

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 10: Obesity

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHS A290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 150 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists the five topics for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before May 15, 2014, in this priority area; and (3) we received five to eight sets of comments from experts between July 1, 2013, and May 23, 2014. (Eleven topics in this priority area were being tracked in the system as of May 15, 2014.) The four topics marked with asterisks emerged as having higher-impact potential on the basis of expert comments and assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by device and then, pharmaceuticals. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 10: Obesity

Topic	High-Impact Potential
1. Aspiration system (AspireAssist) for treatment of obesity	No high-impact potential; archived in horizon scanning system on basis of expert comments
2. * Controlled-release phentermine-topiramate (Qsymia) for treatment of obesity	Lower end of the high-impact-potential range
3. * Intra-gastric dual balloon (ReShape Duo) for treatment of obesity	Lower end of the high-impact-potential range
4. * Liraglutide (Victoza) for treatment of obesity	Moderate
5. * Lorcaserin (Belviq) for treatment of obesity	Lower end of the high-impact-potential range

Discussion

According to a 2013 report from the National Center for Health Statistics, about 68% of American adults are overweight or obese, which is defined by an excess accumulation of body fat. Development of obesity was at one time thought to be simply a product of caloric intake that exceeded energy expenditure. However, researchers now know that other factors including genetics, metabolism, behavior, environment, culture, and socioeconomic status contribute to obesity. Mortality and comorbidities associated with obesity include type 2 diabetes mellitus (T2DM),

coronary artery disease, dyslipidemia, cardiometabolic syndrome, hypertension, stroke, sleep apnea, osteoarthritis, gall bladder disease, and some cancers. In June 2013, the American Medical Association adopted a policy that recognizes obesity as a disease.

Body mass index (BMI), according to the National Institutes of Health, is a measure of an individual's weight relative to his or her height (kg/m^2). BMI is significantly correlated to an individual's body-fat percentage and is used as an easy measure to determine whether someone is overweight or obese. Patients with BMIs of $25 \text{ kg}/\text{m}^2$ or more are considered to be overweight, and patients with BMIs of $30 \text{ kg}/\text{m}^2$ or greater are considered to be obese. Obesity is further classified as extreme or morbid in patients with BMIs of $40 \text{ kg}/\text{m}^2$ or more.

Body fat distribution is also an important determinant of disease risk. Excess body fat in the abdominal area that is out of proportion to total body fat is known to be an independent predictor of morbidity and mortality. Waist circumference positively correlates to the amount of abdominal fat, and it can be used clinically to assess disease risk in patients. A waist circumference of more than 37 inches in men and 31.5 inches in women is associated with increased cardiovascular risk. Because of even greater morbidity risk, therapeutic intervention is considered to be urgently needed in men with a waist circumference greater than 40 inches and in women with a waist circumference of more than 35 inches.

Worldwide, obesity rates have more than doubled since 1980. In 2008, more than 1.4 billion adults aged 20 years or older were overweight; 500 million people were obese.

In the United States, 35.7% of adults are obese. Among children and adolescents aged 2–19 years, one in three is overweight or obese and one in six is obese, and overweight adolescents have a 70% chance of becoming overweight adults. Non-Hispanic blacks have the highest age-adjusted rates of obesity (49.5% are obese), followed by rates for Mexican Americans (40.4%), Hispanics (39.1%), and non-Hispanic whites (34.3%). Non-Hispanic black and Mexican-American men with higher incomes are more likely to be obese than non-Hispanic black and Mexican-American men with low incomes. Low-income women are more likely to be obese than high-income women. Prevalence of obesity in adults has increased across all income and education levels.

Finkelstein and colleagues (2009) estimated total annual U.S. medical costs associated with obesity to be \$147 billion and individual medical costs to be \$1,429 higher for obese people than for individuals of normal weight.

Only one surgical treatment (gastric bypass surgery) has definitively demonstrated long-term efficacy for patients who are morbidly obese. Until mid-2012, orlistat was the only U.S. Food and Drug Administration (FDA)-approved antiobesity pharmacotherapy available for long-term use in the United States. Surgery carries significant risks of morbidity and mortality, and drug therapy can have undesired side effects and limited efficacy in achieving sufficient weight loss. Additional treatment options are highly desired. In addition to the new pharmaceutical options, we are tracking development of some devices. FDA held a public workshop Dec. 19-20, 2013, on obesity medical device innovation to address and discuss concerns about the regulatory pathway for new obesity devices. The outcomes of the meeting remain to be seen.

In September 2011, concerns over the lack of effective pharmacotherapies for treating obesity drove the U.S. Congressional Committee on Appropriations to direct FDA to develop a pathway, by March 30, 2012, to support antiobesity-treatment development. That prompted FDA to work more closely with manufacturers, eventually leading to the summer 2012 approvals phentermine-topiramate (Qsymia[®], Vivus, Inc., Mountain View, CA) and lorcaserin (Belviq[®], Arena Pharmaceuticals, Inc., San Diego, CA). Additionally, liraglutide (Victoza[®], Novo Nordisk a/s, Bagsvaerd, Denmark), an FDA-approved drug for managing T2DM, has been used off label for treating obesity, even while in clinical trials for an obesity indication. A temporary-placement gastric dual-balloon device that is inserted endoscopically is also in development for obesity

treatment, as is a device to enable partial aspiration of stomach contents after eating. Experts commenting on these topics rated them differently, basing their opinions on the available data on efficacy and side effects.

Pricing, reimbursement, and prescribing barriers have been the priority for the manufacturers of lorcaserin and phentermine-topiramate to aid what has initially been slow diffusion and lower-than-projected sales. Liraglutide, which is already on the market for treating diabetes and is being used off-label to treat obesity, might face fewer accessibility issues than lorcaserin and phentermine-topiramate and could present an opportunity to simplify treatment for patients who are both diabetic and obese, which constitutes a large proportion of each separate population. The cost of liraglutide at the dosage used to treat obesity is expected to be higher than for lorcaserin or phentermine-topiramate, and pricing for each drug might change in a competitive market.

Eligible Topic Not Deemed High Impact

- The AspireAssist™ Aspiration Therapy System (Aspire Bariatrics, Inc., King of Prussia, PA) is a weight-loss device/system in development that reduces food portions after a meal by removing stomach food contents approximately 20 minutes after consumption, reducing the calories available for the body to absorb. Patients can control this process through an endoscopically implanted tube that comes through the surface of the abdominal skin, where the opening is closed with a poker chip-sized valve (Skin-Port). Patients can dump “excess” food contents into a toilet. The implantation process is reversible and the device can be implanted or explanted with the patient under conscious sedation. Clinical experts commenting on this topic indicated they would be reluctant to offer this therapy because it could contribute to or exacerbate eating disorders. They saw no potential for high impact in terms of treating obesity. The device remains in trials in the United States; it received a Conformité Européene (CE) mark for marketing in Europe in December 2011. In light of experts’ comments, this topic is being archived in the horizon scanning system.

Antiobesity Device

Intragastric Dual Balloon (ReShape Duo) for Treatment of Obesity

- **Key Facts:** Gastric bypass and some other types of bariatric surgery are the only treatments that have been demonstrated to be effective for weight loss by patients who are morbidly obese and have not had success with conservative treatments (e.g., diet, exercise). However, some patients who are super-morbidly obese are ineligible for surgery because of surgical risks and complications related to their weight. The ReShape Duo® dual intragastric balloon device (ReShape Medical, Inc., San Clemente, CA) might offer a nonsurgical alternative to such patients. The manufacturer purports that, by occupying space in the stomach, the dual intragastric balloon causes patients to reach satiety with less food intake. A clinician inserts ReShape Duo into the patient’s stomach via an endoscope and guidewire. The uninflated balloons are advanced into the stomach with the guidewire and, once in the stomach, are inflated individually with equal volumes of saline. Device placement is a 15–30 minute outpatient procedure that requires only conscious sedation. The Reshape Duo is designed to be kept in the stomach for 6 months and then removed, using an endoscopic procedure similar to balloon placement. ReShape Duo is being investigated in a pivotal clinical trial of patients with BMIs between 30 and 40 kg/m². The company has indicated that it will submit premarket approval application to FDA in 2014. ReShape Duo has been CE marked since 2007 and, after some product revisions, was launched in the United Kingdom in March

2012. In the United Kingdom, ReShape Duo and its associated procedure reportedly cost £4,450, an equivalent to \$7,439 in June 2014.

