



Northern Treatment  
Advisory Group

# **Eluxadoline for treatment of diarrhoea-dominant irritable bowel syndrome**

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## Summary

- Irritable bowel syndrome with predominant diarrhoea (IBS-D) is a chronic bowel disorder which causes abdominal pain, nausea, and altered bowel habit. Diarrhoea may be accompanied by faecal urgency or incontinence, with attendant loss of productivity and distress.
- Current first line management for diarrhoea is loperamide. Co-phenotrope and opioids may also be considered, but are not favoured due to their adverse effect profiles. Anti-motility drugs should be used as needed to produce a soft, well-formed stool
- Eluxadoline is a mixed opioid receptor agonist which has received a positive opinion from the EMA for treatment of IBS-D. This pharmacology is expected to allow opioid analgesia and reduction in intestinal motility, without causing mu-opioid receptor-mediated constipation. Marketing authorisation has not yet been granted, but is expected in the next 1-2 months.
- In two phase III clinical trials, eluxadoline 75 mg or 100 mg twice daily was compared to placebo for the outcome of treatment response, which was defined as improvement in abdominal pain by  $\geq 30\%$  plus Bristol Stool Form  $< 5$  on at least 50% of study days.
- Treatment response after 26 weeks was more common with eluxadoline 75 mg (27%) and eluxadoline 100 mg (31%) than placebo (20%, both comparisons  $p \leq 0.001$ ). When examined separately, stool consistency was significantly improved over baseline but abdominal pain was not.
- There are no available data comparing eluxadoline with other treatments for IBS-D, and efficacy data are limited to 26 weeks. Patients were only eligible for the clinical trials if they were not taking any other anti-diarrhoeal medicines meaning that the trial populations may not be representative of the target population in the UK.
- The most common adverse effects were gastrointestinal (e.g. constipation, nausea, abdominal pain). Several cases of pancreatitis and sphincter of Oddi dysfunction were reported in the eluxadoline groups. History of these conditions is a contraindication to use in the USA, where eluxadoline has been marketed for some time.
- The cost of eluxadoline is not yet known. Loperamide costs £26 to £71 per year, depending on the dose required to control symptoms.

## Introduction and background

Irritable bowel syndrome (IBS) is a chronic disorder which causes abdominal pain and discomfort, bloating, and change in bowel habit. Disease can be classified depending on the effect on bowel habit:<sup>1,2</sup>

- diarrhoea-dominant (IBS-D): >25% stools are loose and <25% are hard
- constipation-dominant (IBS-C): >25% stools are hard and <25% are loose
- mixed (IBS-M): patients alternate between experiencing IBS-C and IBS-D; >25% of stools are loose and >25% are hard

Other symptoms include nausea, dyspepsia, dysphagia, early satiety, faecal urgency and faecal incontinence associated with diarrhoea. Patients may also be susceptible to other symptoms such as migraine, asthma, back pain, lethargy, and urinary disorders.<sup>1</sup> Symptoms of IBS tend to follow a relapsing-remitting course and disease is often lifelong. People with a longer history of disease are less likely to ever recover, as are those experiencing chronic stress. IBS therefore has a potentially large impact on quality of life, productivity and psychological wellbeing.

Disease pathophysiology is not known, although several processes have been suggested as contributing factors. These include visceral hypersensitivity, and abnormal gastrointestinal motility, immune function, autonomic function, or CNS modulation. Similarly, clear disease triggers have not been identified. Suggested causes include gastroenteritis, inflammation, diet (including alcohol intake), antibiotic exposure, surgery, and family history.

IBS is common in the UK, with an estimated prevalence of 10-20% in the general population.<sup>2</sup> This figure may be higher since many patients with symptoms of IBS do not seek medical advice. Around half of sufferers may be undiagnosed in the UK.<sup>3</sup> Symptoms are twice as common in women compared to men. IBS is more common in people aged 20-30 years, but there is also a significant burden of disease in older people.

Opioid receptors in the gut have a role in gastrointestinal motility, secretion, and sensation. Receptors can be divided into several classes, including mu, delta, and kappa. Each class can be further divided into several subtypes, and the precise function of each is not currently clear. In addition receptors can form heterodimers, which alters the binding properties and subsequent physiologic effects.<sup>4</sup>

Eluxadoline (Truberzi®▼, Allergan) is a mixed mu opioid receptor agonist and delta opioid receptor antagonist. It has been suggested that this pharmacology allows opioid analgesia and reduction in intestinal motility, without causing mu-opioid receptor-mediated constipation.<sup>5</sup> Eluxadoline received a positive opinion in July 2016 for use for the treatment of IBS-D in adults. It has not yet received a marketing authorisation; this normally takes 2-3 months following a positive opinion.

