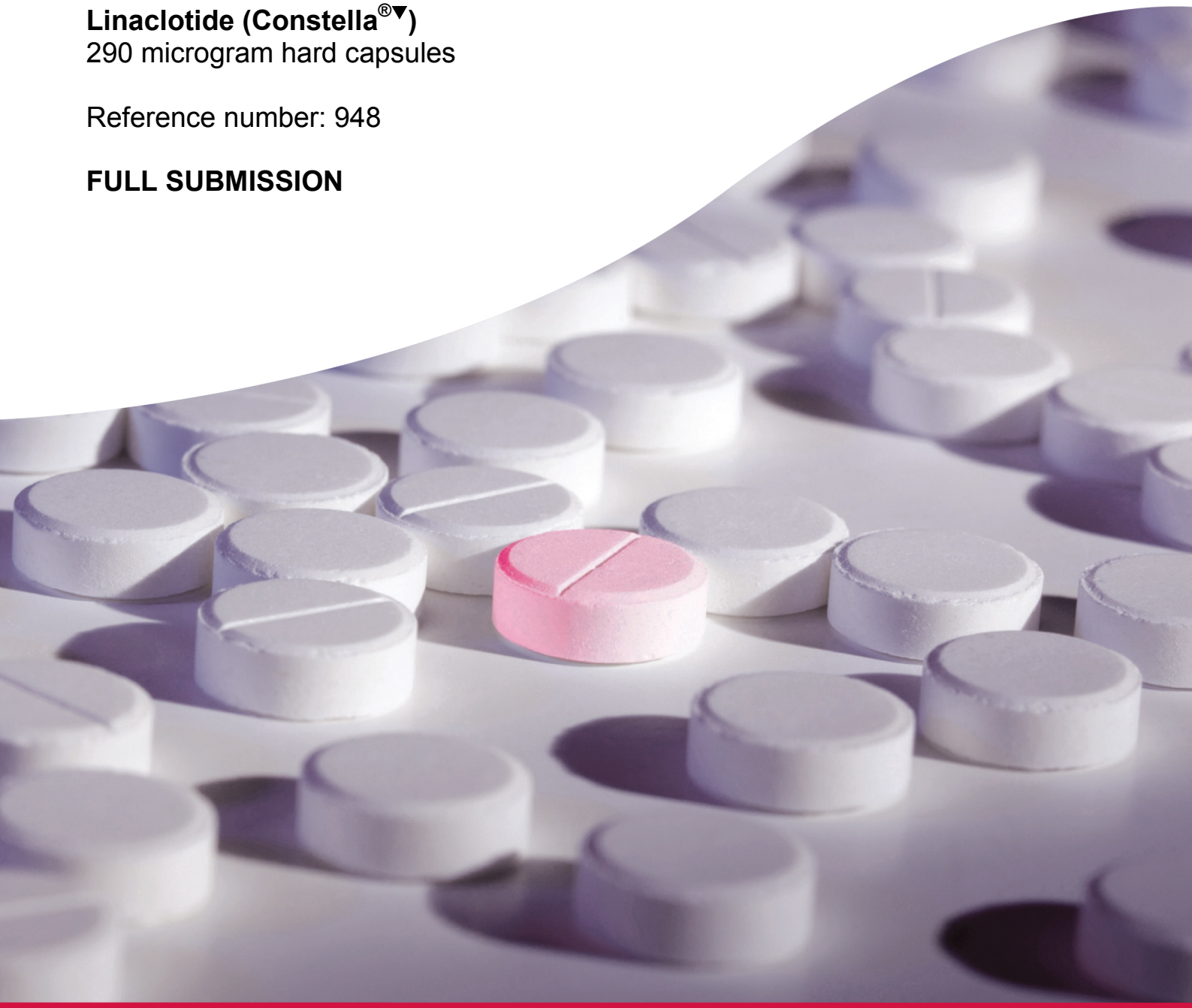
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Linaclotide (Constella®▼)
290 microgram hard capsules

Reference number: 948

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Linaclotide (Constella®▼) 290 microgram hard capsules

This assessment report is based on evidence submitted by Almirall Ltd on 29 August 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Linaclotide (Constella®▼) for the symptomatic treatment of moderate to severe irritable bowel syndrome (IBS) with constipation in adults[2].
Dosing	The recommended dose of linaclotide is one capsule to be taken orally once daily, at least 30 minutes before a meal. If patients have not experienced improvement in their symptoms after four weeks of treatment, the patient should be re-examined and the benefit and risks of continuing treatment reconsidered[2].
Marketing authorisation date	26 November 2012[2].