- **Key Expert Comments:** Overall, experts thought that ReShape Duo has potential to fulfill a large unmet need for patients who are obese and have unsuccessfully tried lifestyle and pharmacotherapeutic approaches to weight loss or who are ineligible for bariatric surgery or both. Experts agreed on the potential of this intervention to improve patient health by promoting short-term weight loss. However, experts generally indicated a need for more trials to determine the safety and efficacy of ReShape Duo. Both patient and clinician acceptance has the potential to be high, experts commented, if the intervention proves to be safe and efficacious in the long term. Experts anticipate a minimal impact on health care delivery processes because required infrastructure is widely available. Experts were unsure about the potential of this intervention to affect cost of care, because of the lack of long-term results.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Antiobesity Drugs

Controlled-Release Phentermine-Topiramate (Qsymia)

- **Key Facts:** Phentermine-topiramate is a controlled-release formulation of two separate FDA-approved drugs; the drug combination acts on the central nervous system as an appetite suppressant. Phentermine is a central norepinephrine-releasing drug that was approved by FDA in 1959 as an appetite suppressant for short-term (3 months or less) obesity treatment at a dosage of 37.5 mg/day. Topiramate is a gamma aminobutyric acid agonist that FDA approved in 1996 for treating epilepsy at a dosage of approximately 400 mg/day, and it has been known to have weight loss as a side effect. Combining a low dose of each medication in a single treatment, phentermine/topiramate promotes weight loss while avoiding side effects potentially caused by high doses of either drug. FDA approved the drug on July 17, 2012, on the basis of two completed, phase III trials. The reported weight loss achieved on average was between 9% and 10% of total body weight. The recommended prescribing by the manufacturer includes an initial low-titration dosage and a mid-titration dosage: a 14-day starting daily dose of 3.75 mg phentermine and 23 mg topiramate and mid-titration (maintenance) daily dose of 7.5 mg phentermine and 46 mg topiramate for 30 days. The company has two introductory pricing programs to support diffusion that provide the initial 14-day dosage for free, reported to be a savings of \$65, and a 30-day pricing strategy for the recommended mid-titration dose of \$75, reported to represent a savings of \$85. Thus, without these programs, the reported cost after the 14-day introduction is about \$160 per month. The online U.S. pharmacy-drug pricing resource, GoodRx, lists pricing for 30-day supplies ranging from about \$164 to \$218 at various pharmacies, with most requiring the use of a coupon. Some health insurance companies and pharmacy benefit management companies have added the drug to their formularies requiring prior authorization and brand-level copayments and may limit the number of 30-day supplies covered. Coverage also depends on the insured individual's benefit level.
- **Key Expert Comments:** Overall, experts noted a significant need for pharmacological treatments for weight reduction, given the frequency of unsuccessful dietary and lifestyle modification programs. Experts generally indicated that both patients and clinicians would accept this drug because of its ease of administration. However, experts commented that acceptance could be limited by cost and safety concerns. Experts' comments during this

recent round of commenting indicated the potential impact to be lower than in earlier Potential High-Impact Intervention reports. Experts generally agreed on the potential of this intervention to improve patient health. However, they expressed concerns regarding long-term safety and efficacy.

- **Potential for High Impact:** Lower end of the high-impact-potential range

Liraglutide (Victoza)

- **Key Facts:** Liraglutide (Victoza) is a synthetic analog of the peptide hormone glucagon-like peptide-1 (GLP-1), which is recognized (Astrup et al., 2009) for its ability to suppress appetite and energy intake as well as delay gastric emptying and is therefore thought to induce a feeling of satiety. Liraglutide is engineered to have a substantially longer half-life than endogenous GLP-1 (13 hours, 1–2 minutes, respectively). Liraglutide is already approved to treat T2DM, and, given the paucity of effective obesity treatments, interest is high in liraglutide as a potential weight-loss treatment that acts independently of the patient’s diabetes status. The drug is already being used off-label for weight loss, according to a survey of primary care physicians published in January 2011. Liraglutide is under investigation for obesity treatment in a four-part, phase III clinical trial (SCALE). In clinical trials, the drug is being administered at a dosage of 3 mg daily in a 6 mg/mL, 3 mL FlexPen® for subcutaneous injection. The dosage used for T2DM is much lower (1.2 mg or 1.8 mg) than that proposed for obesity treatment (3 mg). As of June 2014, GoodRx, a U.S. based online aggregator of prescription drug prices reported prices ranging from about \$575 to \$612 for 1 carton (3 pens) of Victoza 18 mg/3 mL. A generic formulation is not available. If priced similarly to the diabetes indication, this would provide 18, 3 mg doses at a cost of about \$32 to \$34 per dose, the dose for which the manufacturer is seeking FDA approval.
- **Key Expert Comments:** Experts cited the need for safe and effective pharmacologic agents for treating obesity to be a significant unmet need. They noted the potential of this intervention to improve patient health by promoting weight loss and decreasing related comorbidities. Experts generally agreed that wide use of liraglutide could be limited by cost, gastrointestinal side effects, and long-term safety, which has yet to be established in this patient population. Some experts expressed concern over the need for patients to self-administer the drug using an injector pen; however, most experts agreed that patients would require minimal education. Still, the mode of administration could potentially deter patients from using liraglutide, most experts agreed. The cost of this intervention could be offset by the decrease in obesity-related complications, most experts noted, and they agreed that the prevalence of off-label liraglutide prescription indicates the potential for widespread adoption.
- **Potential for High Impact:** Moderate. Note: The other two antiobesity drugs in this chapter were deemed to have lower range of potential high impact, but experts commenting on this topic cited a greater potential for adoption by clinicians because of perceived widespread off-label use. They also cited greater potential for diffusion because of clinician and patient familiarity with liraglutide, because it has been available for treating T2DM.

Lorcaserin (Belviq)

- **Key Facts:** Lorcaserin selectively stimulates the 5-hydroxytryptamine type 2C (5-HT_{2C}) serotonin receptors in the brain, which are involved in controlling appetite and metabolism. FDA approved the drug on June 27, 2012, on the basis of three completed phase III trials. The approved indication is “as an adjunct to a reduced-calorie diet and increased physical

activity for chronic weight management in adult patients with an initial [BMI] of 30 kg/m² or greater (obese), or 27 kg/m² or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes).” The drug has been classified by the U.S. Drug Enforcement Administration as a Schedule IV drug; it became available for prescribing in June 2013. To aid diffusion, the company is offering special pricing programs in which patients can receive a free 15-day supply, for a reported savings of \$100 (50% off the first month). Patients are eligible for savings of \$75 per month if their health insurance copayment or out-of-pocket expense is greater than \$50. GoodRx, a U.S.-based, online aggregator of prescription-drug prices, lists pricing for 30-tablet supplies (10 mg/tablet) ranging from \$110 to \$116 at various pharmacies with most requiring the use of a coupon.

- **Key Expert Comments:** Experts generally agreed on the need for safe and effective pharmacological agents for treating obesity. Available clinical data indicated lorcaserin has potential to improve patient health, experts commented, but they noted that patients would need to be monitored for adverse effects. The drug has moderate potential for adoption by patients and clinicians alike, the experts generally agreed; however, some listed cost as a barrier to patient acceptance. Lorcaserin use is not expected to disrupt health care processes. Its use could reduce overall costs of treating obesity-related complications if it proves to be safe and efficacious in the long term, experts commented. They cited the importance of an ongoing cardiovascular outcomes trial to determine the true potential of this intervention.
- **Potential for High Impact:** Lower end of the high-impact-potential range. Experts’ comments during this recent round of expert commenting indicated the potential impact to be lower than in earlier Potential High-Impact Interventions reports.

Obesity Interventions

Antiobesity Device

Intragastric Dual Balloon (ReShape Duo)

Unmet need: Bariatric surgery is considered to be an effective intervention for treating obesity; however, the procedure is invasive with risks and side effects. Because of this, it is indicated only for morbidly obese patients (body mass index [BMI] of more than 40 kg/m²) or for obese patients with BMIs of 35–40 kg/m² who have related comorbidities. However, morbidly obese patients who are at high surgical risk (e.g. unstable angina, acute congestive heart failure) are typically precluded from such surgery. Therefore, minimally invasive treatments are needed that could enable patients who are super-obese to lose 5% to 10% of their excess body weight, which might also enable them to reduce surgical risk and become eligible for bariatric surgery.¹ The ReShape Duo[®] is a dual intragastric balloon implant being investigated for nonsurgical obesity treatment in patients with BMIs between 30 and 40 kg/m².

Intervention: The ReShape Duo is a dual intragastric balloon designed for nonsurgical obesity treatment. Weight loss with the Reshape Duo is intended to be achieved by reducing the stomach's capacity: the inflated dual balloon occupies space in the stomach, purportedly causing the patient to achieve satiety with less food intake.²

Placement of the Reshape Duo is a 15–30 minute outpatient procedure requiring only conscious sedation. The clinician delivers the dual intragastric balloons to the patient's stomach through the patient's mouth via an endoscope and guidewire. The uninflated balloons are advanced into the stomach with the guidewire; once in the stomach, the balloons are inflated individually with equal volumes of saline totaling 900 cc, or 450 cc for each balloon.^{2,3}

Compared to single intragastric balloons, which are inflated with 400–700 cc of saline, the dual-balloon design of Reshape Duo purportedly allows for a greater stomach volume to be occupied without overdistention.² The company states that the dual balloon is also designed to conform with the stomach's natural curvature and reduce the risk of balloon migration and obstruction that is seen with single intragastric balloons.²

The Reshape Duo is designed to be kept in the stomach for 6 months. After that time, clinicians remove the balloons using an endoscopic procedure similar to the balloon placement. During this procedure, a clinician places the endoscope in the patient's stomach while the patient is under conscious sedation. The endoscope is fitted with a "proprietary suction cap" to drain the saline from the balloons individually in a controlled manner. Once the balloons are drained, the clinician secures the deflated dual balloon's tip with a snare on the endoscope and removes the device through the patient's mouth.³

In a pivotal clinical trial, the ReShape Duo is being investigated in patients with BMIs of between 30 and 40 kg/m².⁴

Clinical trials: In 2011, a manufacturer's press release announced results from a phase I investigational clinical study that assessed the safety and effectiveness of ReShape Duo combined with lifestyle modification in patients with BMIs of 30–40 kg/m².⁵ The study randomly assigned 30 patients (26 women and 4 men) aged 26–59 years across three different sites to the treatment group (21 patients) or control group (9 patients) in a 2:1 ratio.⁶ Patients in the treatment group received ReShape Duo through endoscopic placement, and both groups underwent similar diet and exercise counseling. After 24 weeks, the device was removed from patients in the treatment group. In 2013, Ponce and colleagues reported that after 24 weeks, the mean excess weight loss in the treatment group was 31.8%±21.3% and in the control group was 18.3%±20.9% (p=0.1371).⁶ The authors reported that at 48 weeks, which was 24 weeks after device removal, patients treated with ReShape

Duo maintained 64% of their weight loss.⁶ In reporting on ReShape Duo's safety, the authors reported the following:⁶

No deaths, unanticipated adverse effects, early removals, balloon deflations, or balloon migrations occurred. In the [treatment group], 4 patients were readmitted for severe nausea, 1 had asymptomatic gastritis at balloon removal, and 1 patient experienced transient hypoxia during device removal.