## Guidance and related advice

NICE clinical guideline 61 gives advice on the diagnosis and management of IBS in primary care. Diagnosis should be considered in patients who present with abdominal pain or discomfort, bloating, or change in bowel habit. IBS is diagnosed if the patient has:<sup>6</sup>

- abdominal pain or discomfort which is either:

- relieved by defecation, or
- associated with altered bowel frequency or stool form, AND
- at least two of:
  - altered stool passage (straining, urgency, incomplete evacuation)
  - abdominal bloating, distension, tension or hardness
  - symptoms are exacerbated by eating
  - passage of mucus

Other symptoms outlined above support the diagnosis. No investigations are required to confirm diagnosis, but full blood count, erythrocyte sedimentation rate, c-reactive protein and coeliac antibody testing should be carried out in order to exclude other diagnoses. Patients with any red flag symptoms should be referred to secondary care.

All patients with IBS should be given advice on diet and lifestyle, particularly around regulating their fibre intake. If symptoms persist single food avoidance and exclusion diets may be trialled, but advice should only be given by a healthcare professional with expertise in dietary management. Pharmacological management should be considered when lifestyle measures are inadequate, based on individualised assessment of the nature and severity of symptoms.

Antispasmodic agents such as mebeverine, alverine or peppermint oil should be considered for all patients.<sup>2</sup> Anti-motility drugs should be considered for those with IBS-D. Loperamide, which acts as a mu-opioid receptor agonist in the gut, is the first choice option.<sup>4</sup> It is helpful for controlling diarrhoea in IBS-D, but has little effect on abdominal pain.<sup>3</sup> Co-phenotrope (diphenoxylate and atropine) is licensed for acute diarrhoea and management of chronic and mild ulcerative colitis, but not for IBS-D.<sup>7</sup> It may be considered for use in IBS-D if loperamide treatment is not adequate, but use is associated with confusion and anti-cholinergic effects. Opioids such as codeine may also be considered but the potential for dependence should be taken into account. Patients should be advised to adjust the dose of anti-motility drugs according to response, aiming to produce a soft, well-formed stool (Bristol Stool Form Scale type 4).

If loperamide is not adequate tricyclic antidepressants (TCAs) may be considered, starting with 5-10 mg amitriptyline or equivalent taken once daily at night. Use should be reviewed regularly and the dose adjusted as needed, although not normally beyond 30 mg amitriptyline (or equivalent) daily. Selective serotonin reuptake inhibitors (SSRIs) may be considered if TCAs are ineffective. Use of TCAs and SSRIs for this indication is unlicensed but supported by national guidance, and has been shown to significantly improve global symptoms and abdominal pain.<sup>2,6</sup>

Rifaximin is licensed in the USA for treatment of IBS-D.<sup>8</sup> There appear to be no current plans to seek marketing authorisation for this indication in the UK, where rifaximin is licensed only for treatment of traveller's diarrhoea and reduction of recurrence of hepatic encephalopathy.<sup>9,10</sup> Rifaximin is not recommended by UK guidance on treatment of IBS-D.

Consideration should be given to referring patients who do not respond adequately to pharmacological treatment for psychological interventions such as cognitive behavioural therapy.

## Clinical efficacy

Two phase III trials have been published in a single trial report.<sup>5</sup> The trials had identical designs except that one (IBS-3001) lasted 52 weeks and the other (IBS-3002) lasted 26 weeks. Participants were adults aged 18-80 who had IBS-D according to the Rome III diagnostic criteria. These are broadly in line with NICE diagnostic criteria but with a lower requirement for presence of symptoms:<sup>3</sup>

- Recurrent abdominal pain or discomfort at least 3 days a month in the past 3 months, associated with two or more of:
  - Improvement with defecation
  - Onset associated with a change in frequency of stool
  - Onset associated with a change in form (appearance) of stool
- Criteria must be fulfilled for the past 3 months, with a history of symptom onset at least 6 months before diagnosis.