2.0 DECISION CONTEXT

2.1 Background

Irritable bowel syndrome (IBS) is a chronic, relapsing condition causing abdominal pain or discomfort and is associated with defecation irregularities[3]. The most common symptom profiles for people with IBS are constipation predominant (IBS-C), diarrhoea predominant or alternating symptom profile[4]. Compared with people without the condition, IBS patients have more absenteeism from work, a reduced quality of life and utilise healthcare resources more frequently[3]. IBS affects an estimated 10–20% of the population, of which approximately 24% have the IBS-C symptom profile and is twice as common in women than in men[4,5].

First-line treatments for IBS-C include antispasmodics and laxatives[4]. National Institute of Health and Care Excellence (NICE) guidelines recommends that if these medicines are ineffective, tricyclic antidepressants (TCAs) should be considered as a second-line treatment for their analgesic effect and selective serotonin reuptake inhibitors (SSRIs) can be used as an option if TCAs do not help[4]. However neither TCAs nor SSRIs have marketing authorisations for this indication[1,4,6]. The applicant company has proposed that linaclotide should be considered, within the licensed indication, for patients who have not responded adequately or cannot tolerate antispasmodics and/or laxatives[1]. Linaclotide is an agonist of the guanylate cyclase-C receptor, which lines the luminal surface of the gastrointestinal tract[3]. Activation of the guanylate cyclase-C receptor results in an increase in levels of intracellular and extracellular cyclic guanosine monophosphate (cGMP), which accelerates gastrointestinal transit and is proposed to reduce abdominal pain and discomfort[3].

2.2 Comparators

The comparators included in the company submission are antidepressants (TCAs and SSRIs) and the comparator used in the health economics analysis is amitriptyline[1]. Prucalopride (Resolor®) has not been included as a comparator, although it is reported by the company to be used by a minority of clinicians to treat patients with IBS-C[1].

Prucalopride is indicated for the treatment of chronic constipation (CC) in women, for whom laxatives have failed to provide sufficient relief[7]. However it is not indicated for the treatment of IBS-C and was not available when the NICE guideline was published in 2008[4,7].

2.3 Guidance and related advice

- NICE Pathways. Managing irritable bowel syndrome (2013)[6].
- NICE. Evidence summaries: new medicines (ESNM) 16. Irritable bowel syndrome with constipation in adults: linaclotide (2013)[8].
- NICE Clinical Guideline 61. Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care (2008)[4].
- British Society of Gastroenterology. Guidelines on the irritable bowel syndrome: mechanisms and practical management (2007)[9].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submitted results from two placebo-controlled trials evaluating the effect of linaclotide in patients with IBS-C: LIN-MD-31 (trial 31) a 12-week trial with a four-week randomised withdrawal period and MCP-103-302 (trial 302), a 26-week trial[10,11]. In addition, the company has conducted a post-hoc analysis of trials 31 and 302 to provide clinical comparison between treatment with linaclotide versus treatment with antidepressants[1]. Results from two long-term trials, LIN-MD-02 and MC-103-305 in which patients with IBS-C and patients with CC received linaclotide for up to 78 weeks, were also submitted to provide evidence of safety[1].

3.1 Efficacy of linaclotide versus placebo (trials 31 and 302)

Trials 31 and 302 were phase III, randomised, multicentre, double-blind, parallel-group studies comparing the use of linaclotide with placebo in the treatment of adult patients with IBS-C[10,11]. Patients were randomised (1:1) to receive linaclotide 290 micrograms or placebo once-daily, and those already receiving stable doses of antidepressants were allowed to continue their use[1]. Both trials consisted of up to 21 days of screening and 14–21 days of pre-treatment before randomisation, followed by a 12-week (trial 31) or 26-week (trial 302) double-blind period[3,11]. The proportion of female patients was 90.5% and 89.6% in trials 31 and 302 respectively[3].

