Economic Evaluation of Linaclotide for the Treatment of Adult Patients With Chronic Idiopathic Constipation in the United States

Huan Huang, PhD;1 Douglas C.A. Taylor, MBA;2 Robyn T. Carson, MPH;3 Phil Sarocco, RPh, MSc;2 Mark Friedman, MD;1 Michael Munsell, BA;1 Steven I. Blum, MBA, MA;4 Joseph Menzin, PhD1

1 Boston Health Economics Inc., Waltham, Mass.; 2 Ironwood Pharmaceuticals, Cambridge, Mass.; 3 Allergan Plc, Jersey City, N.J.; 4 Employee of Forest Research Institute, an Allergan affiliate at the time the study was conducted. Mr. Blum currently works for GlaxoSmithKline.

INTRODUCTION

Chronic idiopathic constipation (CIC) is a common gastrointestinal disorder that is estimated to affect approximately 15% of the general United States population, and the prevalence increases with age (Higgins 2004, Stewart 1999). Symptoms include infrequent bowel movements and hard stools, as well as bloating, straining during defecation, and abdominal discomfort (Pare 2001). In addition to its clinical manifestation, CIC can also have a negative impact on patients’ quality of life, work productivity, and health care resource use. A recent analysis of commercially insured patients found that incremental all-cause costs associated with CIC were $3,508 per patient per year ($4,446 among CIC patients with abdominal symptoms) (Cai 2014). An analysis of the U.S. National Health and Wellness Survey reported patients with CIC to have statistically significantly lower levels of health-related quality of life, as measured by the SF-12v2, compared with matched controls, and statistically significantly higher levels of presenteeism (26% vs 19%, respectively) and overall work impairment (34% vs 22%, respectively) (Sun 2011). Patients with CIC were also shown to have statistically significantly more provider and emergency room visits when compared with controls (Sun 2011).

ABSTRACT

Purpose: To evaluate the effectiveness and costs of linaclotide (Linzess) versus lubiprostone (Amitiza) in the treatment of adult patients with chronic idiopathic constipation (CIC).

Design: A decision-tree model using model inputs derived from published literature, linaclotide phase 3 trial data, and a physician survey.

Methodology: Measures of treatment efficacy were selected based on comparability between trial data, with posthoc analyses of linaclotide required to ensure comparability with available lubiprostone data. Response to therapy was defined as (1) having one of the best two satisfaction answers of a 5-point global treatment satisfaction scale at Week 4 or (2) having a weekly spontaneous bowel movement (SBM) frequency ≥4 at Week 4. Patients who do not respond to therapy are assumed to accrue costs associated with a treatment failure. Model time horizon is aligned with the lubiprostone clinical trial duration of 4 weeks. Model outputs include response rates, quality-adjusted life-years (QALYs) and direct costs.

Results: Linaclotide was associated with lower per-patient costs vs lubiprostone for both definitions of response ($946 vs $1,015 for global assessment and $727 vs $737 for SBM frequency). When treatment response was based on a global assessment of treatment satisfaction, linaclotide was associated with higher effectiveness (response: 39.3% vs 35.0%). For SBM frequency, linaclotide was slightly less effective compared to lubiprostone (response: 58.6% vs 59.6%), but also less costly. Base-case results were robust in sensitivity analysis.

Conclusions: Linaclotide is less expensive with similar effectiveness when compared to lubiprostone for the treatment of CIC in adult patients.

Key words: Cost-benefit analysis, constipation, economics

To date, relatively few pharmacological treatments have been approved for the treatment of CIC. Tegaserod was approved for the treatment of CIC in 2004; however, it was withdrawn from the market in 2007 due to concerns regarding an increased risk of cardiovascular events among patients receiving treatment (FDA 2007). Lubiprostone was approved by the U.S. Food and Drug Administration (FDA) for treatment of CIC in men and women in 2006 and until recently was the only prescription drug with a CIC indication in the U.S. Lubiprostone is a chloride-channel activator that promotes bowel transit by increasing the chloride concentration of intestinal fluid, which in turn increases the isotonic fluid in the lumen.