Patients were only included if, in the week prior to randomisation, all of the following applied:

- Mean pain score >3.0 on a scale of 0 (no pain) to 10 (worst imaginable pain)
- Mean Bristol Stool Form score of  $\geq 5.5$  on a scale of 1 (hard stool) to 7 (watery diarrhoea)
- Bristol Stool Form score  $\geq 5$  on at least 5 days
- Mean IBS-D global symptom score of  $\geq 2$  on a scale of 0 (no symptoms of IBS-D) to 4 (very severe symptoms of IBS-D).

Patients were excluded if they had a history of inflammatory bowel disease, coeliac disease, abnormal thyroid function, alcohol abuse, binge drinking, pancreatitis, sphincter of Oddi dysfunction, post-cholecystectomy biliary pain, cholecystitis within the previous 6 months, or a known allergy to opioids. Patients taking drugs affecting stool (antidiarrhoeal drugs, antispasmodics, antiemetics, antacids, opioids or enemas) were also excluded. Those taking antidepressants were eligible as long as the dose had been stable for at least 12 weeks at the time of enrolment.

The studies consisted of several phases:

- Pre-screening – up to 1 week
- Screening – up to 3 weeks
- Double-blind treatment – assessment of safety and efficacy – 26 weeks
- Double-blind treatment – additional assessment of safety – 26 weeks, followed by 2 weeks post-treatment follow-up (trial IBS-3001 only)
- Single-blind follow-up – all patients switched to placebo to assess rebound symptoms – 4 weeks (trial IBS-3002 only)

For the treatment phases, patients were randomised to receive eluxadoline 75 mg or 100 mg twice daily, or matching placebo. During the double-blind treatment phase (and the single-blind follow-up phase of trial IBS-3002) patients recorded daily symptom scores using an interactive voice-response system as an electronic diary. Abdominal pain, discomfort and bloating were each scored on a scale of 0 (no symptoms) to 10 (worst imaginable symptoms). Patients also recorded their stool consistency score, number of bowel movements and whether they were associated with urgency or incontinence, and the IBS-D global symptom score. Adequate relief of IBS symptoms was recorded weekly by patients responding with a yes or no

answer to the question “over the past week, have you had adequate relief of your IBS symptoms?”

The primary endpoint was the proportion of patients who had a composite treatment response, defined as a reduction of  $\geq 30\%$  from average baseline score for worst abdominal pain, plus a stool consistency score of  $< 5$  on  $\geq 50\%$  of study days. On days with no bowel movement, a reduction of  $\geq 30\%$  in abdominal pain was considered adequate for treatment response. The endpoint was evaluated after 26 weeks (182 days), and at least 110 diary entry days were required for the patient to be considered to have a treatment response.

Secondary endpoints were evaluated at 12 weeks, which was the time point chosen for evaluation of efficacy in the United States. The secondary endpoints were:

- Worst case analysis – used the same composite outcome as the primary outcome, but required a positive response on at least 50% of study days, regardless of adherence to the electronic diary. Days with no diary entry were assumed to be non-response days. Therefore during the 12 week assessment period, the worst case analysis required at least 42 positive treatment response days to meet the criteria for the primary endpoint.
- Pain relief – reduction of  $\geq 30\%$  from baseline in score for the worst abdominal pain on  $\geq 50\%$  of days
- Improvement in stool consistency – stool consistency score of  $< 5$ , or absence of bowel movement plus improvement of  $\geq 30\%$  from baseline score for worst abdominal pain
- Score of 0 or 1 in IBS global symptom score, or improvement of  $\geq 2$  points over baseline, on  $\geq 50\%$  of days
- Adequate relief of IBS symptoms in at least  $\geq 50\%$  of study weeks, as assessed by asking “over the past week, have you had adequate relief of your IBS symptoms?”

The studies enrolled a total of 2,428 patients, most of whom were female (approx. 66%) and white (86%). The mean age was approximately 45 years. Treatment response was more common with eluxadoline 100 mg than placebo in both trials (see Table 1). Eluxadoline 75 mg did not produce a significant response in trial IBS-3001, but did in trial IBS-3002. When data from both trials were pooled, both eluxadoline doses were superior to placebo.

There was no significant difference between eluxadoline and placebo in abdominal pain. Other secondary endpoints generally favoured eluxadoline after 12 weeks treatment. After discontinuation, Bristol Stool Scale scores in the eluxadoline groups appear to gradually approach those in the placebo groups. However these data were only provided graphically, with no numerical values. There was no apparent rebound worsening of IBS-D symptoms.

