MTRAC
Midlands Therapeutics Review and Advisory Committee

Considerations for Commissioners

Eluxadoline *(Truberzi®▼)*

For the treatment of diarrhoea-predominant irritable bowel syndrome

Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the commissioning of eluxadoline:

- Current NICE guidance on the management of irritable bowel syndrome (IBS) in adults (CG61) advises loperamide as the first choice antimotility agent for diarrhoea in people with IBS followed by second-line options: tricyclic antidepressants (TCAs; at low dose [5 to 10 mg equivalent of amitriptyline, increase the dose if needed, but not usually beyond 30 mg]) or selective serotonin reuptake inhibitors (SSRIs) if TCAs are ineffective.
- It was the opinion of the committee that eluxadoline may be an alternative treatment option if treatment alternatives described in the NICE guidance have proved inappropriate or ineffective.
- NICE Technology Appraisal guidance on Eluxadoline for treating irritable bowel syndrome with diarrhoea (TA471) is also now available.

Strength of the evidence for efficacy

The evidence for eluxadoline was considered relatively weak. Two double-blind randomised controlled trials (RCTs) showed that eluxadoline-treated patients showed a greater response to a composite outcome of pain relief and stool consistency than with placebo but the European Medicines Agency commented that "this is considered of limited clinical relevance", and "that response rates according to the EMA evaluation did not exceed 32%, meaning that indeed at least 2/3 of the treated population do not experience (full) response".

MTRAC considered eluxadoline as a product that may be used in primary care.

Description of technology

Eluxadoline is an irritable bowel syndrome treatment launched in the UK in June 2017. It is licensed in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-D).

The recommended daily dose is 200 mg (100 mg tablet, twice daily). For people over 65 and those unable to tolerate the 200 mg daily dose, a dose of 150 mg daily can be given (75 mg, twice daily).

For full details see the Summary of Product Characteristics (SPC) including precautions relating to risks of pancreatitis and constipation.[1]

Background

Irritable bowel syndrome (IBS) is a chronic, relapsing and often life-long disorder, characterised by abdominal pain and discomfort associated with defaecation, a change in bowel habit together with disordered defaecation (constipation or diarrhoea or both), and the sensation of abdominal distension (bloating). People with IBS can suffer dehydration, lack of sleep, anxiety and lethargy, and can experience a significant reduction in quality of life as a result of the need for time off work, or the desire to avoid stressful or social situations.[2]

People with IBS can be subdivided according to the form of bowel-habit alteration into: diarrhoea predominant IBS (IBS-D), constipation-predominant IBS (IBS-C) or a group who experience alternating symptoms. Clinical management of the condition is driven by the predominant symptoms. In "IBS with diarrhoea (IBS-D)" patients need to have "loose (mushy) or watery stools in ≥25% and hard or lumpy stool <25% of bowel movements.[3]

IBS is usually diagnosed between the ages of 20 and 30 years. Prevalence in the general population is estimated to be between 10% and 20%; and based on 2013 population data, it is estimated that between 1.8 and 3.6 million people in England have IBS-D.[4] Recent trends indicate that there is also a significant prevalence of IBS in older people.[3] IBS diagnosis should be a consideration when an older person presents with unexplained abdominal symptoms.

The NICE guideline on Irritable Bowel syndrome in adults (CG61) includes advice on: diet, nutrition and lifestyle measures including the need for stress relief and physical exercise.[5]

Pharmacological treatment is dependent on the type of symptoms present: antispasmodics for the treatment of diarrhoea or laxatives for the alleviation of constipation (people should be discouraged from taking lactulose). The guidance advises that loperamide is the first choice of antimotility agent for diarrhoea in people with IBS. If loperamide, laxatives or antispasmodics have not helped, second-line treatment options include tricyclic antidepressants (TCAs; at low dose [5 to 10 mg equivalent of amitriptyline, increase the dose if needed, but not usually beyond 30 mg]) or selective serotonin reuptake inhibitors (SSRIs) if TCAs are ineffective.[5]

The NICE technology appraisal guidance for eluxadoline (TA471)[6] advises that it is an option for treating IBS-D if the condition has not responded to other pharmacological treatments, or they are contraindicated or not tolerated. The guidance also states that it should be started in secondary care.

Clinical evidence for efficacy and safety

Two phase 3 randomised controlled trials (IBS3001

and IBS3002) of similar design evaluated the efficacy of eluxadoline in adults with diarrhoea-predominant irritable bowel syndrome.[3,7]

Participants enrolled in the trials had a diagnosis of diarrhoea according to Rome III diagnostic criteria for IBS.[8] Other inclusion criteria were a minimum level of abdominal pain, stool consistency and bowel symptom score. Exclusion criteria were other gastrointestinal disorders (e.g. inflammatory bowel disease, or intestinal obstruction), a history of cholecystitis or pancreatitis, biliary duct disease, and sphincter of Oddi (SO) dysfunction were also exclusion criteria, as were a history of alcohol abuse or binge drinking. Patients with bile acid malabsorption were not excluded; which was later commented on in the European Medicines Agency (EMA) report[3].

