Eluxadoline for treating irritable bowel syndrome with diarrhoea

Technology appraisal guidance
Published: 30 August 2017
nice.org.uk/guidance/ta471
Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
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1 Recommendations

1.1 Eluxadoline is recommended as an option for treating irritable bowel syndrome with diarrhoea in adults, only if:

- the condition has not responded to other pharmacological treatments (for example, antimitility agents, antispasmodics, tricyclic antidepressants) or
- pharmacological treatments are contraindicated or not tolerated, and
- it is started in secondary care.

1.2 Stop eluxadoline at 4 weeks if there is inadequate relief of the symptoms of irritable bowel syndrome with diarrhoea.

1.3 These recommendations are not intended to affect treatment with eluxadoline that was started in the NHS before this guidance was published. Adults having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.
### The technology

<table>
<thead>
<tr>
<th>Description of the technology</th>
<th>Eluxadoline (Truberzi, Allergan) is an opioid receptor agonist and delta-opioid receptor antagonist that binds to opioid receptors in the digestive system and slows down the movement of food through the gut.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marketing authorisation</td>
<td>Eluxadoline is indicated in adults for the treatment of irritable bowel syndrome with diarrhoea.</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>The most common adverse reactions with eluxadoline are gastrointestinal, including nausea, constipation and abdominal pain. For full details of adverse reactions and contraindications, see the summary of product characteristics.</td>
</tr>
<tr>
<td>Recommended dose and schedule</td>
<td>100 mg twice daily given orally.</td>
</tr>
<tr>
<td>Price</td>
<td>The list price is £88.20 per pack of 56 tablets (company submission). Costs may vary in different settings because of negotiated procurement discounts.</td>
</tr>
</tbody>
</table>
3 Evidence

3.1 The appraisal committee (section 6) considered evidence submitted by Allergan and a review of these submissions by the evidence review group. See the committee papers for full details of the evidence.
4 Committee discussion

4.1 The appraisal committee reviewed the data available on the clinical and cost effectiveness of eluxadoline, having considered evidence on the nature of irritable bowel syndrome with diarrhoea (IBS-D) and the value placed on the benefits of eluxadoline by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Nature of the condition

4.2 The committee was aware of the experiences of people with IBS-D. It heard that IBS-D is diagnosed after physicians rule out other conditions, including inflammatory bowel disease, colorectal cancer and bile acid malabsorption. It heard that the most common symptoms are urgency (an urgent need to defecate) and abdominal pain. The committee understood that the unpredictable nature of symptoms can cause anxiety and affect daily activities (such as travelling with no access to a toilet). It was aware that these symptoms can change over time and in severity and can affect a person's quality of life. The committee heard from the patient expert that a choice of treatment options was desirable, and agreed that people would welcome additional options to treat the condition. The committee concluded that IBS-D is a condition that can greatly impact on a person's quality of life.

Current practice

4.3 The committee heard from the clinical experts that treating IBS-D focuses on controlling symptoms, and generally follows the NICE guideline on irritable bowel syndrome in adults: diagnosis and management. Clinicians first encourage changes in lifestyle, for example, in diet and exercise. Clinicians may then offer patients medication and non-pharmacological treatments such as psychological treatments, like hypnotherapy and cognitive behavioural therapy. The committee heard that there are also several pharmacological treatments available, the choice of which depends on the presence and severity of symptoms, and whether to continue treatment depends on whether the patient improves. It understood that these pharmacological treatments include antimotility agents (such as loperamide and opiates), antispasmodics (such as mebeverine) and that further treatment options include tricyclic antidepressants. The committee was aware that some medications are available...
'over-the-counter', that is they do not need a prescription from the doctor and are not always funded by the NHS. It heard from the clinical experts that opiates were associated with constipation and bloating. The committee concluded that both pharmacological and non-pharmacological treatment options are available.

Position of eluxadoline in the treatment pathway and population

4.4 The committee heard from the clinical experts that they would most likely offer eluxadoline to people whose condition has not responded to other currently available treatments, or when these treatments are contraindicated or not tolerated. Furthermore, it heard that eluxadoline was most likely to be offered in secondary, rather than primary care. The committee noted that, although eluxadoline had a marketing authorisation for the treatment of IBS-D in adults, eluxadoline was placed as a third-line pharmacological treatment in the company's decision problem (that is, after antimotility/antispasmodic treatments and tricyclic antidepressants). It understood from the company that eluxadoline would be used only after all the other treatments (such as loperamide) have been tried. The committee concluded that eluxadoline would be started in secondary care, and that the most appropriate population for eluxadoline included people whose condition had not responded to other pharmacological treatments, or when these treatments are contraindicated or not tolerated.