Several primary and secondary endpoints were utilised, however the two co-primary endpoints, recommended by the European Medicines Agency (EMA) and used in both trials, were the proportion of patients with a 12-week abdominal pain/discomfort response and the proportion of patients with a 12-week IBS degree of relief response (see Glossary for definitions)[10]. During trial 302, the percentage of 26-week abdominal pain/discomfort responders and 26-week IBS degree of relief responders were also recorded as secondary endpoints.

Primary endpoints results, shown in Table 1, were statistically significant in favour of linaclotide compared with placebo. The proportion of IBS degree of relief responders at 12 weeks were 37.0% and 39.4% for linaclotide-treated patients in trials 31 and 302, respectively, versus 18.5% and 16.6% for placebo-treated patients[3,10]. Similarly, the proportions of abdominal pain/discomfort responders at 12 weeks were 54.8% and 54.1% in the linaclotide arms in trials 31 and 302 and 41.8% and 38.5% in the placebo arms. These results were supported by the 26-week responder results in trial 302, which are also displayed in Table 1. In both trials, the proportion of responders was significantly greater for linaclotide versus placebo after the first week of treatment and at each subsequent week[10]. Other secondary endpoints assessing abdominal and bowel symptoms in both trials showed statistical superior improvements for linaclotide versus placebo from baseline to 12 and 26 weeks[3,10].

Additional endpoints in both trials included assessments of IBS-Quality of Life (IBS-QoL), EuroQoL-5 Dimensions (EQ-5D) utility and EQ-5D visual analogue scale (VAS) (see Glossary for definitions)[10]. Scores for the 12-week and 26-week timepoints were higher for linaclotide versus placebo for all endpoints with statistically significant difference, except for the EQ-5D VAS value for trial 31[3].

Table 1. Main primary and secondary endpoints for linaclotide versus placebo in patients with IBS-C[3].

Trial 31 (n=800) 12 weeks treatment		
	Proportion of IBS degree of relief responders	**Proportion of abdominal pain/discomfort responders**
Linaclotide	150/405(37.0%)	222/405 (54.8%)
Placebo	73/395 (18.5%)	165/395 (41.8%)
Odds ratio	2.61 (1.89–3.62)	1.70 (1.28–2.25)
p value	< 0.0001	0.0002
Trial 302 (n=804)12 weeks treatment		
	Proportion of IBS degree of relief responders	**Proportion of abdominal pain/discomfort responders**
Linaclotide	158/401 (39.4%)	217/401 (54.1%)
Placebo	67/403 (16.6%)	155/403 (38.5%)
Odds ratio	3.26 (2.34–4.53)	1.90 (1.43–2.52)
p value	< 0.0001	< 0.0001
Trial 302 (n=804) 26 weeks treatment		
	Proportion of IBS degree of relief responders	**Proportion of abdominal pain/discomfort responders**
Linaclotide	149/401 (37.2%)	215/401 (53.6%)
Placebo	68/403 (16.9%)	145/403 (36.0%)
Odds ratio	2.90 (2.09–4.04)	2.06 (1.55–2.73)
p value	< 0.0001	< 0.0001

Patients who completed all 12 weeks of the trial 31 double-blind treatment period were eligible to enter the double-blind four-week randomised withdrawal period, in which patients initially randomised to receive linaclotide were re-randomised (1:1) to receive linaclotide 290 micrograms or placebo once-daily, and patients previously randomised to placebo were assigned to receive linaclotide 290 micrograms once-daily. Patients who had received linaclotide during the 12-week period and who remained on linaclotide continued to maintain their response, whilst those re-randomised to placebo had a decrease in the improvement they had attained during previous linaclotide treatment. However, no rebound effect was observed[3].

3.2 Efficacy of linaclotide versus antidepressants

In the absence of direct comparative data evaluating the efficacy of linaclotide versus antidepressants to treat patients with IBS-C, the applicant company reports undertaking a systematic review[1]. However, following critical appraisal of the identified published literature, the applicant company concluded that the evidence base was too limited to perform an indirect comparison, and so has conducted a post-hoc analysis using pooled data from trials 31 and 302. The subgroup analysis compares efficacy in patients treated with linaclotide without concomitant antidepressants versus patients in the placebo group who received antidepressants during the studies. Results for linaclotide continue to show a statistically significant improvement across both primary and secondary endpoints (see Table 2).

