Testimony to the FDA Endocrinologic and Metabolic Drugs Advisory Committee

Liraglutide (Saxenda) for Weight Loss

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(We have no financial conflicts of interest)

Reasons for opposing approval of high-dose liraglutide for weight loss

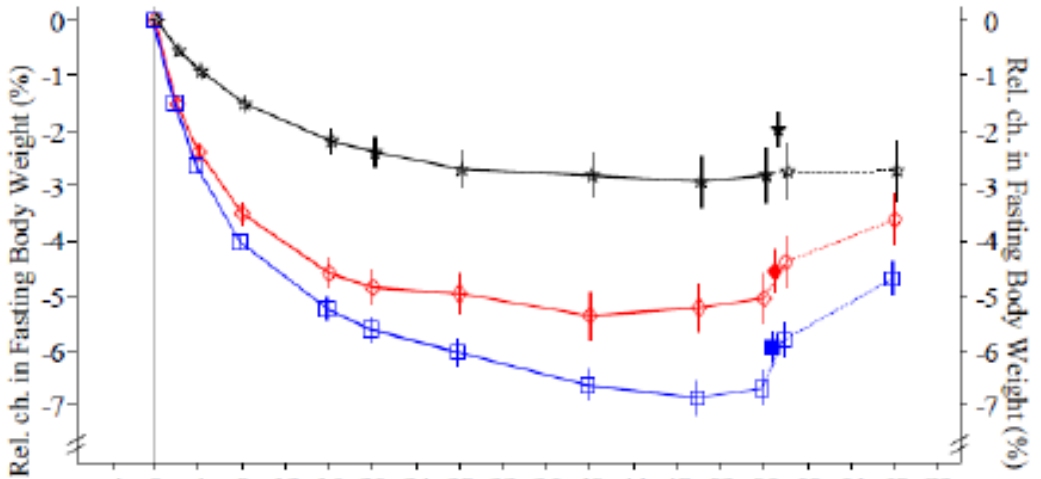
- Efficacy over-estimated by LOCF analyses
- Liraglutide's toxicity (including fetal toxicity) increasingly apparent, in multiple organ systems, at lower, 1.8 mg, daily dose
- Implications for overweight/obese DM patients of first-line 3.0 mg/day Saxenda

Two Largest Trials Failed to Meet FDA's Approval Criteria When Analyzed Using a "Reasonable Set of Assumptions" About Missing Data

- Withdrawal rates of 22-29% by one year
- Last observation carried forward (LOCF) analyses no longer considered optimal by FDA, over-estimate treatment effect
- With FDA statistical reviewers' "preferred approach", accounting for actual end-of-study weights for dropouts, the two largest trials (1839 and 1922) failed to meet FDA's pre-specified 5% mean placebo-subtracted weight loss threshold.

- For those who remain on the drug, the modest weight loss is promptly reversed following discontinuation, meaning Saxenda is a chronic, lifelong therapy – and one with chronic, lifelong, serious (and likely cumulative) risks

Figure 22. Percent Change from Baseline in Body Weight by Treatment Visit, Trial 1922



EAS: Observed value
Error Bar: +-Standard Error (Mean)

Source: NN8022-1922 Clinical Trial Report, Figure 11-1

Recent long-term studies “raise the concern that a pharmacological effect on weight loss may not provide enough assurance of a CV benefit to offset a CV safety issue (such as increased heart rate) associated with a weight loss drug.”

- FDA Clinical Reviewer

Saxenda is the latest in a long line of weight loss drugs. 7 of the drugs below had severe cardiovascular side effects and were banned or delisted for weight loss, while commercial failures Qsymia and Belviq both come with cardiovascular risks. Like Saxenda, some of the drugs caused increases in heart rate in pre-approval trials.

