Eluxadoline: a treatment for IBS with diarrhoea in adults

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Eluxadoline (Truberzi) is an oral mixed opioid-receptor agonist/antagonist licensed for the treatment of irritable bowel syndrome with diarrhoea in adults. This article examines its properties, efficacy in clinical trials and side-effects.

The initial management of irritable bowel syndrome (IBS) entails dietary and lifestyle change and treatment with antispasmodic agents. For people with IBS and diarrhoea, loperamide is the anti-motility agent of first choice, adjusting the dose to achieve optimum stool consistency. If this is unsatisfactory, treatment with a low-dose tricyclic antidepressant should be considered, with an SSRI a further option if this is unsuccessful. Referral for cognitive behavioural therapy, hypnotherapy and/or psychological therapy should be considered for people with refractory IBS when drug treatment is unsuccessful after 12 months.

NICE has now recommended eluxadoline (Truberzi) as an option for treating irritable bowel syndrome with diarrhoea in adults when other drug treatments have failed, are contraindicated or not tolerated. Treatment may be initiated only in secondary care and should be stopped if no improvement is evident after four weeks.

NICE has now recommended eluxadoline (Truberzi) as an option for treating irritable bowel syndrome with diarrhoea in adults. The recommended dosage is 100mg twice daily (reduced to 75mg twice daily if poorly tolerated). Treatment should be initiated at the lower dose in older people (over 65 years) and increased to 100mg twice daily if well tolerated but not sufficiently effective. It is not known what effect renal impairment has on the disposition of eluxadoline but none is anticipated because renal excretion is only a minor route of elimination.

Eluxadoline is contraindicated in patients with impaired hepatic function, those with pancreatitis or risk factors for it, patients with biliary duct obstruction or sphincter of Oddi dysfunction, patients without a gall bladder, those with a history of severe constipation or gastrointestinal obstruction, and patients being treated with ciclosporin and other potent inhibitors of the membrane transporter protein OATP1B1. Clinically significant drug interactions may occur with high-dose statins, angiotensin II-receptor blockers and some CYP3A4 substrates (e.g. pimozide, quinidine, nifedipine).

Mode of action and indications
Eluxadoline is an agonist at mu and kappa opioid receptors and an antagonist at delta opioid receptors. It is taken orally but has very low systemic absorption due to low bioavailability and first-pass metabolism. It therefore acts locally within the gastrointestinal tract, slowing gastrointestinal transit, reducing urgency and improving stool consistency; its abuse potential is low.

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Efficacy
Eluxadoline has been evaluated in two phase 3 trials (IBS-3001 and IBS-3002) involving a total of 2425 patients randomised to receive placebo or treatment with 75 or 100mg eluxadoline twice daily. Eligible patients had IBS with diarrhoea of at least moderate severity with at least mild pain. Loperamide was permitted as rescue medication but was rarely used in any treatment group.

The primary endpoint was the proportion of patients who had a composite response at 12 or 26 weeks (defined as recording on ≥50% of days: a reduction of ≥30% from average baseline score for worst abdominal pain and, on the same days, a stool-consistency score of <5 on the Bristol Stool Form (BSF) scale of 0–7). If the patient did not have a bowel movement on the day of assessment, a response for that day was defined as an improvement of ≥30% in the score for the worst abdominal pain.

At baseline, the study population reported moderate abdominal pain and bloating (mean symptom score approximately 6/10 for each, with 0 indicating no symptoms and 10 the worst imaginable symptoms) and diarrhoea (mean score over 6/7 on the BSF scale). Patients averaged three to four episodes of urgency and five bowel movements per day. About one-third of patients discontinued study participation early, evenly divided between the treatment arms; adverse effects accounted for about 24% of withdrawals from eluxadoline treatment and 13% from placebo.

Response rates were significantly higher with eluxadoline than placebo after 12 and 26 weeks (p<0.001) (see Figure 1). A response was evident within the first week of treatment and was associated with improved stool consistency and less frequency and urgency. Eluxadoline was associated with greater improvement in abdominal pain and, at the higher dose, reduced bloating. Significantly more patients reported adequate symptom relief with eluxadoline (53%–60%) than placebo (44%–49%). Mean IBS-related quality of life scores increased significantly more with eluxadoline than with placebo.

Adverse effects
Adverse events, recorded for 26–52 weeks’ treatment in the phase 3 trials, were not consistently more frequent with the higher dose of eluxadoline. The most frequently reported events were constipation (8% with eluxadoline vs 2.5% with placebo), nausea (7.7% vs 5.1%) and abdominal pain (6.5% vs 4.1%). In pooled studies, 1%–2% of patients taking eluxadoline reported somnolence compared with 0.3% taking placebo, but absolute numbers were small. Pancreatitis (two cases at the lower dose of eluxadoline, three at the higher) and sphincter of Oddi spasm (one and seven cases respectively) were reported with eluxadoline but not with placebo.

References

Declaration of interests
None to declare.

Steve Chaplin is a medical writer specialising in therapeutics