Table 2. Endpoints for post-hoc comparison of linaclotide-treated patients versus patients receiving antidepressants and placebo in studies 31 and 302[1].
[Commercial in confidence data removed]

3.3 Comparative safety

Safety data were available from placebo-controlled trials 31 and 302[1]. Serious adverse events in the pooled data for the two placebo-controlled trials occurred for six patients (0.7%) in the linaclotide arm and for nine patients (1.1%) in the placebo arm. In the pooled data, treatment-emergent adverse events (TEAEs) were experienced by 54.9% (438/798) of patients receiving placebo and 60.8% (491/807) of patients receiving linaclotide[3]. The most common TEAE was diarrhoea, occurring in 19.8% (160/807) of patients in the linaclotide arm and in 3.0% (24/798) of patients in the placebo arm; other TEAEs reported more commonly in the linaclotide arm, together with the percentages of occurrence (in the linaclotide versus placebo arms), included abdominal pain (5.1% versus 3.3%, respectively), flatulence (4.3% versus 1.9%), headache (4.1% versus 3.1%), viral gastroenteritis (2.6% versus 1.4%) and abdominal distension (2.2% versus 1.1%)[3].

In trials 31 and 302, rates of withdrawal due to adverse events (AEs) were 7.9% and 10.2% for linaclotide-treated patients, respectively, versus 2.5% of the placebo group for both studies[3]. Diarrhoea was the main cause for withdrawals in the linaclotide arm; pooled data from the two trials showed that diarrhoea accounted for withdrawal of 5.3% of patients in the linaclotide arm and 0.4% of patients in the placebo arm[1,12].

In the open-label, long-term studies, LIN-MD-02 and MC-103-305, in which all patients received linaclotide, gastrointestinal tract events were the most frequent TEAEs, with diarrhoea occurring in 32.3% (693/2,147) of the IBS-C pooled population, although urinary tract infections and sinusitis were also among the most frequent TEAEs[3]. Approximately 10% of patients discontinued due to AEs, with around half of these due to diarrhoea and most of the remaining discontinuations due to other gastrointestinal events[3].

3.4 AWTTC critique

- Although linaclotide is licensed for the symptomatic treatment of IBS-C[2], no comparison of clinical efficacy was provided versus first-line treatments for IBS, such as antispasmodics and laxatives[1]. The applicant company has suggested that linaclotide should be considered as a second-line treatment, in patients for whom antispasmodics and/or laxatives are not tolerated or ineffective. However, the eligibility criteria of the trials submitted did not specify that patients should have failed to achieve a response following treatment with antispasmodics and/or laxatives[10]. It is unclear to what extent the population enrolled in the trials reflects the use of linaclotide as a second-line therapy.
- The company submission includes a post-hoc analysis of two phase III studies, which provided a comparison of linaclotide versus off-label use of antidepressants[1]. Patients who had been on stable doses of antidepressants before the trial [Commercial in confidence data removed] were allowed to continue this concomitant medication[1]. The company report no significant differences in baseline characteristics between the subgroup of patients with and without concomitant antidepressants. Any conclusions drawn from the post-hoc sub group analysis however should be viewed bearing in mind that the subgroup of patients who received placebo plus antidepressants may have had a worse baseline symptom profile than the subgroup who received linaclotide without antidepressants.
- The Committee for Medicinal Products for Human use (CHMP) notes that for trial 302 the results are robust and highly statistically significant with a net gain in responder rates of just under 20% for abdominal pain/discomfort and just over 20% for IBS degree of relief responders[3].