Comparators

4.5 The committee considered the most appropriate treatments in NHS practice with which to compare eluxadoline. It recognised that the company's clinical evidence and economic modelling compared eluxadoline with non-pharmacological therapy (both allow rescue therapy with loperamide). It noted that this differed from the comparator listed in NICE's final scope, which was best supportive care (such as antispasmodics, antimotility agents and tricyclic antidepressants) without eluxadoline. The committee heard from the clinical experts that most patients would have exhausted other pharmacological and non-pharmacological therapies before starting eluxadoline. It concluded that it was appropriate to compare eluxadoline with non-pharmacological therapy.
Clinical effectiveness

Pivotal clinical trials

4.6 The committee noted that the evidence for eluxadoline came from 3 double-blind randomised controlled trials: IBS-2001 (a phase 2 trial), IBS-3001 and IBS-3002 (both phase 3 trials). The populations were diagnosed with IBS-D using the Rome III criteria and were mainly in the US; the average age was about 45 years. Across all 3 trials, eluxadoline (at doses of 5 mg, 25 mg, 75 mg, 100 mg, 200 mg, twice daily in IBS-2001; 75 mg, 100 mg, twice daily in IBS-3001 and IBS-3002) was compared with placebo, although the trials allowed loperamide as a ‘rescue’ therapy.

Clinical outcomes

4.7 The committee heard that the primary outcome was a composite response of pain and stool consistency, noting that this was not used in the company’s economic modelling (the company instead used IBS-quality of life [IBS-QoL] and pain), see section 4.10. In IBS-3001 and IBS-3002, patients were considered ‘composite responders’ if they had completed at least 50% of their diary entries for pain and stool consistency and their pain score in the past 24 hours had improved by 30% or more compared with baseline (average of daily worst abdominal pain the week before randomisation; and a Bristol Stool Scale score less than 5 or the absence of a bowel movement). In IBS-2001, ‘composite responders’ were defined in a similar way. The committee heard from clinical experts that composite response was not used in NHS practice and understood that there was no widely accepted objective measure of treatment response in clinical practice. It heard from the clinical and patient experts that diarrhoea (as measured by the Bristol Stool Scale score) and pain were the most important outcomes for patients because they relate to patients’ ability to do routine activities and affect their quality of life. The committee considered that the trial outcomes were complicated and differed from those used in the NHS. However, it acknowledged that the definition of the composite response included both the Bristol Stool Scale score and pain. The committee was encouraged that the company had identified IBS-QoL and pain as predictors of quality of life as measured by EQ-5D, which it used in the revised economic modelling (see section 4.10). The committee concluded that the company’s primary outcome (that is, the composite measure of stool consistency and pain) was an appropriate measure of response for eluxadoline in IBS-D, but it was more...
complicated and more specific than outcomes used in current practice. It concluded that individual outcomes (stool consistency, pain, and disease-specific quality of life) were important measures of treatment response.

Clinical effectiveness of eluxadoline compared with placebo

4.8 The committee discussed the results of the clinical trial evidence and noted that the company's meta-analysis used pooled results from IBS-2001, IBS-3001 and IBS-3002. The committee discussed each outcome:

- **Composite response**: the committee noted that a higher proportion of patients randomised to eluxadoline (100 mg twice daily) had a composite response (as defined in section 4.7) than those randomised to placebo across all 3 trials (see table 1). The committee concluded that eluxadoline increased the composite response in people with IBS-D. It observed that the benefit appeared to occur within 4 weeks to 6 weeks of starting treatment.

- **Other outcomes**: the committee noted that the changes in the total score or the Bristol Stool Scale score, the daily pain score, adequate relief of symptoms and IBS-QoL at 26 weeks favoured eluxadoline in the pooled fixed-effects model in the meta-analysis. The committee concluded that people with IBS-D having eluxadoline had greater adequate relief, improved stool consistency, less pain and improved quality of life.

