

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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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

Liraglutide and Thyroid Tumors

- Liraglutide causes C-cell tumors in two animal species, in both genders, at clinically relevant exposures
- No approved drugs are known to cause C-cell tumors in two animal species, but some investigational GLP-1 agonists may
- The applicant has conducted mechanistic studies to assess the clinical relevance of these non-clinical findings
- The applicant also measured serum calcitonin in clinical trials and performed calcitonin stimulation testing in some patients
- FDA reviewed the above data and all cases of thyroid tumors reported in the liraglutide clinical development program

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

Discussion Points

Cardiovascular Safety

- Discuss the adequacy of the statistical methods for measuring sensitivity of the results to analytical method
- 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 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?

Discussion Points

Liraglutide and Thyroid Tumors

- Discuss whether the applicant has provided adequate data to show that the treatment-related thyroid C-cell tumors are rodent-specific and not relevant to humans
- Discuss the calcitonin findings from the clinical trials
- Discuss the numerical imbalance of papillary thyroid cancer reports in the liraglutide clinical trials

Voting Questions

Liraglutide and Thyroid Tumors

- Has the applicant provided adequate data on the animal thyroid C-cell tumor findings to demonstrate that these findings are not relevant to humans? (Yes/No)
 - If voting “Yes”, why?
 - If voting “No”, please explain why not and provide recommendations for clinical trial monitoring for thyroid C-cell tumors in the development programs for other GLP-1 analogs

Voting Questions

Liraglutide and Thyroid Tumors

- Assuming the remainder of the risk:benefit data are acceptable, do the available data on thyroid C-cell tumors permit marketing of liraglutide? (Yes/No)
 - If voting “Yes”, why? Please comment on the need for and approach to post-approval risk management (e.g., whether baseline assessment and/or ongoing monitoring for medullary thyroid cancer is needed for liraglutide-treated patients). If so, what types of assessments should be done?
 - If voting “No”, why not? What additional data related to medullary thyroid cancer are needed to support marketing?

Voting Questions

Liraglutide and Thyroid Tumors

- Assuming the remainder of the risk:benefit data are acceptable, do the available data on papillary thyroid cancer permit marketing of liraglutide? (Yes/No)
 - If voting “Yes”, why? Please comment on the need for and approach to post-approval risk management (e.g., whether baseline assessment and/or ongoing monitoring for papillary thyroid cancer is needed for liraglutide-treated patients). If so, what types of assessments should be done?
 - If voting “No”, why not? What additional data related to papillary thyroid cancer are needed to support marketing?

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