- Despite the clinically relevant results, CHMP points out that approximately 50% of patients will not adequately or fully benefit from linaclotide treatment[3]. To avoid use of linaclotide in patients who are not responsive, the Summary of Product Characteristics (SPC) recommends reconsideration of treatment if symptoms do not improve[2,3].
- Placebo-controlled linaclotide studies show that frequency of diarrhoea as an AE is highest among elderly patients[3]. CHMP expressed concern due to the vulnerability of this population to the consequences of diarrhoea (e.g. hypokalaemia, dehydration, or orthostatic hypotension), and the SPC advises careful and periodic assessment of the benefit-risk ratio in patients > 65 years[2,3].
- IBS is twice as common in women than men[4,5]; however, the patients in the pivotal studies were 90% female, thus limited data were available to support use in male patients[3]. There is also limited data in elderly patients and in patients from ethnic minorities[3]. CHMP suggest that the available data demonstrate similar efficacy for linaclotide in the male and female population[3]. The applicant company also argue that when considered according to demographic and disease characteristics, the IBS-C patient population studied in the pivotal studies: is representative of the IBS-C patient population that seek medical care, is medically diagnosed, and may benefit from pharmacological treatment.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis (CUA) of oral linaclotide (Constella®▼) 290 microgram hard capsules, taken once per day compared against off-label antidepressants, in patients with moderate to severe IBS-C, who have not responded adequately or cannot tolerate antispasmodics and/or laxatives.
This targeted population is a subpopulation of the licensed indication and the applicant company seeks to position linaclotide as second-line therapy. Amitriptyline is chosen as the comparator, on the basis of its price[1].

The analysis is based on a Markov model consisting of four health states defined in terms of treatment satisfaction or death. The company reports treatment satisfaction to be a driver of NHS costs and resource use in Wales and to a lesser extent disease severity. The model assumes four-weekly cycles over a five-year time horizon. Patients enter the model in the 'not satisfied' health state and, following initiation of treatment, either remain in that state or transition to one of the other health states i.e. 'moderately satisfied', 'satisfied' or 'dead'. A stopping rule is included in the model whereby at each four-week cycle the need to continue treatment is assessed. Patients are assumed to be treated with linaclotide until they transition to the 'not satisfied' health state, at which point they discontinue treatment and switch to antidepressants. Patients who discontinue linaclotide are assumed to move through the model based on the transition probabilities in the antidepressant arm. No stopping rule is applied to the antidepressant treatment arm.

The clinical data to populate the model are derived from trials 31 and 302, where treatment satisfaction was a secondary outcome. The five-point treatment satisfaction scale (1 = not at all satisfied, 2 = a little satisfied, 3 = moderately satisfied, 4 = quite satisfied, 5 = very satisfied)[1] is mapped to a three-point scale, by grouping categories.

Transition probabilities are derived for the three treatment satisfaction health states in the model. The transition probabilities for the extrapolation phase of the model (beyond 26 weeks) are based on the average of the transitions observed between 20 and 26 weeks. To support the positioning of linaclotide as second-line therapy, a retrospective sub-group analysis was conducted. Patients in the linaclotide arm not receiving concomitant antidepressants, and patients in the placebo arm receiving concomitant antidepressants, were identified to represent the intervention and comparator arms, respectively.

Utility values for the base case model are based on EQ-5D data collected in the two phase III trials. Average utility values were estimated for each of the five categories of the treatment satisfaction scale and mapped to the three-point scale, to compute treatment-specific health state utility values. Resource use estimates are based on clinical expert opinion and include GP, outpatient visits and accident and emergency attendances for the base case. Inpatient visits, colonoscopy, faecal calprotectin measurement and radiological procedures are included in a sensitivity analysis. The 28-day acquisition costs for the antidepressant arm are assumed to be £1.72, based on a 2 x 10 mg amitriptyline dose[1].

4.1.2 Results

Results of the base case analyses are summarised in Table 3. Linaclotide treatment was estimated to be more costly than off-label antidepressant treatment with amitriptyline by £459.44 and generated an additional 0.0894 quality-adjusted life-years (QALYs), over a five-year horizon. The incremental cost per QALY is £5,139.

Table 3. Results of the base case analysis based on a five-year horizon.

	Linaclotide	Antidepressants	Difference
Total costs	£2,977	£2,518	£459.44
Total QALYs	3.690	3.601	0.0894
ICER (£/QALY gained)	**£5,139**		
ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year			

The results of the one-way sensitivity and scenario analyses are summarised in Table 4. Lower and upper confidence limits were calculated for use in the sensitivity analysis using a Gamma distribution for costs and a Beta distribution for utilities; the standard error was estimated to be 20% of the mean. The one-way sensitivity analyses show the results to be sensitive to the disutility assigned to treatment with antidepressants and linaclotide, but fairly insensitive to the utilities assigned to the treatment satisfaction health states, costs and discount rate parameters.