Manufacturer and regulatory status: ReShape Duo is being developed by ReShape Medical, Inc. (San Clemente, CA). The device is being studied under investigational device exemption status from the U.S. Food and Drug Administration (FDA).² ReShape Medical sponsored a pivotal clinical trial (REDUCE) investigating ReShape Duo's safety and efficacy for weight loss.⁴ In February 2013, the company announced it had completed study enrollment within 6 months; enrollment included 326 patients over eight participating sites.⁵ In November 2013, the company announced that it would submit a premarket approval application to FDA in the second quarter of 2014 after meeting primary efficacy endpoints; however, detailed study results have not been released.⁷ ReShape Duo has been Conformité Européene (CE) marked since 2007 allowing marketing in Europe; after some product revisions, it was launched in the United Kingdom in March 2012.⁸

Diffusion: If ReShape Duo is approved for treating obesity, moderate diffusion is expected as an adjunct to lifestyle modifications. Another intragastric balloon (Garren-Edwards gastric bubble) was withdrawn from the U.S. market because of concerns about safety and efficacy, which might negatively affect how patients and clinicians view ReShape Duo.⁹ In 1987, the U.S. Centers for Medicare & Medicaid Services established a national coverage determination (NCD) for treating obesity using gastric balloons. The NCD indicated that "the use of the gastric balloon is not covered under Medicare, since the long term safety and efficacy of the device in the treatment of obesity has not been established."¹⁰

Because of this determination, intragastric balloons coming to the U.S. market might need to undergo a formal national coverage analysis to establish coverage under Medicare; after Medicare approval, other third-party payers often follow suit. ReShape Duo is expected to cost between \$6,500 and \$8,000, which might make it more appealing than surgical procedures for some patients.¹¹ However, diffusion is likely to be hampered if payers choose not to reimburse for its use.

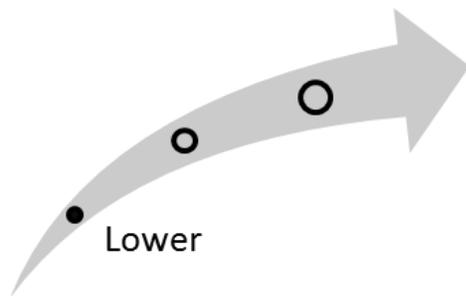
For patients with BMIs between 30 and 40 kg/m², ReShape Duo could compete with available pharmacotherapies for obesity.¹² Weight-loss surgery is indicated for patients only after other therapies have failed or in cases in which patients are experiencing complications related to their obesity. However, these patients typically must have a BMI of 40 kg/m² or more or obesity-related comorbidities with a BMI of 35 kg/m² or more to be recommended for surgery.¹³ Therefore, ReShape Duo will likely compete with these surgeries only in patients with BMIs of 35 kg/m² and obesity-related comorbidities. ReShape Duo also could complement weight-loss surgeries in some patients. Bariatric surgery in patients with BMIs of 50 kg/m² or more can present high surgical risk and technical challenges, and these patients may benefit from preoperative weight loss.¹⁴ If the indications for ReShape Duo include patients with BMIs this high, the device could serve as a noninvasive means for weight loss before bariatric surgery.

ReShape Duo may also compete with other minimally invasive endoluminal treatments that are in development, such as the EndoBarrier[®] endoluminal sleeve. Additionally, intragastric balloons that are approved in other nations may compete with the ReShape Duo if they receive approval in the United States.¹⁵

Clinical Pathway at Point of This Intervention

The National Institutes of Health’s Panel on Weight Loss recommended that patients who are morbidly obese lose 10% of their excess body weight before bariatric surgery to help reduce surgical risks and postoperative complications.¹⁶ However, available preoperative weight loss methods have demonstrated suboptimal success in patients who are morbidly obese. Losing weight through diet and exercise alone has often not been successful in this patient population. Therefore, physicians may also recommend weight-loss medication, and several options are now available.¹⁶ Patients and clinicians are also expected to embrace the availability of other nonsurgical options for treating obesity and/or promoting preoperative weight loss in patients who have not lost weight using conservative treatment options.

Figure 1. Overall high-impact potential: intragastric dual balloon (ReShape Duo) for treatment of obesity



Overall, experts commenting on this intervention agreed that ReShape Duo aims to fulfill a large unmet need for treatments for patients who are obese, have exhausted other weight-loss methods (e.g., medical therapy, behavior therapy), and are ineligible for bariatric surgery. However, experts agreed that available data are insufficient to determine whether ReShape Duo is safe and effective. One expert with a research perspective noted the success of behavioral therapy programs compared with device implantation, which dampened her expectations for the intervention. A clinical expert also highlighted the significant gap between patients who are eligible for bariatric surgery, but choose to decline due to safety concerns. This expert also noted that larger and long-term studies are needed to evaluate the safety and efficacy of this intervention. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems and administration backgrounds, provided perspectives on this topic.¹⁷⁻²² We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Treating obesity remains a major health care challenge, the experts agreed, noting that few effective interventions are available for patients with the condition. ReShape Duo has potential to improve patient health, the experts generally agreed. However, some experts expressed concern regarding long-term efficacy and the potential for patients to regain weight after device removal. One clinical expert commented, “Given the duration of implantation and likelihood of weight regain, any short term gains will likely be neutralized after the device is removed.”²² Most experts agreed that this intervention could provide a nonsurgical option for patients who do not wish to undergo bariatric surgery. Alternatively, it could be used as an initial weight-loss intervention for patients not yet qualified for surgery, some experts commented. However, some experts noted that available data showed no statistically significant improvement in

outcomes for patients receiving gastric balloons compared with patients who underwent behavioral therapy alone. One expert with a research perspective commented, “Results from the only available study are not convincing; average weight loss was 30% for those with the balloons and 20% for those with behavioral therapy.”²³

Acceptance and adoption: Clinicians and patients are likely to accept the ReShape Duo if it demonstrates safety and efficacy in clinical trials, the experts thought. Most experts agreed that clinicians and patients would be willing to try an outpatient procedure that is less invasive than bariatric surgery. Expanding on this, one expert with a clinical perspective commented, “Clinicians are likely to accept this treatment because current medical interventions are not effective, and most patients do not want bariatric surgery.”²⁰ This expert also noted that patients would accept this intervention for similar reasons, but mentioned long-term safety to be a concern. Overall, experts anticipated moderate acceptance due to the lack of effective medical interventions for treating patients with obesity.

Diffusion could largely depend on the level of insurance coverage, some experts opined. For instance, one expert with a clinical perspective commented, “It has the potential to be another tool in the toolbox. If not covered by insurance, uptake will be minimal. If covered by insurance, uptake will be greater....”²²

Health care delivery infrastructure and patient management: Use of this intervention is likely to have a minimal impact on health care delivery and infrastructure, the experts agreed. Most experts commented that device implantation can be performed in existing endoscopy or outpatient surgical suites. One expert with a clinical perspective commented, “This [balloon implantation] can be done routinely by gastroenterologists or surgeons in clinics, healthcare centers and hospitals.”²⁰ This expert also commented that infrastructure may need to be expanded because of the large number of patients eligible to be treated with this intervention.