Table 1: Composite response results

<table>
<thead>
<tr>
<th></th>
<th>'Responder', n (%)</th>
<th>p value</th>
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<tbody>
<tr>
<td><strong>IBS-2001</strong></td>
<td></td>
<td></td>
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<tr>
<td>Eluxadoline 100 mg twice daily (n=163)</td>
<td>18 (11.0)</td>
<td>&lt;0.10</td>
</tr>
<tr>
<td>Placebo (n=159)</td>
<td>9 (5.7)</td>
<td>–</td>
</tr>
<tr>
<td><strong>IBS-3001</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eluxadoline 100 mg twice daily (n=426)</td>
<td>125 (29.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo (n=427)</td>
<td>81 (19.0)</td>
<td>–</td>
</tr>
<tr>
<td><strong>IBS-3002</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eluxadoline 100 mg twice daily (n=382)</td>
<td>125 (32.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo (n=382)</td>
<td>77 (20.2)</td>
<td>–</td>
</tr>
</tbody>
</table>
Placebo response rate

4.9 The committee was aware that all 3 trials were placebo controlled and noted that there was a high placebo response rate in the trials (that is, placebo improved outcomes). It understood from the clinical experts that a large placebo response for overall symptoms was common in trials in people with IBS and that, on average, people with IBS-D on placebo in trials improved by at least 30% from baseline. The committee concluded that the placebo response seen for eluxadoline was typical of IBS-D trials.

Cost effectiveness

Model structure

4.10 The committee considered the company's Markov state transition model used to estimate the cost effectiveness of eluxadoline compared with non-pharmacological therapy. The company identified that IBS-QoL and pain were most strongly predictive of quality of life (as defined by EQ-5D) and so the model contained 1 death state plus 16 health states combining 4 categories of IBS-QoL, 2 categories of pain and 2 categories of stopping treatment:

- IBS-QoL: 4 categories from a change from baseline in IBS-QoL score (less than 0, 0 or more to less than 14, 14 or more to less than 28 and 28 or more)
- pain: 2 categories from change from baselines in pain (less than 30% and 30% or more)
- stopping treatment: 2 categories: people did or did not stop treatment at 4 weeks.

The committee recalled that clinical and patient experts considered that reducing pain was an important clinical outcome. It was encouraged that the results of the company's regression analysis showed that pain and IBS-QoL were the most important factors in predicating ED-5D. The committee was aware that the company used the outcome 'adequate relief' only to model stopping treatment in its model. It understood that the company assumed that a fixed proportion of the people whose condition was inadequately relieved would stop treatment at 4 weeks based on the clinical trials. The committee heard that the evidence review group (ERG) thought that stopping treatment should be linked to the clinical effectiveness in the model structure. The company stated that it had considered this approach, but chose not to incorporate 'adequate relief' because it would have created too many health states. The committee
was aware that, if a model has too many health states, there may not be sufficient data to populate it and accepted the company's explanation. The committee concluded that the model structure was appropriate for decision-making.

**Stopping treatment early**

4.11 The committee discussed how the company modelled stopping treatment in the first 4 weeks. It heard from the clinical experts that the decision to continue or stop treatment would normally happen between 4 weeks and 6 weeks after starting treatment, which was supported by the data on time to treatment effect. The committee understood that a clinical specialist would stop treatment based on a patient's self-assessed relief of symptoms. It was aware that the model included a 'stopping rule', that is, after 4 weeks, people who did not have adequate relief (those who responded negatively to the question 'over the past week have you had adequate relief of your IBS symptoms?') stopped treatment with eluxadoline or stopped non-pharmacological therapy and returned to their baseline utility. The company assumed that the proportion of people in 'real-life' who stopped treatment would be the same as that in the trial. The committee noted that, at 4 weeks, 37.4% of those in the eluxadoline arm and 50.3% in the non-pharmacological treatment arm reported inadequate relief and would stop treatment.

- The committee recalled the intended population included people who do not tolerate, or whose condition does not respond to, antimitotility and antispasmodic treatments. The committee expressed concern over whether treatment could be stopped in the non-pharmacological treatment arm because people in that arm would not be having any treatment.

- The committee was aware of concerns expressed by the ERG that a higher proportion of the non-pharmacological therapy arm (50.3%) had inadequate relief at week 4 compared with the eluxadoline arm (37.4%). Because of this, it removed the observed placebo response from 50.3% of the control arm, such that the modelled benefits for those continuing on eluxadoline did not take into account the placebo response.

- The company explained that the placebo effect was not stripped out because there was little difference in the baseline utility (utility, 0.63) and the utility of those who continued non-pharmacological treatment (utility, 0.65).