In August 2012, linaclotide, a minimally absorbed guanylate cyclase-C (GC-C) agonist, was approved by the FDA for treatment of CIC in both men and women. Linaclotide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. This results in an increase in both intracellular and
extracellular cyclic guanosine monophosphate (cGMP). Consequently, chloride and bicarbonate secrete into the intestinal lumen, resulting in increased intestinal fluid and accelerated transit. In addition, linaclotide has been shown to increase extracellular cGMP, which was shown to decrease the activity of pain-sensing nerves and reduce visceral pain (Castro 2013, Linzess 2014).

With the FDA approval of linaclotide for the treatment of CIC, it becomes important to evaluate the economic impact associated with its use vs alternative prescription drug treatments (i.e., lubiprostone). A previously published economic evaluation of linaclotide vs lubiprostone among adult patients with irritable bowel syndrome with constipation (IBS-C) found linaclotide to be a lower-cost option for the treatment of IBS-C, with equivalent or improved patient response (Huang 2015). The aim of this study is to use techniques of decision analysis and mathematical modeling to evaluate the economic impact of linaclotide vs lubiprostone in the treatment of adults with CIC.

**METHODS**

**Model Overview and Structure**

This model was developed in Microsoft Excel (version 2010) spreadsheet format using a decision-tree modeling technique and draws upon linaclotide clinical trial data (both published and posthoc analyses), published scientific literature, publicly available FDA reviews of lubiprostone, and a survey of practicing physicians on resource utilization associated with treatment failure. The model population is comprised of adults who have been diagnosed with CIC and are candidates for prescription treatment.

The overall model structure follows that of the IBS-C model previously published by Huang and colleagues (Huang 2015). Hypothetical CIC patients enter the model as candidates for either linaclotide 145 mcg once daily or lubiprostone 24 mcg twice daily (Figure 1). Treatment discontinuation can occur immediately after initiation. Patients who discontinue therapy are assumed to show no improvement from their baseline symptoms and are assigned clinical and economic consequences associated with treatment failure. Patients who continue drug therapy have a probability of achieving response to the assigned treatment. Patients who respond to treatment are assumed to accrue the pharmacy costs for linaclotide 145 mcg or lubiprostone 24 mcg and to have higher health utilities (i.e., higher quality of life) compared with those who do not respond. Patients who do not respond to treatment are assumed to accrue treatment failure costs and to have lower health utilities than patients who respond.

The model time horizon is 4 weeks, which is consistent with the publicly available lubiprostone phase 3 clinical trial data (12 weeks of phase 3 clinical trial data are available for linaclotide) (CDER 2006, Lembo 2011). Base-case analyses were performed from the payer’s perspective, including number of patients responding to treatment, quality-adjusted life-years (QALYs), and direct medical costs as model outputs. Indirect costs were also included in scenario analyses to provide results from the societal perspective.

**Model Inputs**

**Treatment Comparators**

Only prescription therapies currently approved and indicated by the FDA for the treatment of CIC were included in the model; therefore, only linaclotide 145 mcg once daily and lubiprostone 24 mcg twice daily were included as treatment options. Over-the-counter (OTC) remedies, such as laxatives (e.g., MiraLAX), were not considered as treatment comparators because of limited published data and lack of FDA approval for the CIC indication. The model assumes that patients are seeking treatment with a prescription agent.

**Treatment Response**

The primary endpoints among linaclotide and lubiprostone phase 3 clinical trials were not directly comparable (CDER 2006, Lembo 2011, Vieira 2012). Therefore, available linaclotide and lubiprostone data from phase 3 clinical trials were reviewed prior to

---

**KEY POINTS**

- Chronic idiopathic constipation is a common condition that affects 15% of Americans.
- The only prescription medications approved by the FDA as treatments are linaclotide (Linzess) and lubiprostone (Amitiza).
- The two drugs have not been compared in a side-by-side trial, so researchers constructed a model to make the comparison. They used data from the phase 3 trials of the two drugs.
- The model shows that per-patient costs are lower for linaclotide than lubiprostone.
- When response was defined by treatment satisfaction, linaclotide edged out lubiprostone (39.3% vs 35.0%). When response was defined by spontaneous bowel movement, lubiprostone was slightly better than linaclotide (59.6% vs 58.6%). The quality-adjusted life-year scores were similar.
- The model only covers 4 weeks of treatment because of the lack of longer-term data for lubiprostone.
Economic Evaluation of Linaclotide for Treatment of CIC