The potential effect of this intervention on patient management is not clear, thought the experts. Minor disruption might occur because of the need for monitoring safety and the eventual device removal. One research expert thought moderate disruption could occur to current patient management¹⁸ and another research expert commented, “The balloon is intended to be temporary, would require a placement and removal procedure, and if a significant number of patients sought treatment, would change the way obese/overweight patients are managed.”²¹

Health disparities: Patient access to this intervention could be limited in people lacking third-party coverage for obesity interventions and unable to afford the device and procedure cost, most experts agreed. For example, one expert with a research perspective commented, “With the cost shown in other countries to be over 7,000 dollars it will create health disparities especially for people with no insurance or no coverage with Medicare services.”¹⁷ But another research expert opined that this intervention would have a minor impact on health disparities if used in place of pharmacotherapy. This expert anticipated that underserved populations would experience similar barriers to care compared with available treatment options.¹⁸

Antiobesity Drugs

Controlled-Release Phentermine-Topiramate (Qsymia)

Unmet need: The increasing prevalence of overweight and obese populations in the United States has generated a need for novel pharmacologic therapies aimed at weight reduction and maintenance when diet and exercise have failed. However, concerns over potential adverse events associated with antiobesity pharmacotherapies significantly elevated the regulatory bar for gaining approval—specifically regarding preapproval safety data and postmarket safety evaluation—set forth by FDA.^{24,25} Until mid-2012, orlistat, a pancreatic lipase inhibitor that blocks about one-third of daily fat absorption, was the only FDA-approved antiobesity drug available for long-term use in the United States and is still the only one approved for adolescent use. Since then, another drug, lorcaserin, has been approved. Given the limited pharmacologic treatment options for obesity, additional pharmaceuticals intended to treat the condition are needed. Phentermine-topiramate (Qsymia[®], formerly Qnexa[®]) provides another option for obese patients seeking medical therapy for weight loss.

Intervention: Phentermine-topiramate is a controlled-release formulation of two separate FDA-approved drugs. This drug combination acts on the central nervous system as an appetite suppressant.²⁶ Both of the active substances are appetite suppressants, but each works by a different mechanism.²⁷ Phentermine is a central norepinephrine-releasing drug that FDA approved in 1959 as an appetite suppressant for short-term (3 months or less) treatment of obesity at a dosage of 37.5 mg daily.^{28,29} Topiramate is a gamma aminobutyric acid agonist that FDA approved in 1996 for treating epilepsy at a dosage of approximately 400 mg/day and has been known to have weight loss as a side effect.^{28,29} Topiramate is believed to increase the body's energy use and reduce appetite, but the exact mechanism is not known.²⁷ Topiramate was studied as a monotherapy for treating obesity; however, dose-dependent neuropsychiatric adverse events precluded further study.²⁸ Combining a low dose of each medication in a single treatment, phentermine/topiramate promotes weight loss while avoiding side effects potentially caused by high doses of either drug.³⁰

The new combination drug is administered daily as an oral medication.^{26,31} Commercially, phentermine plus topiramate is available at the four following dose levels:³²

- Phentermine 3.75 mg plus topiramate 23 mg
- Phentermine 7.5 mg plus topiramate 46 mg
- Phentermine 11.25 mg plus topiramate 69 mg
- Phentermine 15 mg plus topiramate 92 mg

Clinical trials: In 2013, Davidson and colleagues announced results of a 56-week, randomized, double-blind, placebo-controlled, multicenter phase III trial (CONQUER) that evaluated the changes in cardiovascular risk factors in patients with dyslipidemia and/or hypertension.³¹ Patients with BMIs of between 27 and 45 kg/m² were randomly assigned in a 2:1:2 ratio to receive once-daily treatment with placebo, 7.5 mg phentermine (PHEN)/46 mg topiramate extended-release (TPM ER), or 15 mg PHEN/92 mg TPM ER. All patients received lifestyle modification counseling. The authors of the study reported the following:³¹

PHEN/TPM ER produced significantly greater dose-related mean percentage weight loss compared with placebo in the subgroups of participants with dyslipidemia and those with hypertension. Regardless of treatment group assignment, participants with dyslipidemia who lost $\geq 5\%$ of their baseline weight experienced significantly greater reductions in triglycerides (-14.5% to -39.8%), and in non-high-density lipoprotein cholesterol (-9.4% to -14.8%) than those losing $< 5\%$ of their weight ($p < 0.05$). Similarly, participants with hypertension at baseline

showed reduced systolic blood pressure by -7.5 to -11.8 mm Hg ($p < 0.001$ vs those with $< 5\%$ weight loss). In conclusion, the dose-related weight loss induced by PHEN/TPM ER treatment was accompanied by significant improvements in cardiovascular disease risk factors in participants who had dyslipidemia or hypertension at baseline, suggesting that facilitating weight loss by augmenting lifestyle changes with pharmacotherapies may decrease the risk for cardiovascular disease in obese and overweight patients with co-morbidities.

In 2011, Kushner and colleagues announced results from a phase III clinical trial (SEQUEL) evaluating the safety and efficacy of phentermine-topiramate in 675 patients with BMIs of between 27 and 45 kg/m² and two or more obesity-associated comorbidities. This study is an extension of the CONQUER trial. Authors reported the following:^{33,34}

Patients treated with [Qsymia] had significant, sustained weight loss compared to those in the placebo group over two years. Average weight loss at week 108 was -9.3% and -10.5%, respectively, for the mid- and top-dose as compared to -1.8% for the placebo group (least-squares mean ITT-LOCF [intention to treat—last observation carried forward]). [Qsymia] patients had improved cardiovascular and metabolic risk factors and a decrease in the need for associated medications in comparison with the placebo group. Placebo patients had a three times greater likelihood to progress to type 2 diabetes mellitus (T2DM) compared to subjects receiving top-dose [Qsymia] and a two times greater likelihood than patients on mid-dose [Qsymia].

In 2011, Allison and colleagues had announced results from a 56-week clinical trial (EQUIP) evaluating the safety and efficacy of phentermine-topiramate in 1,267 patients who were morbidly obese. The authors reported the following:³⁵

Least-squares (LS) mean weight loss for phentermine-topiramate patients who completed the EQUIP study was 14.4% and 6.7% with top-dose phentermine-topiramate and low-dose phentermine-topiramate, respectively, compared to 2.1% in the placebo group ($p < 0.0001$); in the ITT-LOCF analysis, LS mean percent weight loss at week 56 was 10.0% and 5.1% for the top and low dose, respectively, as compared to 1.6% for the placebo group ($p < 0.0001$).³⁶

The authors also reported that among patients who completed top-dose treatment of phentermine-topiramate, the following losses were observed:³⁶

- 83.5% lost 5% or more of their baseline weight
- 67.7% lost 10% or more of their baseline weight
- 48.1% lost 15% or more of their baseline weight

Common adverse events reported in this study were paresthesia (tingling), dysgeusia (taste alteration), and xerostomia (dry mouth).³⁶

Manufacturer and regulatory status: Vivus, Inc. (Mountain View, CA), makes phentermine-topiramate. FDA approved the drug on July 17, 2012, basing its decision on two completed phase III trials. The approved indication is as “an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 or greater (obese), or 27 or greater (overweight) in the presence of at least one weight-related comorbidity, such as hypertension, type 2 diabetes mellitus or high cholesterol (dyslipidemia).”³⁷

FDA required a Risk Evaluation and Mitigation Strategy (REMS) for phentermine-topiramate approval, informing prescribers and “female patients of reproductive potential” of potential risks associated with the drug, including fetal orofacial cleft development during the first trimester of pregnancy, and citing the need for pregnancy preventive practices for females of reproductive

potential and immediate drug discontinuation in event of pregnancy.³⁷ Additionally, the “REMS program includes a Medication Guide, Healthcare Provider training, distribution through certified pharmacies, implementation system and a time table for assessments.”³⁷ FDA has required the manufacturer to conduct 10 postmarketing studies, including a long-term cardiovascular outcomes trial to assess the effect of phentermine-topiramate on the risk of patients developing major adverse cardiac events, such as heart attack and stroke.³⁸

Diffusion: On September 17, 2012, this drug became commercially available in the United States. The company initially had a limited distribution system, posing a major, initial barrier to diffusion.^{39,40} Patients’ out-of-pocket costs for phentermine-topiramate initially ranged from \$120 to \$185 per month,^{32,41} raising concerns because of lack of coverage by third-party payers and high out-of-pocket costs for patients.⁴⁰ However, in December 2012, the drug was added to a number of health plan formularies; coverage depends on the insured’s benefit level. The prescription typically requires prior authorization, and some insurers limit the number of 30-day prescriptions offered. With copayments and manufacturer incentive programs, the expected average out-of-pocket cost to a patient is about \$50–\$60 per month.⁴² The company’s two introductory pricing programs provide the initial 14-day dosage for free, reported to be a savings of \$65, and a 30-day pricing strategy for the recommended mid-titration dose of \$75, reported to represent a savings of \$85. Thus, without these programs and without insurance, the reported cost to a patient after the initial 14-day treatment is about \$160 per month. As of June 2014, a U.S.-based, online aggregator of prescription-drug prices, GoodRx, listed pricing for 30-day supplies ranging from nearly \$170 to \$204 at various pharmacies.⁴³

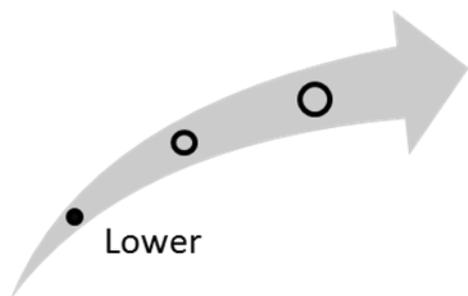
In April 2013, FDA approved the REMS modification for phentermine-topiramate, allowing access to the drug through certified retail pharmacies, rather than offering it exclusively through certified mail-order pharmacies. Also in April 2013, phentermine-topiramate was added to the Medco Health Solutions national formulary, which could have wider implications for patients’ access.⁴⁴ In July 2013, the manufacturer announced nationwide availability in about 8,000 retail pharmacies.⁴⁵ Continued reimbursement progress is anticipated for phentermine-topiramate.⁴⁴ Diffusion could also be hastened by physicians’ ability to prescribe phentermine and topiramate separately and off label to significantly mitigate patient out-of-pocket expenses.