- The committee heard that the ERG preferred to equalise the proportion of those stopping in each arm (that is, 37.4% in both the eluxadoline arm and the non-
pharmacological arm) at 4 weeks, and to assume that people stop treatment then 'return' to their utility at baseline. The committee was unconvinced by this approach and considered that this would be a 'worst case' scenario.

The committee agreed that there was still uncertainty about the impact of any placebo effect and the stopping rule. It concluded that, despite the uncertainty, including a 'stopping rule' at 4 weeks was appropriate, and that it considered the company's methods to be more plausible than the ERG's.

**Stopping treatment beyond 4 weeks**

4.12 The committee was aware that, to estimate the rate of stopping treatment after 4 weeks, the model extrapolated data on the duration of treatment in the pooled clinical trials. The committee noted that the company used log-normal curves in each arm to extrapolate beyond the trial data. For people who stopped treatment after 4 weeks and, as such, did not have ongoing measures of quality of life, the company carried forward the person's last observed quality of life for the rest of the model. People who stopped eluxadoline continued to have 25% of the relative benefit for the remainder of the model, despite having stopped treatment. The committee noted some concerns from the ERG:

- The treatment duration data in the trial showed little difference between the eluxadoline arm and the non-pharmacological treatment arm but, once extrapolated, showed that fewer people having eluxadoline stopped treatment compared with non-pharmacological therapy.

- The health-state utilities in the trials were generally higher in the eluxadoline arm. Fewer people having eluxadoline stopped treatment once the data were extrapolated, so the magnitude of benefit in the eluxadoline arm was increased.

- The plausibility of 25% of the relative benefit of eluxadoline being maintained over the lifetime of the model (5 years) was uncertain, and no longitudinal data was presented to verify this benefit. The ERG highlighted that the company based this assumption on clinical opinion.

The ERG suggested that an alternative approach to stopping treatment after 4 weeks was to assume both people on eluxadoline and people not on eluxadoline would be have the same utility values by using a single extrapolation curve for both arms, and to assume no relative benefit. The committee considered it unlikely that there was a
continuing benefit after stopping treatment, and highlighted that the company presented no clinical evidence to support this assumption. It also agreed with the ERG that the benefits to those stopping treatment should be the same in each arm. The committee concluded that assuming that a 25% relative benefit of eluxadoline would be maintained over the life time in the model was implausible. It also concluded that a single treatment curve should be used to extrapolate those who stop treatment for both arms.

Health-related quality of life

4.13 The committee noted that EQ-5D scores were collected in IBS-2001 and used by the company to populate its cost-effectiveness model. The committee noted that the company combined the eluxadoline and placebo groups to estimate health-related quality of life for the health states. It was aware that IBS-3001 and IBS-3002 did not collect EQ-5D data, but noted that the company explored mapping the health outcomes collected in the trials to estimate EQ-5D scores. The committee examined the results and noted that using mapped utility scores did not have a large impact on the cost-effectiveness results:

- company base-case incremental cost-effectiveness ratio (ICER) using IBS-2001 only, £5,576 per quality-adjusted life year (QALY) gained
- company's mapped ICER (using IBS-2001, IBS-3001 and IBS-3002), £6,124 per QALY gained.

4.14 The committee noted that using EQ-5D scores reported directly from patients was a preferred method in NICE’s guide to the methods of technology appraisal 2013 (section 5.3.1) and it concluded that the utilities measured in the trial provided by the company were appropriate for decision-making.

Costs and resource use

4.15 The committee considered the resource use estimated by the company in the model. It was aware that even small changes in costs changed the estimates of cost effectiveness. It noted that the company had surveyed GPs to estimate the resource use of patients with IBS-D, but had a number of concerns. The committee recalled that clinical experts had previously stated that specialists rather than GPs would prescribe eluxadoline and that the GP survey overestimated the number of endoscopies per patient per year and might have been subject to recall bias. The committee concluded at its first meeting that an
alternative source from the literature (Fisher et al., 2016 – a scenario analysis) provided the most plausible estimate available. In its response to the appraisal consultation document, the company conducted a questionnaire with 12 UK gastroenterologists, to reflect using eluxadoline in secondary care. The committee was encouraged to see that the survey was conducted in secondary care, but noted the ERG's concern that the company applied costs of scoping (sigmoidoscopy, endoscopy and colonoscopy) as an annual ongoing cost for the life time of the model. The committee considered that these diagnostic procedures were unlikely after a diagnosis of IBS-D. It concluded that the questionnaire with gastroenterologists was satisfactory for decision-making, but ongoing scoping costs of diagnostic procedures should not be included.