Model development and measures of treatment efficacy were selected based on comparability between trial data and suitability for use as definitions of response within the model framework. Among trial endpoints that were included in clinical trials of both treatments (e.g., global assessment of treatment satisfaction, spontaneous bowel movement [SBM] frequency), reported measures were analyzed using different definitions of treatment response or did not report findings necessary for robust economic modeling. Therefore, posthoc analyses of linaclotide clinical trial data were conducted to help ensure comparability with the data reported from the lubiprostone clinical trials (further details of posthoc analyses are described in a previous publication [Huang 2015]).

Treatment response was defined by: (1) having one of the best two satisfaction answers of a 5-point global treatment satisfaction scale at Week 4 or (2) having weekly SBM frequency ≥4 at Week 4. The primary endpoint in the phase 3 lubiprostone clinical trial was number of SBMs per week, where a responder was defined as a patient with weekly SBM ≥4 at Week 4 (Barish 2010, CDER 2006). Phase 3 clinical trials for both treatments included similar assessments of global treatment satisfaction using 5-point response scales (“not at all satisfied/effective” to “extremely satisfied/effective”) (Barish 2010, Lembo 2011). Response for treatment satisfaction was defined as having either of the top two answers (i.e., quite or extremely satisfied/effective) at Week 4. While not a primary endpoint in the clinical trials of either treatment, this definition of response was selected due to the consistency of measure collection and definition between trials, as well as its ability to evaluate treatment effectiveness globally from a patient perspective.

Only means and standard deviations were reported for the global assessment of treatment satisfaction at Week 4 for lubiprostone; however, the model requires the percentage of patients with either of the top two answers (i.e., a score of 4 or 5 on the 5-point assessment at Week 4) to define response. To address this issue, a beta distribution was fitted to the reported lubiprostone mean and standard deviation, using the properties of the cumulative distribution function to estimate the percentage of patients with a score ≥4. The choice of using a beta distribution was validated with the patient-level linaclotide clinical trial data by testing the goodness-of-fit using the sum of squared differences. The fit of the beta distribution was found acceptable but had a tendency to slightly underestimate the required percentage. To be conservative, a fitted linaclotide response, rather than the actual response from the posthoc analyses, was used. Response-rate data for linaclotide were derived from data on the pooled intent-to-treat (ITT) populations of the clinical trials.

Because SBM frequency was the primary endpoint in the lubiprostone clinical trial, SBM frequency response rates were calculated as the pooled average from the two publicly available lubiprostone trials (CDER 2006). While SBM frequency during each week was evaluated during the linaclotide phase 3 clinical trials, the proportion with frequency ≥4 was not. Therefore, posthoc analyses of linaclotide trial data using the same response definition as lubiprostone were conducted to ensure comparability between response rates.

For both definitions of response defined above, placebo-adjusted odds ratios (OR) of response for linaclotide vs lubiprostone were constructed.

Additional Inputs
Additional model inputs include the rate of treatment discontinuation, drug costs, direct/indirect cost of treatment failure, and response-specific health utilities. Values for each input are documented in Table 1 (next page) and were derived using various data sources and estimation techniques. The methodology for constructing these model inputs are documented in a previous publication (Huang 2015). Note that daily drug costs have been updated to 2015 values (Red Book Online 2015).