Phentermine-topiramate’s main anticipated market competitor is lorcaserin (Belviq®), a 5-hydroxytryptamine type 2C (5-HT_{2C}) receptor agonist that selectively stimulates the 5-HT_{2C} serotonin receptors in the brain, which are involved in controlling appetite and metabolism.⁴⁶ According to the manufacturer, the drug is available nationwide in about 8,000 retail pharmacies.⁴⁵

Clinical Pathway at Point of This Intervention

Individuals who are obese are screened for other comorbid conditions, such as diabetes and hypothyroidism, that may influence treatment decisions and outcomes.⁴⁷ Medication use must also be assessed because some drugs—such as oral contraceptives, certain antipsychotics, and antidiabetes medicines—may interfere with weight loss or contribute to excessive weight gain.⁴⁸ Patients with BMIs of 30 kg/m² or more or BMIs of 25 kg/m² or more with comorbid obesity-related risk factors or diseases (e.g., hypertension, dyslipidemia, coronary artery disease, T2DM, sleep apnea) may be candidates for drug therapy.⁴⁸ Drug therapy is typically offered in conjunction with a program of physical activity, nutrition counseling, and behavior management. Controlled-release phentermine-topiramate provides an additional nonsurgical option to orlistat, lorcaserin, or off-label liraglutide for overweight patients with BMIs of between 30 and 40 kg/m².

Figure 2. Overall high-impact potential: phentermine-topiramate (Qsymia) for treatment of obesity



Expert comments during this recent round of expert commenting indicated the potential impact to be lower than in earlier Potential High-Impact Interventions reports. Experts commenting on this drug combination agreed on a significant need for pharmacological treatments aimed at weight reduction, citing the lack of effective therapies. Both patients and clinicians would accept this drug because of its ease of administration, the experts generally agreed. However, they commented that acceptance could be limited by safety concerns. Further, physicians may be reluctant to prescribe this drug based on the history of weight loss medications, as a clinical expert noted. Experts also determined cost and lack of insurance coverage to be potential barriers to adoption for patients. Although experts commenting on this intervention agreed on a moderate potential to improve patient health, many expressed concerns regarding long-term safety and efficacy. Overall, experts considered the drug to be an additional option for treating obesity when diet and exercise are unsuccessful. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on phentermine-topiramate.⁴⁹⁻⁵⁴ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Experts generally agreed that a significant unmet need exists for pharmacological treatments aimed at weight reduction. Although dietary and lifestyle changes are recommended for weight loss, they are often unsuccessful. “Patients are often looking for an easier solution to their obesity than lifestyle modification,” one expert with a research perspective commented. “Taking a pill is often an easier alternative, and for some may be more effective.”⁵³

Most experts agreed on a moderate potential for this intervention to affect patient health outcomes. They cited the weight loss of 5% to 15% from baseline as clinically significant. “Qsymia treatment produces a clinically significant weight loss associated with improvement in glucose and lipids,” commented one expert with a clinical perspective.⁵¹ However, some experts questioned the drug’s long-term safety and efficacy. As one expert representing a research perspective noted, “Serious potential adverse events (cardiovascular) have been implicated with long-term use and warrant additional investigation in clinical trials.”⁵² Experts noted that this intervention has the potential to achieve a greater weight loss effect than other antiobesity drugs.

Acceptance and adoption: Phentermine-topiramate has high potential for patient and clinician acceptance, the experts generally agreed, citing ease of administration and patient compliance with oral pharmacotherapy. One expert with a research perspective opined that because it is “a convenient, oral drug option that available data suggests is more effective at achieving weight loss compared to available competitor lorcaserin, I foresee many clinicians prescribing Qsymia for their eligible patients.”⁵² But experts also noted a potential barrier to acceptance: the uncertainty about

long-term adverse events. One expert representing a research perspective commented, “With a large percentage of population being obese, this drug has the potential to be widely prescribed, however the acceptance may be based on risk factors and adverse effects of the drugs.”⁴⁹

Antiobesity pharmacotherapy is typically not covered by third-party payers, several experts noted, and they thought that patients would bear the costs out of pocket. One expert with a research perspective commented, “With a majority of insurance companies having no policies on the drug and the fact that Medicare and Medicaid has it up to their discretion if a patient has a comorbidity, it may be an expensive treatment to have without insurance, especially for people who may be of low economic status.”⁴⁹ However, recent positive coverage changes may indicate that payers are looking at antiobesity drugs differently now because of the known obesity-related comorbidities. Reducing or eliminating long-term complications from obesity might ultimately reduce per-patient costs over time, most experts agreed. As one expert representing a clinical perspective opined, “Initial healthcare cost is high because Qsymia is expensive and needs to be taken for long periods. However, the long-term healthcare cost may be reduced if this drug improves diabetes, hyperlipidemia, hypertension and other obesity-related diseases.”⁵¹

Health care delivery infrastructure and patient management: As an oral agent, this drug would not significantly disrupt the health care delivery infrastructure, a majority of experts agreed. However, some experts highlighted the need for clinicians to educate and monitor patients. For instance, one expert representing a clinical perspective commented that adding lifestyle modification counseling by prescribing physicians could disrupt the way patients are managed.⁵⁴ Further, this intervention could disrupt the health care model in two opposing ways, noted an expert with a research perspective.⁵² On one hand, phentermine-topiramate use could reduce the need for bariatric surgery in some patients, this expert opined. On the other hand, this expert noted, it might also be used to make severely obese patients eligible for surgery (after using it for presurgery weight loss) who were not previously eligible.

Health disparities: Health disparities related to obesity could increase, the experts generally agreed, saying that costs associated with antiobesity pharmacotherapies and many third-party payers’ unwillingness to cover these drugs might serve as barriers to access for uninsured and low-income patient populations. One expert representing a clinical perspective commented, “Obesity differentially impacts individuals from lower socioeconomic groups and who may be unable or unwilling to pay for the medication out of pocket. Thus, health insurance plans for these individuals would need to provide substantial coverage for the medication in order to impact health disparities in an appreciable way.”⁵⁴

Liraglutide (Victoza) for Treatment of Obesity

Unmet need: The increasing prevalence of overweight and obese populations in the United States has generated a need for novel pharmacologic therapies aimed at weight reduction and maintenance when diet and exercise have failed. However, concerns over potential adverse events associated with antiobesity pharmacotherapies significantly elevated the regulatory bar for gaining approval—specifically regarding preapproval safety data and postmarket safety evaluation—set forth by FDA.^{24,25} Until mid-2012, orlistat, a pancreatic lipase inhibitor that blocks about one-third of daily fat absorption, was the only FDA-approved antiobesity drug available for long-term use in the United States and is still the only one approved for adolescent use. Since then, two other drugs, phentermine/topiramate (Qsymia) and lorcaserin (Belviq), have been FDA approved. Liraglutide (Victoza[®]), which has been submitted to FDA for marketing approval, would provide another option for patients who are obese and seeking medical therapy for weight loss.

Intervention: Liraglutide is a synthetic analog of the peptide hormone glucagon-like peptide-1 (GLP-1) that has been shown to suppress appetite and energy intake and delay gastric emptying, which may induce a feeling of satiety.⁵⁵ The drug is FDA approved for managing blood glucose levels in patients with T2DM.⁵⁶ GLP-1 is a naturally occurring incretin hormone that stimulates insulin production in the presence of hyperglycemia and blocks the effects of glucagon, a hormone produced in the pancreas that signals the liver to release stored sugar into the bloodstream.⁵⁷

Endogenous human GLP-1 has a short half-life (1–2 minutes); however, liraglutide has been modified to allow binding to serum albumin, which increases its half-life to about 13 hours. It has been demonstrated to help blood glucose control by stimulating insulin release and lowering glucagon secretion in response to high glucose levels.⁵⁵

Liraglutide is administered once daily via subcutaneous injection using an automatic injection pen. In clinical trials, liraglutide is being self-administered in daily doses ranging from 1.2 to 3.0 mg.⁵⁵ In practice, given that many patients with diabetes are also obese, the drug fulfills a double role of managing both diabetes and obesity. Nonetheless, the manufacturer is pursuing a labeled indication for treating overweight and obesity.

Clinical trials: Liraglutide's manufacturer is investigating the drug in a four-part, phase III randomized controlled trial, SCALE[™] (Satiety and Clinical Adiposity-Liraglutide Evidence in Non-diabetic and Diabetic people).⁵⁶ The trial includes more than 5,000 patients who are either overweight (BMIs of 27 kg/m² or more) with comorbidities (e.g., hypertension, dyslipidemia, T2DM) or obese (BMIs of 30 kg/m² or more). In the first SCALE trial (SCALE[™] Maintenance) 422 patients were pretreated with a 4- to 12-week, low-calorie diet, then randomly assigned to receive either liraglutide 3 mg daily administered in a 6 mg/mL, 3 mL FlexPen[®] for subcutaneous injection or placebo 3 mL daily FlexPen for subcutaneous injection. Authors reported the following:⁵⁸

Mean run-in weight loss for all individuals who were randomised was 6.0% (6.3 kg). After 56 weeks of treatment, liraglutide provided statistically significant improvements in all measures of weight loss change from run-in compared to placebo treatment... (p<0.0001 in all analyses). During treatment, net weight changes post-run-in were -6.1% vs 0.1% (-5.7 kg vs +0.2 kg) for liraglutide vs placebo, respectively. Significantly more liraglutide vs placebo recipients maintained run-in weight loss and lost additional run-in weight. More than twice as many participants on liraglutide lost >5% additional run-in weight compared to those on placebo. Completion rates, serious AEs [adverse events] and withdrawals due to AEs were similar for each group. More nausea and vomiting were reported during liraglutide vs placebo treatments, occurring mainly during dose-escalation;

64% of liraglutide nausea cases were mild, and most cases declined in frequency by 4-6 weeks. Psychiatric AEs were reported by 11% and 12% of subjects in each arm, respectively.

