketing trial(s) generally not necessary

CI=confidence interval
*with a reassuring point estimate

FDA Cardiovascular Analyses

- The applicants initially used different approaches to analyze cardiovascular safety
- FDA requested that both applicants re-analyze their data using a uniform approach
 - Treatment periods
 - Endpoints - “SMQ MACE” and “Custom MACE”
 - Statistical analyses

FDA Cardiovascular Analyses

Two Treatment Periods:

- Randomized, controlled periods for all completed phase 2/3 trials up to the primary efficacy (HbA1c) timepoint
- Randomized, controlled periods for all completed phase 2/3 trials, including controlled periods beyond the primary efficacy (HbA1c) timepoint

FDA Cardiovascular Analyses

Treatment Periods – Saxagliptin:

- “Short-term” Period
- “Short-term” + “Long-term” Periods
- Long-term period
 - Patients entered the long-term period after completing the short-term period or upon requiring glycemic rescue
 - Double-blind, non-voluntary extensions
 - Patients remained on original randomized treatment

FDA Cardiovascular Analyses

Treatment Periods – Liraglutide:

- “Population A”
- “Population B”
 - Includes unblinded, voluntary extensions
 - Patients remained on original randomized treatment
- Patients in Population A or B requiring glycemic rescue were withdrawn from the study

MedDRA

- “Medical Dictionary for Regulatory Activities” developed by the International Conference on Harmonisation (ICH)
- Used to code adverse events
- Investigators can report the same adverse event in different ways – impractical to use these verbatim terms to tabulate the incidence of various adverse events
- Coders trained in MedDRA review the verbatim terms and match to a “Lowest Level Term”

MedDRA (continued)

- Each Lowest Level Term is linked to a single “Preferred Term” (PT)

Example: “Arrhythmia”, “Dysrhythmias” and “Arrhythmia not otherwise specified” would all be linked to the single Preferred Term “Arrhythmia”

- Analyses of adverse events are performed using PTs, which represent single medical entities

Standardised MedDRA Queries (SMQs)

- MedDRA's size/complexity may result in different users selecting different sets of PTs when trying to retrieve cases related to a particular safety issue
- Standardised MedDRA Query (SMQ) = grouping of Preferred Terms potentially related to a defined medical condition of interest
- SMQs have been developed to standardize the sets of Preferred Terms that should be included when evaluating a particular safety issue

SMQ: An example

- “Myocardial infarction SMQ” = group of 30 PTs (version 11.1)
 - Acute myocardial infarction
 - Coronary artery occlusion
 - Blood creatine phosphokinase increased
 - Electrocardiogram Q wave abnormal
- Patients reported to have experienced any of these 30 PTs are counted as having had a myocardial infarction
- Some of these PTs could be consistent with myocardial infarction, but there may be another explanation in some patients (e.g., “Blood creatine phosphokinase increased” could be due to exercise, trauma, medications, etc.)

FDA Cardiovascular Analyses

FDA Requested Two MACE Endpoints

- “(Broad) SMQ MACE” – composite of
 - Cardiovascular death and the following two SMQs
 - “Myocardial infarction”
 - “Central nervous system haemorrhages and cerebrovascular accidents”
- “Custom MACE”
 - Subset of Preferred Terms from SMQ MACE considered more likely to represent events of myocardial infarction and stroke, as reported by investigators

Custom MACE

- Panel of 3 FDA clinical reviewers independently reviewed all PTs contained in the SMQ MACE
- “If I had a patient who actually had a myocardial infarction or stroke, is this a Preferred Term that I might actually have chosen for such an event?”
- The three reviewers compared their “Custom” lists and reached unanimous agreement for all PTs
- This is not the same as post-hoc adjudication

Example of SMQ MACE vs. Custom MACE

Preferred Term	SMQ MACE	CUSTOM MACE
Blood creatine phosphokinase increased	X	
Coronary artery occlusion	X	
Coronary artery thrombosis	X	X
Electrocardiogram ST segment abnormal	X	
Infarction	X	
Myocardial infarction	X	X
Scan myocardial perfusion abnormal	X	
Silent myocardial infarction	X	X

FDA Cardiovascular Analyses

Statistical Analyses

- FDA requested results be stratified by study and that an exact method be used for at least 1 analysis
- FDA used multiple analyses to assess consistency of results (e.g., 2 populations, 2 endpoints, multiple comparators, various statistical methodologies)
- FDA used the same statistical approach for both products but will present a subset of the analyses that best represent cardiovascular risk

Important Considerations Regarding the Cardiovascular Analyses

- The saxagliptin and liraglutide new drug applications were submitted to FDA prior to publication of the cardiovascular guidance
- These programs were not prospectively designed for systematic measurement of cardiovascular risk
- Cardiovascular events rates were low
- There were no pre-specified definitions for major cardiovascular events of interest

Important Considerations Regarding the Cardiovascular Analyses (continued)

- The applicants and FDA conducted post-hoc analyses of cardiovascular safety based on MedDRA PTs
- No prospective adjudication of cardiovascular events
- Post-hoc adjudication was not conducted because many events had insufficient information
- FDA used a uniform approach with saxagliptin and liraglutide to assess cardiovascular safety
- Each application should be evaluated on its own merits (development programs differed and cross-program comparisons should not be performed)

Discussion Points

Cardiovascular Safety

- Discuss whether the low cardiovascular event rates permit a reliable assessment of cardiovascular safety
- Discuss whether the endpoints and post-hoc analyses permit a reliable assessment of cardiovascular safety
- Offer suggestions for improvements to the endpoints and analyses that may be applied to Phase 3 programs that were completed or near-completion when the guidance was issued
- Discuss the adequacy of the statistical methods for measuring sensitivity of the results to analytical method

Discussion Points

Cardiovascular Safety

Saxagliptin-Specific

- Discuss whether the trial design affects interpretation of cardiovascular results for the short-term period and for the combined short-term and long-term periods

Liraglutide-Specific

- Discuss the relevance of the differences noted by type of comparator and the role of these separate types of comparators in the evaluation of cardiovascular risk for future diabetes drug applications

Voting Questions

Cardiovascular Safety

- Based on the preceding discussion, has the applicant provided evidence of cardiovascular safety to conclude that saxagliptin / liraglutide rules out unacceptable excess cardiovascular risk relative to comparators, including evidence that the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratios is less than 1.8? (Yes/No)
 - If voting “No”, what additional cardiovascular data are needed to address any limitations resulting from the completed clinical development program and to support approvability, including satisfying the 1.8 non-inferiority margin?

Voting Questions

Cardiovascular Safety

Saxagliptin-Specific

- For the Custom MACE endpoint, the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratio was less than 1.3. These data involved a total of 11 cardiovascular events in the 24-week, double-blind, short-term study periods and a total of 40 cardiovascular events in the combined short-term and long-term study periods of median 62-week exposure. Are these data adequate to conclude that post-marketing cardiovascular safety trial(s) are unnecessary? (Yes/No)
 - If voting “No”, please comment on the limitations of the completed NDA program that will require additional post-marketing trial(s)

Conclusions

- The saxagliptin and liraglutide programs were completed prior to the diabetes cardiovascular guidance
- These programs were not prospectively designed to measure cardiovascular risk
- Nonetheless, FDA requests that these programs provide adequate evidence of cardiovascular safety to support marketing

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