MTRAC
Midlands Therapeutics Review and Advisory Committee

On the horizon:

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.

Strength of the evidence for efficacy

The evidence for eluxadoline was considered to be 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 new product that may be used in primary care. This information is provided in advance of the product launch and may be subject to change.

Description of technology

Eluxadoline is a new IBS-D treatment that received a marketing authorisation from the European Medicines Agency in September 2016, but has not yet been launched as a new product for use in the UK. 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 draft EU 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. People with IBS should be advised how to adjust their doses of laxative or antimotility agent according to their clinical response. The dose should be titrated according to stool consistency, with the aim of achieving a soft, well-formed stool (corresponding to Bristol Stool Form Scale type 4).[5]

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]

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.[6] Data are reported from the published article in the New England Journal of

Medicine[6], with additional notes from the European Public Assessment Report (EPAR) for eluxadoline.[3]

Participants enrolled in the trials had a diagnosis of diarrhoea according to Rome III diagnostic criteria for IBS.[7] The inclusion criteria also specified a minimum level of abdominal pain, stool consistency and bowel symptom score. Exclusion criteria related to other gastrointestinal disorders (e.g. inflammatory bowel disease, or intestinal obstruction). A history of cholecystitis was also a reason for exclusion, as well as a history for pancreatitis, biliary duct disease, and sphincter of Oddi (SO) dysfunction. Patients with bile acid malabsorption were not excluded; which was later commented on the EMA report. Patients with a history of alcohol abuse or binge drinking were also excluded.

Participants were randomised to treatment with twice daily doses of eluxadoline 75 mg, eluxadoline 100 mg or placebo for 26 weeks. In trial IBS3001, participants continued treatment 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 the proportion of patients who had a composite treatment response defined as a reduction of at least 30% from their average baseline score for their worst abdominal pain on at least 50% of the days they reported symptoms 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: pain relief (reduction of at least 30% from baseline in the score for the worst abdominal pain on at least 50% of days), improvement in stool consistency (stool consistency score of less than 5, or the absence of a bowel movement if accompanied by an improvement of at least 30% in the score for the worst abdominal pain, on at least 50% of days), 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), and 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 there was a significantly greater proportion of responders in the eluxadoline 100 mg twice daily group (29.3%) *versus* placebo (19.0%; $p < 0.001$), but no significant difference 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 showed a response to treatment versus placebo ($p \leq 0.001$).[6]

No significant improvement was seen in the mean scores for the worst abdominal pain or in the percentage of patients who reported an improvement of 30% or more in the score for the worst abdominal pain. 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).[6] 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.[6]

Adverse events

Safety data were collected over 26 weeks in trial IBS3002 and over 52 weeks in trial IBS3001.[6] The most common adverse events were nausea, constipation, and abdominal pain. The rate of discontinuation due to constipation was 1.1% among patients who received eluxadoline at a dose of 75 mg, 1.7% among patients who received eluxadoline at a dose of 100 mg, and 0.2% among patients who received placebo.[6]

The rate of discontinuation due to nausea was 0.6% and 0% among patients who received 75-mg and 100-mg doses of eluxadoline, respectively, and 0.5% among patients who received placebo.[6]

Considerations for cost impact

The manufacturer estimates that the yearly cost of eluxadoline 100 mg twice daily will be £945.35. This estimate may be subject to change following the NICE technology assessment appraisal.

References

1. EU Draft Summary of Product Characteristics. EMA 2016
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. Lembo AJ et al. Eluxadoline for Irritable Bowel Syndrome with Diarrhea. *N Engl J Med* 2016; 374(3):242-253.
7. Guidelines on the irritable bowel syndrome: mechanisms and practical management. Gut 2007 http://www.bsg.org.uk/pdf_word_docs/ibs.pdf