The second trial of the series (SCALE™ Diabetes) was a double-blind study of 846 overweight or obese patients with T2DM who were randomly assigned in a 2:1:1 ratio to receive 3 mg liraglutide, 1.8 mg liraglutide, or placebo. After 56 weeks, patients discontinued treatment and were observed for an additional 12 weeks.⁵⁶ A company press release reported the following results regarding weight-loss in the patient population with mean baseline weight of about 106 kg and BMI of 37 kg/m²:⁵⁶

The weight loss for people treated with liraglutide 3 mg and liraglutide 1.8 mg after 56 weeks were 6% and 5%, respectively compared to a 2% weight loss for people treated with placebo. The proportion of people achieving a weight loss of at least 5% or 10% was 50% and 22% for liraglutide 3 mg, 35% and 13% for liraglutide 1.8 mg, and 13% and 4% for placebo treatment. All differences for both doses of liraglutide were statistically significantly different from placebo and the trial met all three co-primary endpoints. During the 12-week follow-up period after treatment discontinuation, people in both liraglutide treatment groups experienced a moderate weight regain.... Liraglutide was generally well tolerated and the 56-week completion rate was 77%, 78% and 66% for liraglutide 3 mg, liraglutide 1.8 mg and placebo, respectively. Withdrawals due to adverse events were below 10% in all treatment groups. In line with previous liraglutide trials, the most common adverse events were related to the gastrointestinal system and diminished over time. No other apparent differences between the treatment groups were observed with respect to adverse events and standard safety parameters.

The third trial (SCALE™ Obesity and Prediabetes) was a 56-week, double-blind trial evaluating liraglutide's potential to induce and maintain weight loss in nondiabetic patients. Investigators randomly assigned 3,731 patients who were overweight or obese (mean baseline weight of 106 kg and BMI of 38 kg/m²) in a 2:1 ratio to receive treatment with 3 mg liraglutide daily or placebo, in combination with diet and exercise.⁵⁹ A company press release reported the following:⁵⁹

The average weight loss for people treated with liraglutide 3 mg at 56 weeks was 8.0% compared to 2.6% for people treated with placebo. The proportion of people achieving a weight loss of at least 5% was 64% for liraglutide 3 mg and 27% for placebo. The proportion of people achieving a weight loss of at least 10% was 33% for liraglutide 3 mg and 10% for placebo treatment. All differences between liraglutide and placebo were statistically significantly different and the trial met all three co-primary endpoints.

Of all people participating in the trial, 61% had prediabetes at randomisation. At 56 weeks, 69% of the prediabetes subgroup treated with liraglutide 3 mg no longer showed signs of prediabetes, compared to 33% for the placebo-treated group. Of the 39% of the people without prediabetes at randomisation, 7% of the liraglutide 3 mg treated people developed prediabetes, compared to 21% of the people in the placebo group. Both differences between liraglutide 3 mg and placebo were statistically significant...liraglutide was generally well tolerated. The 56-week completion rate was 72% and 64% for liraglutide 3 mg and placebo, respectively. Withdrawals due to adverse events were below 10% in both treatment groups. The most common adverse events were related to the gastrointestinal system and they diminished over time.

The fourth SCALE trial (SCALE™ Sleep apnea) (n=340) is investigating the safety and efficacy of once-daily 3 mg liraglutide in combination with diet and exercise for reducing the severity of obstructive sleep apnea.⁵⁹

Manufacturer and regulatory status: Liraglutide is an FDA-approved treatment for managing blood glucose levels in patients with T2DM.⁵⁶ According to the manufacturer, Novo Nordisk a/s (Bagsvaerd, Denmark), as of December 2013, liraglutide “is not approved for weight management and should not be prescribed for its treatment;” however, results from a 2011 survey (discussed below) suggest widespread off-label use of the drug for treating obesity.^{56,60} The company expected to complete its pivotal SCALE trial in the third quarter of 2013 and to submit liraglutide (3 mg daily dose) for regulatory review as an obesity treatment in the United States and European Union “around the turn of the year.”⁵⁹ In December 2013, the manufacturer announced that it had submitted liraglutide (3 mg dose) for regulatory review as an obesity treatment in the United States and European Union.⁶¹

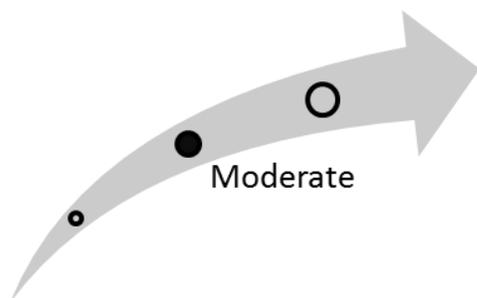
Diffusion: A survey of primary care physicians published in January 2011 suggests that liraglutide and a second GLP-1 analog approved to treat T2DM, exenatide (Byetta®), are already being used off-label to treat obesity. About one-third of surveyed primary care physicians listed one of these GLP-1 analogs as the obesity drug they perceive as being most efficacious.⁶⁰ Therefore, although liraglutide is not marketed as an antiobesity treatment, this survey suggests widespread off-label use for such treatment.⁶⁰ The dosage currently approved for diabetes is much lower than that intended for obesity treatment: liraglutide is currently approved and marketed at doses of 1.2 and 1.8 mg once-daily in the United States, as well as 0.9 mg in Japan. As of June 2014, GoodRx, an online aggregator of prescription drug prices, reported prices ranging from about \$575 to \$612 for one 3-pen carton of Victoza 18mg/3mL. If pricing is similar for the obesity indication, such a carton would provide 18 doses at the 3 mg dose (about \$32 to \$34 per dose) for which the manufacturer is seeking FDA approval.

Most third-party payers do not provide coverage for antiobesity medications, and those that do, typically require that a patient have a comorbid condition (e.g., hypertension, T2DM). For liraglutide, at least one third-party payer (Aetna) considers weight-loss pharmacotherapy medically necessary in patients being treated in clinical trials.⁶² If liraglutide’s efficacy is demonstrated to rival or exceed that of available antiobesity drugs, third-party payers would probably reimburse its use in the appropriate patient populations. Head-to-head comparative controlled trials are needed to determine which antiobesity medications work best.

Clinical Pathway at Point of This Intervention

Individuals who are obese are screened for other comorbid conditions, such as diabetes and hypothyroidism, that may influence treatment decisions and outcomes.⁴⁷ Medication use must also be assessed because some drugs—such as oral contraceptives, certain antipsychotics, and antidiabetes medicines—may interfere with weight loss or contribute to excessive weight gain.⁴⁸ Patients with BMIs of 30 kg/m² or more or BMIs of 25 kg/m² or more with comorbid obesity-related risk factors or diseases (e.g., hypertension, dyslipidemia, coronary artery disease, T2DM, sleep apnea) may be candidates for drug therapy.⁴⁸ Drug therapy is typically offered in conjunction with a program of physical activity, nutrition counseling, and behavior management. Liraglutide would represent a novel mechanism of action that provides an additional nonsurgical option to orlistat, phentermine-topiramate, or lorcaserin for overweight and obese patients.