**Cost-effectiveness results**

4.16 The committee noted that the company's base-case ICER for eluxadoline compared with non-pharmacological treatment was £5,576 per QALY gained. It recalled some of its earlier conclusions, specifically:

- An ongoing 25% benefit in people who have stopped eluxadoline after 4 weeks should not be applied (see section 4.12).

- The same costs and benefits should be applied for people who stop treatment after 4 weeks, irrespective of which treatment arm they are in (see section 4.12).

- Ongoing scoping (sigmoidoscopy, endoscopy and colonoscopy) costs should not be included in the model (see section 4.15).

4.17 The committee examined a scenario analysis provide by the ERG that contained most of its preferred assumptions (see section 4.16). It noted that the ICER for eluxadoline was £12,049 per QALY gained compared with non-pharmacological treatment. The committee was aware that this scenario limited scoping costs to 2 years, but did not remove them completely (see sections 4.15 and 4.16). It was confident that this change would only marginally increase the ICER. Therefore, the committee concluded that the ICER was likely to be within the range normally considered a cost-effective use of NHS resources.
Innovation

4.18 The committee noted that the company considered eluxadoline to be an innovative technology. It was aware that the company claimed that eluxadoline was the first in its class, had a different mechanism of action from other drugs and addresses multiple symptoms of IBS-D. However, the committee heard from the clinical experts that eluxadoline was not substantially new and different from currently available treatments. The committee was aware that opioid agonists have a long history in treating diarrhoea. The committee concluded that it did not consider eluxadoline a step-change in the treatment of IBS-D.

Pharmaceutical Price Regulation Scheme 2014

4.19 The committee was aware of NICE’s position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Conclusion

4.20 The committee recalled its earlier conclusion that IBS-D can have a substantial impact on a person's quality of life. It noted that eluxadoline is likely to be used secondary care in people whose condition has not responded to other pharmacological treatments, or when these treatments are contraindicated or not tolerated. In addition, it noted that treatment is likely to be stopped at 4 weeks if there is inadequate relief of symptoms. It also noted that the ICER was likely to be within the range normally considered a cost-effective use of NHS resources. Therefore, the committee concluded that eluxadoline could be recommended as a treatment option for IBS-D provided that it is stopped at 4 weeks if there is an inadequate relief of symptoms.
### Summary of appraisal committee’s key conclusions

<table>
<thead>
<tr>
<th>TA471</th>
<th>Appraisal title: Eluxadoline for treating irritable bowel syndrome with diarrhoea</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key conclusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eluxadoline is recommended as an option for treating irritable bowel syndrome with diarrhoea (IBS-D) in adults, only if:</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>• the condition has not responded to other pharmacological treatments (for example, antimotility agents, antispasmodics, tricyclic antidepressants) or</td>
<td></td>
<td></td>
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<tr>
<td>• pharmacological treatments are contraindicated or not tolerated, and</td>
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<tr>
<td>• it is started in secondary care.</td>
<td></td>
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<tr>
<td>Stop eluxadoline at 4 weeks if there is inadequate relief of the symptoms of irritable bowel syndrome with diarrhoea.</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>The committee recalled its earlier conclusion that IBS-D can have a substantial impact on a person’s quality of life. It noted that eluxadoline is likely to be used secondary care in people whose condition had not responded to other pharmacological treatments, or when these treatments are contraindicated or not tolerated. In addition, it noted that treatment is likely to be stopped at 4 weeks if there is inadequate relief of symptoms. It also noted that the incremental cost-effectiveness ratio (ICER) was likely to be within the range normally considered a cost-effective use of NHS resources. Therefore, the committee concluded that eluxadoline could be recommended as a treatment option for IBS-D provided that it is stopped at 4 weeks if there is an inadequate relief of symptoms.</td>
<td>4.20</td>
<td></td>
</tr>
<tr>
<td><strong>Current practice</strong></td>
<td></td>
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</tr>
<tr>
<td>Clinical need of patients, including the availability of alternative treatments</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Both pharmacological treatments (such as antimotility agents, antispasmodics and tricyclic antidepressants) and non-pharmacological treatment options (such as dietary advice, hypnotherapy and cognitive behavioural therapy) are available to treat IBS-D.</td>
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<table>
<thead>
<tr>
<th>Proposed benefits of the technology</th>
</tr>
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<tbody>
<tr>
<td>The committee was aware of the clinical history of opioid agonists in treating diarrhoea. It noted statements from the company that eluxadoline was the first in its class, had a different mechanism of action from other drugs and addresses multiple symptoms of IBS-D. However, the committee concluded that it did not consider eluxadoline a step-change in treatment of IBS-D.</td>
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<table>
<thead>
<tr>
<th>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</th>
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<tbody>
<tr>
<td>The committee concluded that eluxadoline would be started in secondary care and that the most appropriate population for eluxadoline included people whose condition had not responded to other pharmacological treatments, or when these treatments are contraindicated or not tolerated.</td>
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</table>