Model Outcomes
Model outcomes are primarily from
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Range</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubiprostone response (24 mcg BID)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on global assessment of treatment satisfaction(^a)</td>
<td>35.0%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Based on SBM frequency(^b)</td>
<td>59.6%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>OR linaclotide 145 mcg once daily vs lubiprostone 24 mcg BID (indirect comparison using placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on global assessment of treatment satisfaction(^c)</td>
<td>1.20</td>
<td>0.88</td>
<td>1.53</td>
<td></td>
</tr>
<tr>
<td>Based on SBM frequency(^d)</td>
<td>0.96</td>
<td>0.70</td>
<td>1.22</td>
<td></td>
</tr>
<tr>
<td><strong>Discontinuation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linaclotide 145 mcg once daily</td>
<td>0.0%</td>
<td>N/A</td>
<td>9.6%</td>
<td></td>
</tr>
<tr>
<td>Lubiprostone 24 mcg BID</td>
<td>0.0%</td>
<td>N/A</td>
<td>14.3%</td>
<td></td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug (daily)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linaclotide 145 mcg once daily(^e)</td>
<td>$9.24</td>
<td>$8.32</td>
<td>$10.16</td>
<td></td>
</tr>
<tr>
<td>Lubiprostone 24 mcg BID</td>
<td>$9.99</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Treatment failure (per patient)(^f)</td>
<td>$1,132</td>
<td>$361</td>
<td>$2,002</td>
<td></td>
</tr>
<tr>
<td>Indirect cost (per patient)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on global assessment of treatment satisfaction(^g)</td>
<td>$10.87</td>
<td>$8.15</td>
<td>$13.59</td>
<td></td>
</tr>
<tr>
<td>Based on SBM frequency</td>
<td>$6.88</td>
<td>$5.16</td>
<td>$8.60</td>
<td></td>
</tr>
<tr>
<td><strong>Utilities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on global assessment of treatment satisfaction(^h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>0.92</td>
<td>0.91</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Nonresponse/discontinued</td>
<td>0.89</td>
<td>0.88</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Based on SBM frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>0.91</td>
<td>0.91</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Nonresponse/discontinued</td>
<td>0.89</td>
<td>0.88</td>
<td>0.90</td>
<td></td>
</tr>
</tbody>
</table>

Data sources:
\(^a\) Response rate ("quite a bit" or "extremely" effective) derived through fitting to a beta distribution based on mean and standard deviation reported in Table 10 and 22 in the FDA 2006 Statistical Review, ITT population (CDER 2005).
\(^b\) Response rate (weekly SBM frequency ≥4) obtained from pooled data from Table 4 and 16 in FDA Statistical Review, ITT population (CDER 2005).
\(^c\) Placebo-adjusted odds ratios derived from response rate ("quite" or "very" satisfied) of linaclotide (posthoc analysis of phase 3 clinical trial data) vs lubiprostone. Lubiprostone response calculated as described above in source \(^a\). Low and high estimates were derived from bootstrapping results.
\(^d\) Placebo-adjusted odds ratios derived from response rate (weekly SBM frequency ≥4) of linaclotide (posthoc analysis of phase 3 clinical trial data) vs lubiprostone. Lubiprostone response calculated as described above in source \(^b\). Low and high estimates were derived from bootstrapping results.
\(^e\) Discontinuation assumed to be zero in the base case; discontinuation rate for “any reason” used for sensitivity analysis from the linaclotide (posthoc analysis of phase 3 clinical trial data) and lubiprostone clinical trials (CDER 2005, Lembo 2011).
\(^f\) Truven Health Analytics Red Book 2015 WAC price for linaclotide. Low and high estimates only used for probabilistic sensitivity analysis; assumed to be ±10\% of the base-case value.
\(^g\) Truven Health Analytics Red Book 2015 WAC price for lubiprostone.
\(^h\) Derived from the findings from a one-time, web-based survey of physicians on treatment patterns and resource use for patients with CIC who had/did not have a response to a recent treatment course. The low bounds of the interquartile range (IQR) of the estimated base-case costs were used as the low estimates. The high estimates were taken from a retrospective database analysis of Medicaid administrative claims.
\(^i\) Derived from data collected from the Work Productivity and Activity Impairment (WPAI) Questionnaire in the phase 3 clinical trials for linaclotide. Low and high estimates were calculated as ±25\% of the base-case value.
\(^j\) Derived from the EQ5D scores from phase 3 clinical trials for linaclotide.
\(^\) BID=twice daily, N/A=not available, SBM=spontaneous bowel movement, WAC=wholesale acquisition cost.
the third-party commercial payer’s perspective and include the percentage of patients responding to each treatment, as well as the direct medical costs and QALYs associated with response/nonresponse.