Figure 3. Overall high-impact potential: liraglutide (Victoza) for treatment of obesity



Overall, experts commenting on this drug generally agreed that liraglutide has potential as a pharmacological therapy for treating obesity. Most experts noted that other pharmacotherapies for treating obesity are available, but a significant need for safe and effective treatment exists. Liraglutide has the potential to improve patient health outcomes, some experts commented, citing fewer adverse events compared with available therapies. One research expert considered liraglutide to have a great potential to fulfill dual needs in treating diabetes and obesity. Some experts expressed concern about the long-term safety of this intervention, citing the history of previously discontinued antiobesity drugs, but most experts anticipated widespread acceptance of this intervention by patients and clinicians alike, citing well documented off-label use of the drug. Some experts noted daily self-injection and gastrointestinal side effects to be potential deterrents to patients. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range. Note: The other two antiobesity drugs in this chapter were deemed to have lower range of potential high impact, but experts commenting on this topic cited a greater potential for adoption by clinicians because of perceived widespread off-label use. They also cited greater potential for diffusion because of clinician and patient familiarity with liraglutide, because it has been available for treating T2DM.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on liraglutide.⁶³⁻⁶⁹ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: An important need exists for nonsurgical weight-loss options with favorable safety profiles, the experts generally agreed. This intervention has the potential to improve patient health outcomes by promoting weight loss and reducing obesity-related conditions, such as diabetes mellitus, most experts commented. For instance, one expert representing a clinical perspective commented, “The weight loss seen with liraglutide at 3 mg daily appears to be at least 5% which should improve some obesity related comorbidities. The weight loss noted in the trials is similar to medications currently approved by the FDA.”⁶³ But several experts expressed concern regarding gastrointestinal side effects and listed a need for long-term studies to evaluate safety. And the durability of the drug’s effects was questioned by one expert representing a research perspective, who commented, “Short term improvements are promising however it is unclear if these improvements will persist long term.”⁶⁷ Multiple experts commented that liraglutide is already widely used off label to treat obesity, which diminishes the unmet need. Although other pharmacotherapies are available for treating obesity, experts cited a significant unmet need for new treatments. One clinical expert opined, “Obesity causes numerous morbid conditions and increases mortality however, few durable, effective, pharmacologic options are available. Victoza presents a potential pharmacologic option for treatment of this common disease.”⁶⁸

Acceptance and adoption: Liraglutide as a weight-loss option would be well-accepted by both patients and clinicians, the experts generally agreed. One expert representing a research perspective commented, “Based on the off-label use numbers, there is a good chance that the drug will be widely adopted by physicians.”⁶⁴ Another research expert expressed optimism about the potential for a nonsurgical treatment for obesity, but cited the daily requirements of self-injection to be a deterrent to patient acceptance.⁶⁵ Other notable barriers to wide acceptance of liraglutide listed by experts were cost and the potential for more gastrointestinal side effects. Several experts commented that patients would require initial training on how to properly self-inject the drug, but they did not anticipate this issue to be a barrier to acceptance.

Health care delivery infrastructure and patient management: Only a minor disruption to health care delivery infrastructure would be seen with liraglutide use, the experts generally agreed. Several experts listed patient education and training to have a potentially minor impact. For instance, an expert with a research perspective commented, “This medication is a self-administered injection that is prescribed by either a PCP [primary care physician] or another clinician. Other than initial training on how to use the injection pen, there is no reason to anticipate disruption.”⁷⁰

Similarly, patient health management would not undergo a major disruption, the experts thought. One expert representing a health administration perspective commented that patients should be counseled regarding dietary and lifestyle changes when using this intervention.⁶⁷

Health disparities: Health disparities could increase because the cost of this intervention and its lack of insurance coverage might serve as barriers to access for uninsured and low-income patient populations, the experts generally agreed. Along this line of reasoning, one expert representing a research perspective opined, “Since anti-obesity drugs are not typically covered by third-party payers (except for specific patient populations with comorbidities), patients will typically have to bear the costs of the drug. Thus patients with lower economic status may not have access to the drug.”⁶⁴

Lorcaserin (Belviq) for Treatment of Obesity

Unmet need: The increasing prevalence of overweight and obese populations in the United States has generated a call for novel pharmacologic therapies aimed at weight reduction and maintenance when diet and exercise have failed. However, concerns over potential adverse events associated with antiobesity pharmacotherapies significantly increased the regulatory bar for gaining approval—specifically regarding preapproval safety data and postmarket safety evaluation—set forth by FDA. Until recently, orlistat was the only FDA-approved antiobesity drug available for long-term use in the United States and is still the only one approved for adolescent use. Since then, another drug, phentermine/topiramate, has been approved. Thus, other medications with fewer side effects are desired by patients and their physicians. Lorcaserin (Belviq), also approved by FDA in 2012, offers another treatment option.⁷¹

Intervention: Lorcaserin is an oral therapy intended for use in conjunction with diet, exercise, and behavior modifications in patients who are overweight or obese. Lorcaserin is a serotonin receptor agonist (activator) that selectively stimulates 5-HT_{2C} receptors in the brain. These receptors are involved in controlling appetite and metabolism.⁴⁶ Although targeting 5-HT_{2C} receptors has been a promising weight-loss target, nonselective serotonergic drugs have been reported as causing central nervous system and cardiac adverse events, which are thought to be caused by activity at the 5-HT_{2A} and 5-HT_{2B} receptors, respectively.⁷² Researchers hypothesize that the selectivity of lorcaserin for 5-HT_{2C} may provide the weight-loss benefits of serotonergic drugs while avoiding these adverse events. Results from early clinical trials of the drug suggested that lorcaserin acts through increasing satiety; patients taking lorcaserin reduced their energy intake, but did not demonstrate significant reductions in energy expenditure.⁷³

In phase III trials, lorcaserin was investigated in obese and overweight patients with at least one comorbid condition. In these trials, lorcaserin was self-administered orally once or twice daily at 10 mg per dose.^{74,75} The product labeling states that the drug dosage is “10 mg administered orally twice daily.”⁷⁶ The drug has been classified by the U.S. Drug Enforcement Administration (DEA) as a Schedule IV drug (i.e., with a low potential for abuse and low risk of dependence); it became available for prescribing in June 2013. To aid diffusion, the company is offering special pricing programs in which patients can receive a free 15-day supply, for a reported savings of \$100 (50% off the first month). Patients are eligible for savings of \$75 per month if their health insurance copayment or out-of-pocket expense is greater than \$50.⁷⁷

Clinical trials: Lorcaserin’s safety and efficacy have been investigated in three major clinical trials: BLOOM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management),⁷⁸ BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity Management),⁷⁹ and BLOOM-DM (BLOOM in Diabetes Mellitus).⁸⁰ The BLOOM study included 3,182 adults who were obese (BMIs of 30–45 kg/m²) or overweight (BMIs of 27.0–29.9 kg/m²) with at least one obesity-related comorbidity (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea). Patients were randomly assigned to receive either lorcaserin 10 mg twice daily or placebo twice daily, for 1 year. At week 52, patients in the lorcaserin group were again randomly assigned, receiving either lorcaserin or placebo. All subjects received diet and exercise counseling. The authors reported the following results:⁷⁸

At 1 year, 55.4% of patients (883 of 1595) receiving lorcaserin and 45.1% of patients (716 of 1587) receiving placebo remained in the trial; 1553 patients continued into year 2. At 1 year, 47.5% of patients in the lorcaserin group and 20.3% in the placebo group had lost 5% or more of their body weight ($P < 0.001$), corresponding to an average loss of 5.8±0.2 kg with lorcaserin and 2.2±0.1 kg

with placebo during year 1 ($P < 0.001$). Among the patients who received lorcaserin during year 1 and who had lost 5% or more of their baseline weight at 1 year, the loss was maintained in more patients who continued to receive lorcaserin during year 2 (67.9%) than in patients who received placebo during year 2 (50.3%, $P < 0.001$). Among 2472 patients evaluated at 1 year and 1127 evaluated at 2 years, the rate of cardiac valvulopathy was not increased with the use of lorcaserin. Among the most frequent adverse events reported with lorcaserin were headache, dizziness, and nausea. The rates of serious adverse events in the two groups were similar.

In the BLOSSOM trial, 4,008 patients (aged 18–65 years, with BMIs between 30 and 45 kg/m² or from 27.0 to 29.9 kg/m² with an obesity-related comorbid condition) were randomly assigned in a 2:1:2 ratio to lorcaserin 10 mg twice daily (BID), lorcaserin 10 mg once daily (QD), or placebo. All patients received diet and exercise counseling. The authors of the study reported the following:⁷⁹

Significantly more patients treated with lorcaserin 10 mg BID and QD lost at least 5% of baseline body weight (47.2 and 40.2%, respectively) as compared with placebo (25.0%, $P < 0.001$ vs. lorcaserin BID). Least squares mean (95% confidence interval) weight loss with lorcaserin BID and QD was 5.8% (5.5–6.2%) and 4.7% (4.3–5.2%), respectively, compared with 2.8% (2.5–3.2%) with placebo ($P < 0.001$ vs. lorcaserin BID; least squares mean difference, 3.0%). Weight loss of at least 10% was achieved by 22.6 and 17.4% of patients receiving lorcaserin 10 mg BID and QD, respectively, and 9.7% of patients in the placebo group ($P < 0.001$ vs. lorcaserin BID). Headache, nausea, and dizziness were the most common lorcaserin-related adverse events. U.S. Food and Drug Administration-defined echocardiographic valvulopathy occurred in 2.0% of patients on placebo and 2.0% on lorcaserin 10 mg BID.

The BLOOM-DM trial evaluated 604 patients (aged 18–65 years) with glycated hemoglobin (HbA_{1c}) of between 7% and 10% and BMIs between 27 and 45 kg/m². They were treated with metformin or a sulfonylurea drug or both. Patients received diet and exercise counseling and were randomly assigned in a 1:1:1 ratio to placebo, lorcaserin 10 mg once daily, or lorcaserin 10 mg twice daily. The study authors reported the following:⁸⁰

More patients lost $\geq 5\%$ body weight with lorcaserin BID (37.5%; $p < 0.001$) or lorcaserin QD (44.7%; $p < 0.001$) vs. placebo (16.1%; modified intent to treat/last observation carried forward). LSmean (\pm sem) weight change was $-4.5 \pm 0.35\%$ with lorcaserin BID and $-5.0 \pm 0.5\%$ with lorcaserin QD vs. $-1.5 \pm 0.36\%$ with placebo ($p < 0.001$ for each). HbA_{1c} decreased 0.9 ± 0.06 with lorcaserin BID, 1.0 ± 0.09 with lorcaserin QD and 0.4 ± 0.06 with placebo ($p < 0.001$ for each); fasting glucose decreased 27.4 ± 2.5 mg/dL, -28.4 ± 3.8 mg/dL and 11.9 ± 2.5 mg/dL, respectively ($p < 0.001$ for each). Symptomatic hypoglycemia occurred in 7.4% of patients on lorcaserin BID, 10.5% on lorcaserin QD and 6.3% on placebo. Common adverse events were headache, back pain, nasopharyngitis, and nausea. Lorcaserin was associated with significant weight loss and improvement in glycemic control in patients with type 2 diabetes.