The results of the scenario analyses are most sensitive to the alternative groupings for mapping the five-point treatment satisfaction scale to the three treatment satisfaction health states, as well as the inclusion of all resource uses and the assumptions surrounding treatment continuation. When alternative health state groupings are used, linaclotide dominates treatment with antidepressants (i.e. is less costly and more effective) for both alternative groupings. Linaclotide is also dominant when all resource use is considered in the model. An ICER of £8,837 per QALY gained resulted when treatment with linaclotide is assumed to continue regardless of treatment satisfaction. In all cases the ICER remained substantially below £20,000–£30,000 per QALY. The probabilistic sensitivity analysis (PSA) indicates that the probability of linaclotide being cost-effective is 92% and 95% based on cost-effectiveness thresholds of £20,000 and £30,000 per QALY, respectively. Threshold analysis indicates the effectiveness of linaclotide, in terms of patient satisfaction, could be reduced by 12.7% and 15.4% before the cost per QALY increases to £20,000 and £30,000, respectively.

Table 4. Results of sensitivity and scenario analyses.

Scenarios	ICER	Plausibility
Base Case	£5,139	
One-way sensitivity analyses		
Antidepressant daily costs		Initially patients are started on a low dose and the dose can be increased.
£1.38	£5,474	
£2.06	£4,802	
Cost of satisfied health state		There is uncertainty around the elicitation of resource utilisation in the model.
£6.26	£4,765	
£13.81	£5,589	
Cost of moderately satisfied health state		
£26.89	£6,090	
£59.34	£3,982	
Cost of not satisfied health state		
£48.20	£6,297	
£106.39	£3,729	
Satisfied health state utility		As determined by different patient satisfaction groupings.
0.86	£5,481	
0.88	£4,841	
Moderately satisfied health state utility		
0.76	£4,893	
0.78	£5,404	
Not satisfied health state utility		
0.70	£4,781	
0.74	£5,542	
Treatment disutility		Arbitrarily chosen.
Linaclotide = -0.02	£9,903	
Antidepressants = -0.02	£2,053	
Costs discount rate		
0%	£5,518	
6%	£4,895	
Outcomes discount rate		
0%	£4,830	
6%	£5,356	
Scenario analyses		
Alternative treatment satisfaction mapping five-point scale to three health states (two alternatives)	Dominant	Same limitations as in the base case
Antidepressant effectiveness. Satisfaction transitions based on placebo group from both phase III trials instead of comparator subgroup	£1,567	Data on add-on linaclotide to concomitant antidepressants would seem irrelevant to the sought indication.
Extrapolation of satisfaction transitions based on 8 to 26 weeks	£2,288	Same limitations as in the base case. No data beyond 26 weeks.
Extrapolation of satisfaction transitions based on 12 to 26 weeks	£2,187	
Extrapolation of satisfaction transitions based on 16 to 26 weeks	£3,933	

Table 4. (continued).

Scenarios		ICER	Plausibility
Scenario analyses (continued)			
Resource Utilisation. Not only GP, outpatient and accident and emergency departments		Dominant	Uncertainty regarding methodology used to derived resource use estimates for satisfied, moderately satisfied and not satisfied
Satisfied	- £9.67 per patient		
Moderately satisfied	- £79.42 per patient		
Not satisfied	- £201.49 per patient		
No stopping rule		£8,837	Whether linaclotide treatment would be discontinued on the basis of patient dissatisfaction alone is uncertain.
Cost of antidepressant therapy. Patients prescribed 1 x 10 mg daily of antidepressants = £0.80, instead of 2 x 10 mg daily = £1.72		£5,978	A more conservative case
Six-month time horizon		£3,300	The time horizon may not appropriately reflect the chronic nature of IBS-C
One-year time horizon		£3,475	
Ten-year time horizon		£4,938	The longer term horizon would more appropriately reflect the chronic nature of IBS-C

4.1.3 AWTTC critique

Strengths of the economic evidence include:

- Cost-utility analysis is based on available direct comparative clinical trial data.
- The company conducted a range of sensitivity and scenario analyses to test key assumptions.