**Table 1. Proportion of patients with treatment response [% (treatment difference compared to placebo)]**

	Eluxadoline		Placebo
	75 mg BD	100 mg BD	
<b>IBS-3001</b>	<b>n=426</b>	<b>n=427</b>	<b>n=427</b>
Composite treatment response, 24 weeks*	23.4% (4.4, p=0.11)	29.3% (10.3, p<0.001)	19.0%
Worst case analysis, 12 weeks	23.4% (p=0.01)	24.2% (p=0.006)	16.6%
Abdominal pain, 12 weeks	42.4% (p=0.40)	43.2% (p=0.28)	39.6%
Stool consistency, 12 weeks	30.0% (p=0.008)	34.3% (p<0.001)	22%
IBS-D global symptoms, 12 weeks	35.1% (p=0.05)	34.7% (p=0.06)	28.8%
Adequate relief of IBS symptoms, 12 weeks	52.9% (p=0.008)	54.2% (p=0.002)	43.8%
<b>IBS-3002</b>	<b>n=382</b>	<b>n=382</b>	<b>n=381</b>
Composite treatment response, 24 weeks*	30.4% (10.2, p<0.05)	32.7% (12.5, p<0.001)	20.2%
Worst case analysis, 12 weeks	28.3% (p<0.001)	28.3% (p<0.001)	13.9%
Abdominal pain, 12 weeks	48% (p=0.45)	51% (p=0.11)	45.3%
Stool consistency, 12 weeks	37% (p<0.001)	35.6% (p<0.001)	20.9%
IBS-D global symptoms, 12 weeks	43.6% (p<0.001)	42.4% (p<0.001)	29.6
Adequate relief of IBS symptoms, 12 weeks	60.1% (p=0.003)	58.4% (p=0.01)	49.2%
<b>Pooled</b>	<b>n=806</b>	<b>n=809</b>	<b>n=808</b>
Composite treatment response, 24 weeks*	26.7% (7.2, p=0.001)	31.0% (11.5, p<0.001)	19.5%

\* Primary endpoint.

P values represent comparison to placebo; eluxadoline doses were not compared.

## Safety

Safety data were collected for 52 weeks (IBS-3001) or 26 weeks (IBS-3002) and pooled to create one safety population. Adverse effects (AEs) affected 55-60% of participants (see table 2), while serious AEs were reported by 3-5%. There were no deaths during the trials. The most commonly reported AEs were gastrointestinal effects such as constipation, nausea, abdominal pain and vomiting.

Euphoria was reported by 2 patients in the eluxadoline 100 mg group (0.2%). A feeling of drunkenness was reported by one patient in each eluxadoline group (0.1% in each). Neither of these effects were reported in the placebo group, and there were no reports of any other opioid-like mood alterations.

Several cases of pancreatitis and spasm of the sphincter of Oddi were reported in the eluxadoline groups. The sphincter of Oddi, also known as the hepatopancreatic

sphincter, regulates entry of bile and pancreatic enzymes into the duodenum. Dysfunction can result in pancreatitis or elevated hepatic enzymes.<sup>11</sup> In the USA biliary duct obstruction, sphincter of Oddi dysfunction, history of pancreatitis and structural diseases of the pancreas are contraindications to use of eluxadoline. All patients without a gallbladder should be monitored during use and new or worsening abdominal pain, or biliary pain with elevation of liver or pancreatic enzymes, warrant discontinuation of eluxadoline in these patients.

The USA prescribing information also contraindicates eluxadoline in patients with a, severe (Child-Pugh class C) hepatic impairment, alcohol abuse, history of chronic or severe constipation, or suspected mechanical gastrointestinal obstruction. Patients who develop severe constipation for >4 days are recommended to discontinue use. There is no information on prescribing in special populations such as the elderly, children, or pregnant or breastfeeding women.