**Sensitivity Analyses**
Indirect work productivity costs were not included in the base-case analysis; however, they were incorporated in a separate analysis to test the robustness of model results and include results from a societal perspective.

Sensitivity analyses to assess uncertainty in the results based on potential variation in base-case model inputs were also performed. Low and high estimates for the following parameters were included in the one-way analysis: direct and indirect costs for treatment failure; OR for treatment response; health utility values; and discontinuation rates. High estimates for discontinuation rates (9.6% for linaclotide [posthoc analyses] and 14.3% for lubiprostone [CDER 2006]) include the discontinuation rate for “any reason” from each treatment’s phase 3 clinical trial.

Probabilistic sensitivity analyses were undertaken using a second-order Monte Carlo simulation. The OR for treatment response (using a log-normal distribution with standard errors obtained from bootstrapping techniques), drug cost for linaclotide (uniform distribution between low and high estimates; assumed to be ±10% of the actual drug cost), the cost of treatment failure (using gamma distribution), and health utilities (using a uniform distribution) were varied within the model.

**Model Assumptions**
The demographic and clinical characteristics of the modeled patient populations are assumed to be consistent with the patient populations in the linaclotide and lubiprostone phase 3 clinical trials. It is assumed that all efficacy reported in the clinical trials is attributable to the study treatment effect of linaclotide and lubiprostone (i.e., the improvement in response rate vs placebo observed in the trials is attributable to linaclotide or lubiprostone, not due to other reasons such as difference in demographics).

Patients who respond to treatment are assumed to respond immediately upon treatment initiation, and all responders have the same health utility, regardless of treatment (same assumption for nonresponders).

Treatment costs are based on recommended dosing and frequency of administration in each product’s prescribing information. The results from the physician survey on patient management (diagnostic tests, procedures, and physician visits) for a hypothetical patient reporting no satisfactory symptom relief during treatment are assumed to be representative of all patients who experience treatment failure. In addition, the Medicare fee schedule used to estimate costs of diagnostic test, procedures, and physician visits is assumed to be applicable to private payers.

**RESULTS**

**Base-case Results**
When response was based on global treatment satisfaction, linaclotide 145 mcg once daily was found to be less expensive and more effective when compared to lubiprostone 24 mcg twice daily. The percentage of responders was 39.3% and 35.0% for patients receiving linaclotide 145 mcg once daily and lubiprostone 24 mcg twice daily, respectively. Total direct costs were estimated to be $946 per linaclotide treated patient and $1,015 per patient treated with lubiprostone.

QALYs were numerically similar between linaclotide and lubiprostone over the 4-week analysis period (Table 2).

When response was based on SBM frequency, the percentage of responders was 58.6% and 59.6% for

---

**TABLE 2**
Cost-effectiveness model results for 1,000 patients with chronic idiopathic constipation (direct costs only)

<table>
<thead>
<tr>
<th>Comparator arms</th>
<th>Global treatment satisfaction responder</th>
<th>SBM frequency responder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Direct cost per patient</td>
<td>Responders (%)</td>
</tr>
<tr>
<td>Lubiprostone 24 mcg BID</td>
<td>$1,015</td>
<td>35.0</td>
</tr>
<tr>
<td>Linaclotide 145 mcg once daily</td>
<td>$946</td>
<td>39.3</td>
</tr>
<tr>
<td>Incremental (linaclotide-lubiprostone)</td>
<td>–$69</td>
<td>4.3</td>
</tr>
</tbody>
</table>

BID=twice daily, QALY=quality-adjusted life-year, SBM=spontaneous bowel movement.

[a] Global treatment satisfaction responder: Having either of the best two satisfaction answers (i.e., “quite” or “extremely/very”) of a 5-point global treatment satisfaction scale at Week 4.