Limitations of the economic evidence include:

- The extent to which the retrospectively identified subgroup represents the sought positioning of linaclotide, i.e. for patients who have not responded adequately or cannot tolerate antispasmodics and/or laxatives, is uncertain. The criterion applied to define the subgroup is based solely on the use of concomitant antidepressants; the use of prior treatments or duration of disease is not considered.
- The model health states are based on the secondary outcome measure of treatment satisfaction, considered by Welsh clinicians to be a driver of resource utilisation. The model is therefore reliant on associations between patient satisfaction with treatment, resource utilisation and utility weights. Although, the company assumes disease worsening to correspond to patient dissatisfaction with treatment and symptom relief to correspond to increased satisfaction with treatment, the relationship between patient satisfaction with treatment, disease progression and resource utilisation is unclear.
- The methods used, to estimate resource utilisation for each health state, lack robustness and are subject to uncertainty. It is not clear whether this reflects expected resource use associated with current treatment of IBS-C throughout Wales.
- The model relies on short-term comparative data to model potentially life-long treatment outcomes, which is an inevitable source of uncertainty and/or bias. Scenario analyses have explored varying assumptions.
- The reliability of the PSA is contingent upon the plausibility of the model structure and parameter inputs.

- There are no data available to compare prior antidepressant treatment and duration of disease, as well as efficacy results for the two subgroups of the overall population. It is somewhat unclear how the subgroup which received linaclotide but not antidepressants differed from the subgroup of patients receiving placebo with concomitant antidepressants at entry to the trials.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on published studies and Welsh population statistics, the applicant company estimated that there are 255,297 adults with IBS in Wales, of which 61,527 will have the IBS-C subtype[1,5]. It is estimated that 46.7% of patients receive regular prescribed medication for IBS[5], and 38.5% of these patients are not satisfied[1,13] with their current treatment, and therefore 10,925 patients are considered to be eligible for linaclotide[1]. In year one, 2% linaclotide market share is expected and a 36% discontinuation rate is assumed. Thus it is estimated that 140 Welsh patients would be treated with linaclotide in year one, rising to 1,409 by year five[1].

5.1.2 Results

The gross impact on the medicines budget is estimated to be £68,424 in year one, rising to £689,726 in year five. The company expects linaclotide, however, to reduce healthcare resource use costs due to improvement in the symptoms of IBS-C when displacing antidepressants. It further expects more patients on linaclotide treatment to experience greater treatment satisfaction and progress from 'not satisfied' to 'moderately satisfied' to 'satisfied', thereby reducing primary/secondary resource use as seen in Table 5. The net budget impact is estimated to be approximately £38,037 in year one rising to £300,900 in year five.

Table 5. Company-reported costs associated with use of linaclotide for the treatment of moderate to severe IBS-C[1].

	Year 1 (2013)	Year 2 (2014)	Year 3 (2015)	Year 4 (2016)	Year 5 (2017)
Currently treated patients	10,925	10,946	10,968	10,990	11,012
Number of eligible patients	218	547	987	1,539	2,202
Uptake (%)	2%	5%	9%	14%	20%
Treated patients	140	350	631	984	1,409
Net costs					
Medication costs	£68,424	£171,401	£309,139	£481,845	£689,726
Primary/Secondary care	−£27,251	−£77,028	−£148,593	−£241,934	−£357,126
Overall net cost†	**£38,037**	**£86,518**	**£146,378**	**£217,827**	**£300,990**
† the company consider that costs due to administration and monitoring, staffing, infrastructure and personal social services are not applicable[1].					