With the approval, FDA required that the manufacturer conduct six postmarketing studies, including a long-term cardiovascular outcomes trial (CVOT) to assess the effects of the drug on the risk of major adverse cardiac events such as heart attack and stroke.⁷¹

The manufacturer planned to start CVOT in the second half of 2013, with anticipated completion in 2017 and final reporting by the end of 2018. It also has plans to investigate lorcaserin in combination with phentermine and metformin.⁸¹

Manufacturer and regulatory status: Arena Pharmaceuticals, Inc. (San Diego, CA), makes lorcaserin, and the drug is marketed under an agreement between Arena and Eisai Pharmaceuticals (Woodcliff Lake, NJ) a subsidiary of Eisai Co., Ltd. (Tokyo, Japan).⁸² FDA approved the drug on June 27, 2012, following release of the BLOOM-DM study results. It was the first drug approved to treat obesity since 1999.^{71,80,83} The approved indication is as follows:

BELVIQ is indicated to be used along with a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of:

- 30 kg/m² or greater (obese), or
- 27 kg/m² or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, T2DM)

Limitations of Use:

- The safety and efficacy of co-administration of BELVIQ with other products intended for weight loss including prescription drugs (e.g., phentermine), over-the-counter drugs, and herbal preparations have not been established
- The effect of BELVIQ on cardiovascular morbidity and mortality has not been established

Diffusion: Lorcaserin competes with orlistat and phentermine-topiramate extended-release (Qsymia) and off-label use of liraglutide. Lorcaserin's availability after its approval was delayed for about 1 year as DEA evaluated how to schedule the drug.⁸³ On June 7, 2013, lorcaserin debuted as a Schedule IV controlled substance.⁸⁴ This classification allows physicians, including general practitioners, to prescribe the drug electronically through local pharmacies for a 3-month supply at a time, so logistical barriers to obtaining the drug are not expected.^{84,85} DEA also ruled to permit the combined use of lorcaserin with phentermine, which could potentially accelerate the drug's weight-loss benefits and hasten its diffusion.⁸⁴ Lorcaserin is expected to cost about \$1,800 per year (less when special pricing programs from the manufacturer are considered), and some payers have announced they will provide coverage.⁸⁴ A U.S.-based, online aggregator of prescription-drug prices, GoodRx, lists pricing for 30-tablet (10 mg/tablet) supplies ranging from \$110 to \$117 at various pharmacies with the use of a coupon.⁸⁶ To aid diffusion, the company is offering special pricing programs in which patients can receive a free 15-day supply, for a reported savings of \$100 (50% off the first month). Patients are eligible for savings of \$75 per month if their health insurance copayment or out-of-pocket expense is greater than \$50.⁷⁷

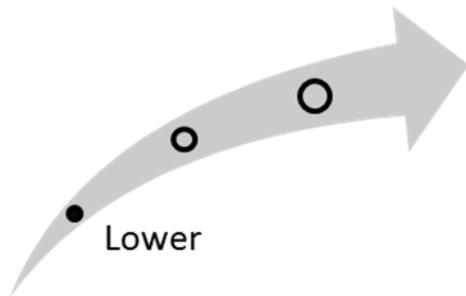
Lorcaserin binds the same receptor as two other previously broadly used nonselective serotonergic weight-loss drugs, fenfluramine and dexfenfluramine, now withdrawn from market because of their association with cardiac valvular fibrosis and pulmonary hypertension when combined with phentermine (Fen-Phen).⁷² Fears of similar serious adverse events could slow lorcaserin diffusion, at least until data from the postapproval CVOT become available.⁸⁷

Clinical Pathway at Point of This Intervention

Individuals who are obese are screened for other comorbid conditions, such as diabetes and hypothyroidism, that may influence treatment decisions and outcomes.⁴⁷ Medication use must also be assessed because some drugs—such as oral contraceptives, certain antipsychotics, and antidiabetes medicines—may interfere with weight loss or contribute to excessive weight gain.⁴⁸ Patients with BMIs of 30 kg/m² or more or BMIs of 25 kg/m² or more with comorbid obesity-related risk factors or diseases (e.g., hypertension, dyslipidemia, coronary artery disease, T2DM,

sleep apnea) may be candidates for drug therapy.⁴⁸ Drug therapy is typically offered in conjunction with a program of physical activity, nutrition counseling, and behavior management. If proved efficacious, lorcaserin could represent a novel mechanism of action that provides an additional nonsurgical option to orlistat, phentermine-topiramate, and off-label liraglutide for overweight patients with BMIs of between 30 and 40 kg/m².

Figure 4. Overall high-impact potential: lorcaserin (Belviq) for treatment of obesity



Expert comments during this recent round of expert commenting indicated the potential impact to be lower than in earlier Potential High-Impact Interventions reports. Experts commenting on this drug agreed that obesity is a major public health problem and that diet and exercise alone have typically been ineffective for maintaining weight loss. Experts agreed that lorcaserin's impact potential depends heavily on the drug's long-term efficacy and comparisons to other oral antiobesity drug therapies. Some experts expressed optimism for the drug's potential to improve patient health outcomes by promoting weight loss. Several experts commented that long-term safety monitoring should be assessed to determine its true potential impact on patient health. Moderate acceptance by both clinicians and patients is anticipated by experts. Some experts listed safety, cost, and the lack of insurance coverage to be potential barriers to adoption for patients. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on lorcaserin.⁸⁸⁻⁹³ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Safe and effective pharmacological treatments are needed to combat the growing obesity epidemic in the United States, the experts generally agreed. Patient health outcomes have the potential to improve with lorcaserin's ability to promote weight loss and reduce obesity-related comorbidities, several experts noted. For instance, one expert representing a clinical perspective commented, "Published studies have shown significant long-term reduction in weight in patients treated with lorcaserin. The drug also decreases glucose levels. Obesity and diabetes are major risk factors for cardiovascular diseases and cancer, hence, an effective medical therapy could have major benefits on health."⁸⁹ However, an expert with a research background opined that obesity drugs do not address underlying causes, thus anticipating a minimal improvement to patient health.⁹⁰ Further, several experts expressed concerns regarding cardiovascular issues associated with lorcaserin. One clinical expert opined that an ongoing safety trial would likely determine the future of the drug.⁹¹ This expert also noted the potential for this intervention to reduce the incidence of obesity-related comorbidities, but expressed other safety concerns. The clinical expert opined, "The weight loss likely to be seen with continued use will, for some, lead to improvements in weight related comorbidities. However, the concerns about

cardiovascular issues and breast cancer, as well as the likelihood that patients will not use the medications long enough to lose enough weight to improve health, limit the potential.”⁹¹

Acceptance and adoption: Experts generally agreed on a moderate potential for adoption by patients and clinicians alike. Several opined that citing ease of administration and patient compliance with oral pharmacotherapy. “Obese patients are aware of the limitations of diet and lifestyle modification, hence most are likely to accept lorcaserin treatment,” noted one expert with a clinical perspective. “The drug is easily administered and has few side effects. Thus, patient compliance is likely to be good.”⁸⁹ However, another clinical expert commented that physicians may be hesitant to prescribe this drug because of cardiovascular concerns and the general history of weight loss medications.⁹¹

In terms of patient acceptance, most experts noted that lorcaserin is easy to prescribe and requires minimal patient education. However, several experts list cost to be a potential barrier to patient acceptance. One expert representing a clinical perspective commented, “Lorcaserin is expensive, and the costs for long-term treatment of a large percentage of obese patients will be high. CMS [U.S. Centers for Medicare & Medicaid Services] and private insurance companies need to develop uniform policies regarding how much of the cost of lorcaserin will be borne by them, and whether they can negotiate lower prices with the manufacturer for large numbers of patients eligible for the drug.”⁸⁹

Health care delivery infrastructure and patient management: Overall, lorcaserin has minimal potential to disrupt health care processes, the experts agreed. One clinical expert commented that the recommended medical monitoring could potentially increase office visits and thus create a minor disruption.⁹¹ Experts generally agreed that lorcaserin has minimal potential to disrupt the way patients are managed. One research expert noted that the disruption would be minimal since patients are already being managed with other available antiobesity pharmacotherapies.⁹⁰

Health disparities: Health disparities might increase because the cost of this intervention and its lack of insurance coverage might serve as barriers to access for uninsured and low-income patient populations, several experts agreed. “Though the medication isn't overly-expensive, obesity affects a larger percentage of the population with low-income background,” one expert representing a health devices perspective commented. “Although there is a plan to partially reimburse the cost of the medication, a truly effective plan to treat obesity may have to involve assistance from federal agencies.”⁹²

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