Drug	Year Approved	Year Taken Off Market	Serious Adverse Effects
Thyroid Hormone	1893	1949	Hyperthyroidism (which includes cardiac effects)[1]
Amphetamine	1937	1971	Known cardiovascular toxicity
Aminorex	1967	1972	Pulmonary Hypertension[2]
Fenfluramine	1973	1997	Heart Valve Insufficiency and Primary Pulmonary Hypertension[3,4]
Phenylpropanolamine	1960	2000	Hemorrhagic Stroke[1]
Ephedra	n/a	2004	Heart Attack and Stroke[5]
Sibutramine	1997	2010	Heart Attack and Stroke[6]
Belviq & Qsymia	2012	??	Heart Valve Damage (Belviq) and Increased Resting Heart Rate, Fetal Toxicity (Qsymia)

CV safety not established

- Saxenda Phase III trials “not powered or designed to rule out a pre-specified degree of cardiovascular risk.”
- Ongoing CV safety study with Victoza 1.8 mg dose in diabetics not completed; different dose and population may preclude accurate extrapolation to Saxenda
- But if extrapolation will be done, why not wait for the study to be completed before approving Saxenda?
- If not, it will be several years before a required post-approval CV safety study is completed.

Thyroid Cancer Concerns

- FDA "did not identify any other approved or investigational drug causing thyroid c-cell tumors in mice." (Victoza Briefing Document)
- Consistently higher calcitonin levels in Saxenda vs. placebo in Phase III trials
- Six post-marketing cases of medullary thyroid cancer "possibly related to liraglutide…remain under internal review"
- Numerical imbalance in (non-C-cell) papillary/follicular thyroid malignancies across both liraglutide development programs:
  - Victoza: 2.1 vs. 0.7 per 1,000 patient-years
  - Saxenda: 5 vs. 1 cases

Victoza source: FDA Briefing Doc, April 2, 2009 Victoza EMDAC meeting

Pancreatitis/Cholecystitis

- Acute pancreatitis in pooled Phase III trials:
  - 7 liraglutide (5 severe) vs. 1 placebo (mild)

- FDA Medical Reviewer: “imbalance…very similar to the 4:1 imbalance…seen in the Victoza pre-approval trials.”
  - Saxenda: 2.3 vs. 0.6 per 1,000 patient-years
  - Victoza: 2.2 vs. 0.6 per 1,000 patient-years

- Cholecystitis: 22 liraglutide vs. 3 placebo

- But 5 of 7 liraglutide acute pancreatitis cases *not* clearly associated with cholelithiasis, further indicating, as has long been suspected, that liraglutide is directly toxic to the pancreas

Potent teratogen in rats, rabbits

- Women of childbearing age a key target population for 3.0 mg/day Saxenda.
- Victoza increased congenital malformations and preterm birth, and reduced fetal weight, in all studies of rats and rabbits at exposures less than the human exposure from a 1.8 mg/day dose.
- By contrast, Qsymia, classified as Pregnancy Category X, displayed teratogenic effects only at multiples greater than the max. rec. human dose.
- Therefore, Saxenda would unequivocally meet Category X criteria, necessitating a Qsymia-like REMS required to prevent potential fetal toxicity

Diabetes Treatment Implications

Because of its myriad risks, liraglutide is currently second-line therapy for DM at a dose of 1.8 mg/day. As Victoza nears the end of its market exclusivity, Novo Nordisk will undoubtedly shift its marketing strategy towards the 3.0 mg/day Saxenda, including for use in overweight/obese diabetic patients, with an aim to “transition” as many DM Victoza users as possible to the more lucrative Saxenda as a first-line weight loss therapy. What this will mean for generally sicker DM patients who comprised just 14% of all subjects in the Saxenda development program remains to be seen.

Conclusion

No study has yet been published demonstrating a benefit of any weight loss drug on mortality or a significant measures of morbidity. It is virtually certain that high-dose liraglutide will not be any different and its multiple toxicities clearly outweigh any minor effects on weight loss in most, otherwise healthy overweight and obese patients.