[b] SBM frequency responder: Having weekly SBM frequency ≥4 at Week 4.
patients receiving linaclotide 145 mcg once daily and lubiprostone 24 mcg twice daily, respectively. Total direct costs were estimated to be $727 per linaclotide-treated patient and $737 per patient treated with lubiprostone (Table 2).

**Sensitivity Analysis Results**

When indirect costs were included in the analysis (i.e., cost of lost work productivity), results were similar to that of the base-case results (data not shown).

Using the definition of response based on global assessment of treatment satisfaction, linaclotide 145 mcg once daily was less expensive and more effective versus lubiprostone 24 mcg twice daily in all one-way sensitivity analyses except one. When the placebo-adjusted OR for treatment response (linaclotide vs lubiprostone) was set at the low estimate (0.88), linaclotide had a lower per-patient cost ($1,022 vs $1,033) and a slightly lower response rate (32% vs 35%).

When the definition of response was based on SBM frequency, linaclotide 145 mcg once daily was less expensive but less effective compared to lubiprostone in all one-way sensitivity analyses except for the following four cases: (1) When the placebo-adjusted OR for treatment response (linaclotide versus lubiprostone) was set to the high estimate (1.22), linaclotide was less expensive and more effective compared to lubiprostone; (2) When the placebo-adjusted OR for treatment response was set to the low estimate (0.70), linaclotide was more expensive and less effective than lubiprostone; (3) When a 9.6% discontinuation rate was assumed for linaclotide and 14.3% for lubiprostone (both from trial data), linaclotide was less expensive and more effective compared to lubiprostone; and (4) When price of linaclotide was set to the high estimate ($10.16), linaclotide had higher per patient costs when compared to lubiprostone ($755 vs $740, with the inclusion of indirect costs).

For treatment response based on a global assessment of satisfaction, the distribution of 1,000 Monte Carlo simulations showed that the majority of cost per additional responder scenarios were in Quadrant 4 of the incremental cost vs response plane, indicating linaclotide to be more effective and less expensive than lubiprostone for the treatment of CIC (Figure 2a). Analysis using the SBM frequency definition of response resulted in approximately 50% of the cost per additional responder scenarios in Quadrant 4 of the incremental cost vs response plane (linaclotide more effective and less expensive than lubiprostone $755 vs $740, with the inclusion of indirect costs).

**FIGURE 2A**

**Probabilistic sensitivity analysis results for cost per patient and probability of response (response based on global assessment of satisfaction)**

*Note: Each point on graph represents the result of 1 of 1,000 iterations of a second-order Monte Carlo simulation.

**FIGURE 2B**

**Probabilistic sensitivity analysis results for cost per patient and probability of response (response based on SBM frequency)**

*Note: Each point on graph represents the result of 1 of 1,000 iterations of a second-order Monte Carlo simulation.
than lubiprostone). The other 50% were distributed among Quadrant 2 (linaclotide less effective and more expensive than lubiprostone) and Quadrant 3 (linaclotide less effective and less expensive than lubiprostone) (Figure 2b).

DISCUSSION
Results from this decision-analytic model show that linaclotide is associated with lower per-patient costs than lubiprostone when used for the treatment of CIC among adult patients ($946 vs $1,015 and $727 vs $737 for global assessment and SBM frequency definitions of response, respectively) from a third-party commercial payer’s perspective over a duration of 4 weeks. This observed difference in per-patient costs has the potential for significant effects on aggregate total costs for large health care organizations, particularly given the short time horizon in which a cost difference is established, as well as the high prevalence rate of CIC among the aging adult population. When treatment response was based on a global assessment of treatment satisfaction, linaclotide was also associated with somewhat higher response (39.3% vs 35.0%) and similar QALYs compared with lubiprostone. When treatment response was based on SBM frequency, linaclotide and lubiprostone had similar response rates and effects on QALYs. These results were robust in one-way sensitivity analyses, as well as with the addition of indirect work productivity costs as a model input. With only minor differences in response rates for either response definition, it is valid to conclude that both treatment options would provide similar effectiveness in a clinical setting. Therefore, under most scenarios and assumptions, linaclotide is a lower cost treatment option, with similar effectiveness, for patients with CIC when compared with lubiprostone.