<table>
<thead>
<tr>
<th>What is the position of the treatment in the pathway of care for the condition?</th>
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<tbody>
<tr>
<td>The committee concluded that eluxadoline would be started in secondary care and that the most appropriate population for eluxadoline included people whose condition had not responded to other pharmacological treatments, or when these treatments are contraindicated or not tolerated.</td>
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</table>

### Evidence for clinical effectiveness

<table>
<thead>
<tr>
<th>Availability, nature and quality of evidence</th>
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<tbody>
<tr>
<td>The committee noted that the evidence for eluxadoline came from 3 double-blind randomised controlled trials: IBS-2001 (a phase 2 trial), IBS-3001 and IBS-3002 (both phase 3 trials).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relevance to general clinical practice in the NHS</th>
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<tbody>
<tr>
<td>The committee noted that the individual outcomes (used in the trials) were important measures of treatment response.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Uncertainties generated by the evidence</th>
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<tbody>
<tr>
<td>The committee noted that composite response was not used in NHS practice.</td>
</tr>
<tr>
<td>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</td>
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<td>---</td>
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</table>
| Estimate of the size of the clinical effectiveness including strength of supporting evidence | A higher proportion of patients randomised to eluxadoline (100 mg twice daily) had a composite response than those randomised to placebo across all 3 trials. Composite response rates:  
- IBS-2001: eluxadoline, 11.0%; placebo, 5.7%  
- IBS-3001: eluxadoline, 29.3%; placebo, 19.0%  
- IBS-3002: eluxadoline, 32.7%; placebo, 20.2%. | 4.8 |

**Evidence for cost effectiveness**

| Availability and nature of evidence | The company presented an alternative measure of treatment success in its revised model structure at the second committee meeting, after identifying IBS-quality of life and pain as the most strongly predictive of EQ-5D based on regression analyses. | 4.10 |
| Uncertainties around and plausibility of assumptions and inputs in the economic model | The committee expressed concern about the plausibility of the company’s assumption around stopping treatment. Notably whether:  
- treatment could be stopped in the non-pharmacological treatment arm  
- 25% of the relative benefit of eluxadoline being maintained over the life time of the model was plausible. | 4.11, 4.12 |
<table>
<thead>
<tr>
<th>Incorporation of health-related quality-of-life benefits and utility values</th>
<th>EQ-5D scores were collected in IBS-2001 and used by the company to populate its cost-effectiveness model. No substantial health-related benefits were identified that were not included in the economic model.</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are the key drivers of cost effectiveness?</td>
<td>The plausibility and application of assumptions around stopping treatment had the biggest impact on the ICER.</td>
</tr>
<tr>
<td>Most likely cost-effectiveness estimate (given as an ICER)</td>
<td>The committee noted a scenario analysis provided by the evidence review group that contained most of their preferred assumptions resulted in an ICER of £12,049 per quality-adjusted life year gained. It was aware that this scenario limited scoping costs to 2 years, but did not remove them completely. However, it was confident that this would marginally increase the ICER.</td>
</tr>
<tr>
<td>Additional factors taken into account</td>
<td>PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>End-of-life considerations</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equalities considerations and social value judgements</td>
<td>No equality issues were identified during the appraisal.</td>
</tr>
</tbody>
</table>
5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has irritable bowel syndrome with diarrhoea and the doctor responsible for their care thinks that eluxadoline is the right treatment, it should be available for use, in line with NICE's recommendations.
6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Henry Edwards
Technical Lead

Jasdeep Hayre
Technical Adviser

Jenna Dilkes
Project Manager

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