

Southampton Health Services

September 21, 2014

To: Staff and our Clients at Southampton Health Services

Subject: SHS Policy and background information regarding two new appetite suppressants, *Saxenda* and *Contrave*.

The U.S. Food and Drug Administration (FDA) recently approved another two new weight-loss medications, *Saxenda* and *Contrave*. At this time, SHS will not be prescribing either of these medicines.

As background, SHS has provided a safe weight reduction program for over 30 years. We have 5 internal medicine specialists with expertise in Bariatrics who continually review the medical literature and adjust our weight reduction protocols accordingly. We did not support the use of *Belviq* or *Qsymia* when they were approved last year as appetite suppressants due to our concern that they could be more risky while not showing any additional benefit beyond what we already prescribe. That both of these medicines have sold poorly supports that we made the right decision.

How effective are these new medicines?

The FDA considers any medication that enables a weight loss of 5% or more as “clinically meaningful”. To put it into perspective, patients at SHS must lose 12 pounds over the first three months of the program, which is usually about 5% of their body weight. Within one year, our patients commonly lose 20 to 30% of their weight.

How do these medicines work and are they safe?

Saxenda (liraglutide) is a “GLP-1 (glucagon-like peptide) agonist. Medications of this class work by increasing insulin secretion and are used to treat diabetes. Liraglutide is currently marketed as *Victoza* which is given as a once-per-day subcutaneous injection at a dose of 0.6 to 1.8 mg to treat diabetes. *Saxenda* is given as a 3 mg/day injection.

GLP-1 regulates appetite and food intake by decreasing hunger and increasing feeling of fullness after eating.

Trials of patients *Saxenda* have shown it to be effective in weight reduction.

In the SCALE Trial, overweight or obese patients were given a *Saxenda* or a placebo injection daily along with a low calorie diet and exercise program for one year.

| Results: | Saxenda | Placebo |
|-----------------|---------|---------|
| 5% weight loss | 64% | 27% |
| 10% weight loss | 33% | 10% |
| Overall | 8% | 2.6% |

Thus it provides benefit. One could also look at this study and **realize diet and exercise alone provide benefit!**

PROs;

- The dual action of Saxenda on both appetite and blood glucose may make it a good agent for patients with obesity, with and without diabetes.

CONs;

- In animal studies, *Victoza* caused thyroid tumors, including thyroid cancer in rats and mice.
- There are post-marketing reports of *Victoza* causing fatal and non-fatal pancreatitis. (*Saxenda* should not be prescribed in any patient who has had pancreatitis).
- It causes a slight increased heart rate by 2 to 3 beats/minute, felt acceptable.
- It requires daily injections.
- The most common adverse reactions, reported to be $\geq 5\%$ of patients treated with *Victoza* than in those treated with placebo are: headache, nausea, diarrhea and anti-liraglutide antibody formation.
- Cost: Novo Nordisk, the manufacturer, intends to price Saxenda at \$9,000/year, considerably more than existing oral drugs. Such a high price may also indicate that it is to be a niche product rather than a mass-market weight loss pill, especially since it requires a daily injection.

UNKNOWNs;

- No long-term safety data regarding increased risk for thyroid or breast cancers or pancreatitis.
- No data regarding possible cardiovascular (heart, blood vessel, stroke) risks.
- The FDA has required more studies now that it is on the market.

Contrave is a tablet containing 8 mg naltrexone and 90 mg of bupropion. It is prescribed as one pill per day for one week and gradually increased to two pills twice per day over a one month time period which is the most effective dose.

Naltrexone is used to combat alcohol and opioid dependence. It is an opioid antagonist.

Bupropion is an antidepressant which is used to treat depression and seasonal affective disorder and as an aid to smoking cessation.

How the medication works is not exactly known. It is thought that the combination of the two medicines work on two areas of the brain: the hypothalamus, which contains the appetite regulatory center and the mesolimbic dopamine circuit which is the "reward center".

Studies up to one year long have shown 42% of patients taking *Contrave* lost at least 5% of their body weight compared to 17% given placebo.

It took over four years after its first application to get approved by the FDA due to potential risks.

CONs;

- It carries a black box warning owing to bupropion causing increased risk of suicidal thoughts and behaviors in adolescents and young adults as well as serious neuropsychiatric events including depression, mania, psychosis, hallucinations, paranoia, anxiety, agitation, panic attacks, trouble sleeping (insomnia), irritability, aggression, anger, violence, suicidal thoughts and suicide among

other unusual changes in behavior or mood. While taking CONTRAVE, you or your family members should pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings and maintain communication with your healthcare provider.

- It causes a dose-related increase risk for seizures and should not be given to anyone with a seizure disorder.
- It can increase heart rate and blood pressure thus should not be given to patients with poorly controlled hypertension.
- It can also cause liver damage (hepatitis), visual problems (angle-closure glaucoma), and increases risk of low blood sugar (hypoglycemia) in people with type 2 diabetes mellitus who also take medicines to treat their diabetes (such as insulin or sulfonylureas).
- The drug should not be given to anyone pregnant or those trying to get pregnant.
- The FDA said that people taking *Contrave* should be evaluated after 12 weeks of treatment. Patients who have failed to lose at least 5% of their body weight should discontinue the drug. Longer treatment risks and outcomes have not yet been determined.

UNKNOWNs;

- Effect on cardiovascular morbidity and mortality has not been established.
- The FDA is requiring Orexigen, the manufacturer, to perform a cardiovascular outcomes trial.

BOTTOM LINE

These two new medications are not “silver bullets”. In the trials leading to their approval, neither of them provided any greater weight loss than the current SHS medications we prescribe.

We feel that *Contrave* has too many dangerous and life-threatening side-effects, and will not likely ever incorporate it into our weight-management armamentarium.

On the other hand, if *Saxenda* appears to be safe in post-marketing trials and becomes affordable, we may consider using it in those patients that are willing to give themselves a daily injection rather than take a pill.

The physicians at SHS will continue to use our current appetite suppressant medications. With our regimen and team approach, our patients routinely lose 20-30% of their weight.

Our goal remains to provide safe and effective weight management.

David Connito MD
Medical Director
Southampton Health Services