5.1.3 AWTTC critique

- It is assumed that patients who are not satisfied with current treatment are considered eligible for linaclotide. However, it is unclear if the number of eligible patients is representative of the number of patients who do not respond adequately or cannot tolerate antispasmodics and/or laxatives.
- The estimates to inform the prevalence of IBS-C subtype were taken from a UK-based survey, which would seem appropriate for Wales[5]. The estimate to inform the percentage of patients who are not satisfied with treatment, although not UK-specific, does include a subgroup of UK patients[13].
- The budget impact assumes a market uptake rate of 2% for year one. The justification for this rate and those for subsequent years is unclear. The rates may be underestimated given that the remaining non-linaclotide patients are considered to be unsatisfied with current treatment.
- The proportion of patients assumed to discontinue linaclotide due to being unsatisfied with treatment is 36%. There is uncertainty regarding the source of this estimate and no treatment acquisition cost of linaclotide is assumed for these patients prior to discontinuation.
- The model assumes an average primary/secondary resource use cost savings per patient based on patient satisfaction levels (satisfied, moderately satisfied, not satisfied), associated with the treatment of linaclotide instead of antidepressants. As these costs are based on the resource use estimates of the cost-effectiveness model, the limitations of this model equally apply to the budget impact analysis.

5.2 Comparative unit costs

Table 6. Examples of medicine acquisition costs[1,14].

Medicine	Example Dose regimen	Approximate costs per patient per year
Linaclotide (Constella®▼) 290 microgram hard capsules	290 micrograms once daily	£489.62
Laxatives†		
Bisacodyl 5 mg tablets	5 mg to 20 mg orally once daily	£13 to £50
Ispaghula husk 3.5 g sachet	one sachet up to twice daily	£27 to £54
Antispasmodics†		
Peppermint oil capsules (Mintec®)	one to two capsules three times daily	£92 to £184
Peppermint oil capsules (Colpermin®)	one to two capsules three times daily	£132 to £264
Hyoscine butylbromide 10 mg coated tablets	10 mg to 20 mg three to four times daily	£59 to £156
Mebeverine 135 mg tablets	135 mg three times daily	£52
Antidepressants*		
Amitriptyline 10mg and 25 mg film-coated tablets	10 mg to 30 mg once daily	£12 to £35
Fluoxetine 20 mg capsules	20 mg once daily	£13

† first line treatments; * second line treatments, off-label use
This table does not imply therapeutic equivalence of medication or the stated doses. Management may require the use of a combination of treatments. All costs are based on MIMS list prices as of 11 October 2013[14] with the exception of linaclotide (company-provided price)[1]. See SPCs for full details of appropriate use of the above products[2,15–22]

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, linaclotide (Constella®▼) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission highlighted an open-label, long-term safety trial, NCT00765999, of patients with IBS-C and CC treated with linaclotide which is expected to be published prior to August 2014[23].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 5 September 2013
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Definition of 12-week abdominal pain/discomfort responder[10]
Patients assessed their worst abdominal pain and abdominal discomfort, over the last 24 hours on an eleven-point scale from zero (none) to ten (very severe). A 12-week abdominal pain/discomfort responder was a patient who for ≥ 6 weeks out of the first 12 weeks of treatment, had an improvement of ≥ 30% from baseline in either mean worst abdominal pain score or mean abdominal discomfort score in a week, with neither score worsening from baseline during the week. Similarly, a 26-week abdominal pain/discomfort responder during trial 302 had improvement for ≥ 13 weeks.

Definition of 12-week IBS degree of relief responder[10]
Patients rated their IBS symptoms weekly via interactive voice response system telephone calls. A seven-point scale was used ranging from one, indicating "completely relieved", to seven, indicating "as bad as I can imagine". A 12-week IBS degree of relief responder was a patient who recorded a score of one or two for ≥ 6 weeks out of the first 12 weeks of treatment. Similarly, a 26-week IBS degree of relief responder during trial 302 had a score of one or two for ≥ 13 weeks.

Irritable bowel syndrome quality of life (IBS-QoL) instrument[10,24]
Patients scored themselves, at baseline and following treatment, for dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual and relationships. An overall average score was derived from these eight sub-scores.

EuroQoL-5 Dimensions (EQ-5D) utility[10,25]
Patients' responses, both at baseline and following treatment, to questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression were converted to a utility index.

EuroQoL-5 Dimensions visual analogue scale (EQ-5D VAS)[10,25]
Patients used a visual analogue scale to score their health state from 0 (worst imaginable) to 100 (best imaginable) at baseline and after treatment.

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