Participants were randomised to treatment with twice daily doses of eluxadoline 75 mg, eluxadoline 100 mg or placebo for 26 weeks. In trial IBS3001, treatment continued for an additional 26 weeks for safety assessment only, whilst in trial IBS3002, participants were then switched to placebo in order to assess withdrawal effects.

The primary outcome measure was a composite treatment response defined as a reduction of at least 30% from the average baseline score for the worst reported abdominal pain on at least 50% of the days reporting symptoms (relief from abdominal pain) and, on the same days, a stool-consistency score less than 5. If the participant did not have a bowel movement, an improvement of at least 30% in the score for the worst abdominal pain was sufficient for a response on that day.

Secondary endpoints included:

- relief from abdominal pain (as defined above)
- improvement in stool consistency (score of less than 5, or the absence of a bowel movement if accompanied by relief from abdominal pain),
- improvement in the global symptom score (a score of 0 or 1, or an improvement of ≥ 2 over the baseline score, on ≥ 50% of days),
- adequate relief of IBS symptoms (a response of "yes" on ≥ 50% of the weeks to the following question: "Over the past week, have you had adequate relief of your IBS symptoms?").

In addition, the change from baseline in the IBS-QOL questionnaire score was assessed. As a secondary end-point, the composite response was also evaluated over each 4-week interval.

Results

After 26 weeks' treatment in trial IBS3001 a greater proportion of participants were responders in the eluxadoline 100 mg twice daily group (29.3%) *versus* placebo (19.0%; $p < 0.001$), but no significant difference was seen for treatment with eluxadoline 75 mg twice daily (23.4%). In the IBS-3002 trial, and in the pooled data analyses from both trials, significantly greater proportions of participants receiving either dose of eluxadoline responded to treatment *versus* placebo ($p \leq 0.001$).[7] There was no significant improvement in the mean scores for the worst abdominal pain, or in the percentage of patients who reported an improvement of 30% or more for the worst abdominal pain score. In the Supplementary appendix to the article, data is included for more stringent measures of pain reduction (i.e., ≥ 40% and ≥ 50%), that show that significance was reached for eluxadoline at a dose of 100 mg in both study periods assessed (weeks 1 through 12 and weeks 1 through 26).[7] In addition, both doses of eluxadoline showed significantly greater improvement than placebo with respect to stool consistency, frequency, and urgency, although no significant reduction in episodes of incontinence was noted.[7]

In a further analysis of pooled data from trials IBS3001 and IBS3002, there was a significantly greater response to the composite primary outcome in patients receiving eluxadoline 100mg or 75mg *versus* placebo, who previously reported inadequate prior treatment with loperamide. In those reporting adequate prior treatment, only the 100 mg eluxadoline dose showed a significantly greater response than placebo.[9]

Adverse events

26-week safety data were available from trial IBS3002, and 52-week data from trial IBS3001.[7] Analyses of pooled data from both trials (n = 2,814)[10] showed that the most common adverse events were constipation, nausea, upper respiratory tract infection, abdominal pain, headache and vomiting. Constipation occurred in 7 to 8% of eluxadoline-treated participants *vs*. 2.5% of those receiving placebo. The incidence of pancreatitis as a serious adverse event was 0.4% (7/1,839 patients).[10]

Considerations for cost impact

At current prices, the yearly cost of eluxadoline (100 mg twice daily) for the treatment of IBS-D is £1,149.75.

References

1. Allergan Ltd. Truberzi 100 mg film-coated tablets. EMC 2018
2. Irritable bowel syndrome. NICE CKS 2013
3. Assessment report: Truberzi. EMA 2016
4. Single Technology Appraisal: Eluxadoline for treating irritable bowel syndrome with diarrhoea (Final scope). NICE 2016
5. Clinical guideline CG61: Irritable bowel syndrome in adults - diagnosis and management. NICE 2008
6. Eluxadoline for treating irritable bowel syndrome with diarrhoea (TA471). NICE 2017
7. Lembo AJ et al. *N Engl J Med* 2016; 374(3):242-253.
8. Guidelines on the irritable bowel syndrome: mechanisms and practical management. Gut 2007
9. Lacy BE et al. *Am J Gastroenterol* 2017; 112(6):924-932.
10. Cash BD et al. *Am J Gastroenterol* 2017; 112(2):365-374.