**Limitations**
This study has various limitations, including a short time horizon and the need for additional analyses for several parameter estimates where available data were lacking. The time horizon for this model is relatively short (i.e., 4 weeks) due to the lack of longer-term comparable data for lubiprostone, as well as the chronic nature of CIC. However, there is some suggestion that the benefits of treatment may extend over time. For example, in the 4-week randomized withdrawal period after completion of the 12-week phase 3 linaclotide clinical trial in CIC, it is observed that treatment efficacy outcomes (i.e., increase in weekly complete spontaneous bowel movements) are sustained for the patients who remain on treatment (Lembo 2011). For patients who discontinued treatment after the 12-week trial duration, weekly complete spontaneous bowel movements returned to a similar rate as baseline. The lack of comparable 12-week treatment trial evidence for lubiprostone limited the model to 4 weeks in duration. Further, longer-term clinical results would help extend the findings from this decision-tree economic model.

The direct costs associated with treatment failure were derived from the findings from a one-time, web-based survey of 20 primary care physicians (PCPs) and 21 gastroenterologists that asked about treatment patterns and resource use among patients with CIC who were not responding to recent treatment. The classification of patient response and treatment duration in the survey differed from the response definition and time horizon used for the clinical inputs in the model. Additionally, several assumptions were required in calculating the cost estimate, including the assumption that all patients were seen by a primary care physician prior to being referred to a GI specialist. Therefore, there may be some bias in the estimates of direct medical costs. For instance, treatment failure costs may be slightly overestimated in the model given that all procedures specified in the survey may not occur during the 4-week model time horizon. This survey was undertaken because there are no published studies that present data on this issue. Resource use estimates from this survey of 41 physicians may be reasonably generalizable given that the surveyed physicians were heterogeneous in age, sex, patient volume, years of practice, and U.S. geographic region. In addition, costs are based on Medicare fee schedules, which are lower compared with those of a private payer and therefore provide conservative cost estimates (Nguyen 2013).

There are no available head-to-head trials that compare linaclotide with lubiprostone; therefore, placebo-
adjusted estimates of relative efficacy were derived. For the definition of response based on SBM frequency, posthoc analyses of linaclotide clinical trial data were conducted using the same definition as lubiprostone to ensure comparability of response rates, given the inconsistent definition between the linaclotide and lubiprostone trials. Due to this data limitation, the definition of response for SBM was required to be ≥4 per week (i.e., the primary efficiency endpoint in lubiprostone phase 3 clinical trials). A response definition of ≥3 SBM per week would have been a more clinically relevant definition of response, given that Rome III criteria defines constipation as fewer than 3 defeac-tions per week (Longstreth 2006).

Additionally, due to a lack of sufficient data from the publicly available FDA review of lubiprostone clinical trials, the global assessment of treatment satisfaction measure of response required curve-fitting techniques to impute the percentages of subjects who achieved the defined threshold of response for both linaclotide and lubiprostone, which may not exactly reflect the clinical trial results.

The results from the model are likely conservative given the response rate derived for linaclotide from the curve-fitting technique produced a lower OR of response compared to the OR calculated if response rates from the actual linaclotide clinical trial data were used.

The model assumes that those patients who discontinue therapy incur costs for 1 month (4 weeks) of drug treatment, and that patients who respond take the medication once daily for the full time horizon of the model (4 weeks). In actual clinical practice, initial prescription days supplied could be shorter, and actual use of the treatments may be less frequent than daily.

Finally, the model is based on a homogenous clinical trial population and treatment protocol, which may not be representative of real-world clinical practice. Studies of the comparative effectiveness of linaclotide and lubiprostone through analysis of real-world data would be valuable.

**CONCLUSION**

In a model based on published clinical data, linaclotide was found to be a less costly treatment option with similar effectiveness for patients with CIC when compared with lubiprostone. The results of this study are intended to provide useful information for determining effective treatment options in the absence of direct head-to-head clinical or economic evaluations.

**REFERENCES**