**Table 2. Pooled safety events from trials IBS-3001 and IBS-3002**

	Eluxadoline		Placebo (n=808)
	75 mg BD (n=807)	100 mg BD (n=859)	
All adverse events	486 (60.2%)	500 (58.2%)	450 (55.7%)
Serious adverse events	34 (4.2%)	41 (4.8%)	24 (3.0%)
Discontinuation due to adverse events	64 (7.9%)	69 (8%)	34 (4.2%)
Cardiac events	12 (1.5%)	17 (2.0%)	8 (1.0%)
Pancreatitis	2 (0.2%)	3 (0.3%)	0
Spasm of the sphincter of Oddi	1 (0.1%)	7 (0.8%)	0
<b>Most common adverse events (reported by ≥2% of patients in any study group)</b>			
Constipation	60 (7.4%)	74 (8.6%)	20 (2.5%)
Discontinuation due to constipation	1.1%	1.7%	0.2%
Nausea	65 (8.1%)	64 (7.5%)	41 (5.1%)
Discontinuation due to nausea	0.6%	0	0.5%
Abdominal pain	47 (5.8%)	62 (7.2%)	33 (4.1%)
Vomiting	32 (4.0%)	36 (4.2%)	11 (1.4%)
Abdominal distention	21 (2.6%)	22 (2.6%)	13 (1.6%)
Gastroenteritis	36 (4.5%)	19 (2.2%)	27 (3.3%)
Flatulence	21 (2.6%)	27 (3.1%)	18 (2.2%)
Upper respiratory tract infection	27 (3.3%)	47 (5.5%)	32 (4.0%)
Bronchitis	26 (3.2%)	27 (3.1%)	18 (2.2%)
Sinusitis	27 (3.3%)	24 (2.8%)	26 (3.2%)
Nasopharyngitis	33 (4.1%)	23 (2.7%)	27 (3.3%)
Dizziness	21 (2.6%)	28 (3.3%)	17 (2.1%)
Anxiety	10 (1.2%)	19 (2.2%)	14 (1.7%)
Increased ALT	17 (2.1%)	26 (3.0%)	12 (1.5%)

## Dosage and administration

Both the 75 mg and 100 mg strength tablets have been recommended for licensing by the EMA, but details of licensed posology and administration are not yet available.<sup>12</sup> The licensed dose in the USA is 100 mg, to be taken twice daily with food.<sup>11</sup> This is reduced to 75 mg twice daily in patients:

- without a gallbladder
- unable to tolerate 100 mg twice daily due to adverse effects
- receiving concomitant therapy with inhibitors of the transporter protein OATP1B1 (e.g. such as ciclosporin, gemfibrozil, antiretrovirals, rifampin or eltrombopag)
- with mild or moderate (Child-Pugh class A or B) hepatic impairment

## Cost analysis

The cost of eluxadoline is not yet available.

Loperamide is currently the first choice of anti-motility drug for IBS-D.<sup>2</sup> Loperamide 2 mg capsules are listed in the Drug Tariff as a category M product, currently £1.17 for a pack of 30.<sup>13</sup> The dose should be individualised in IBS-D to achieve a dose which produces a soft, well-formed stool, so the cost of treatment is variable. The BNF recommends a starting dose of 4-8 mg daily (costing £26 to £57 per person per year), and up to a maximum of 16 mg daily in divided doses (£71 per person per year).<sup>14</sup>

The cost impact of eluxadoline will depend on the difference in price compared to loperamide, and the proportion of patients who are switched from one drug to the other.

## Points to consider

Eluxadoline is licensed for treatment of adults with IBS with diarrhoea. The current first line option for this indication is loperamide, which has been shown to help with diarrhoea but has little effect on abdominal pain. The pivotal eluxadoline trials found a similar pattern of symptom relief with eluxadoline. It was not reported whether previous experience with loperamide is predictive of response to eluxadoline.

Eluxadoline appears to be effective at reducing symptoms of IBS-D. However, IBS is a disease of relapse and remission, and inclusion criteria required that recruited patients had pain, loose stools and a moderate IBS-D global symptom score in the week prior to randomisation. Some of the changes in symptoms scores may therefore be due to the normal natural history of the disease, or “regression to the mean”.

Patients taking anti-diarrhoeal and anti-spasmodic medicines prior to randomisation were excluded from the pivotal trials. Eluxadoline would likely be used in the UK following failure of the currently available treatment options, which includes routine use of anti-diarrhoeals and anti-spasmodics. The trial populations are therefore likely not representative of the UK target population. Similarly, the efficacy of eluxadoline on patients switching directly from loperamide is not known. There are no data available comparing eluxadoline with other drugs for diarrhoea, and no published efficacy data on use past 26 weeks.

**Author's declaration:** The author has no relevant interests to declare.

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