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Advising on new medicines for Scotland
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NHS SCOTLAND
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eluxadoline, 75mg and 100mg film-coated tablets (Truberzi®)

SMC No 1292/18

Allergan Ltd

8 December 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

eluxadoline (Truberzi®) is not recommended for use within NHS Scotland.

Indication under review: in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-D).

Eluxadoline showed superiority over placebo in producing a composite response, which included abdominal pain response and stool consistency response, in patients with IBS-D.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Eluxadoline is indicated in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-D).[1]

Dosing Information

The recommended dose is 200mg daily (one 100mg tablet, twice daily) with food. For patients who are unable to tolerate one 100mg tablet, twice daily, the dose can be lowered to 150mg daily (one 75mg tablet twice daily).[1]

Product availability date

June 2017

Summary of evidence on comparative efficacy

Eluxadoline is a mixed mu and kappa opioid receptor agonist, and a delta opioid receptor antagonist. It acts locally on the gastrointestinal tract and has poor bioavailability. It is considered to play a role in normalising gastrointestinal transit times.[1, 2]

Irritable Bowel Syndrome (IBS) is a chronic, relapsing disorder of the gastrointestinal system characterised primarily by intestinal pain and/or discomfort and associated alterations of defecation and/or bowel habit. IBS can also be associated with other symptoms, such as abdominal distension, bloating, constipation, and/or diarrhoea. IBS-diarrhoea (IBS-D) is a subtype of IBS with diarrhoea predominant.[3] The submitting company has requested that SMC considers eluxadoline when positioned for use in patients who have not responded adequately to, or cannot tolerate all other suitable treatment options, including loperamide, antispasmodics and antidepressants. Eluxadoline should be stopped after four weeks if treatment response is inadequate.

The key evidence comes from IBS-3001 (n=1,282) and IBS-3002 (n=1,146), which were phase III, randomised, double blind, parallel group, multicentre studies comparing two doses of eluxadoline (75mg or 100mg twice daily) with placebo in adult patients with IBS-D. Both studies had similar inclusion criteria and patients were required to meet the following criteria during the screening period prior to randomisation: a diagnosis of IBS-D based on Rome III criteria; a worst abdominal pain (WAP) score of >3.0 (scale of 0 to 10, with 0 indicating no pain and 10 being the worst imaginable pain); an average stool consistency score of ≥5.5 and at least five days with a Bristol Stool Scale (BSS) score ≥5 (scale of 1 to 7, with 1 indicating hard to pass stool and 7 indicating watery diarrhoea); average daily IBS-D global symptom score of ≥2.0 (on a scale of 0 to 4, with 0 indicating no symptoms and 4 very severe symptoms). Following pre-screening and screening periods, patients were randomised equally to eluxadoline 100mg twice daily, eluxadoline 75mg twice daily or placebo twice daily, stratified by country.[4] Following randomisation patients were allowed to use loperamide as rescue therapy to mitigate the potential for attrition.

The primary outcome in both studies was the composite clinical response based on improvements from baseline in worst daily abdominal pain and daily stool consistency scores over 26 weeks, measured in the intention-to-treat population. A daily abdominal pain response was defined as a ≥30% improvement in WAP in the past 24 hours compared to baseline (measured during the screening period prior to randomisation). A daily stool consistency response was defined as a BSS score of <5 or the absence of a bowel movement, if in conjunction with a daily abdominal pain response.[3] Patients recorded daily

symptoms of IBS-D and a patient was defined as a clinical responder if they met the daily response criteria for at least 50% of the days with diary entries. The primary outcome from both studies and a pooled analysis is presented in table 1.

Table 1. Primary outcome from week 1 to 26.[4]

Study	IBS-3001	IBS-3002	Pooled data
Eluxadoline 100mg, % composite responder, (n)	29.3 (125/427) p<0.001	32.7 (125/382) p<0.001	31.0(251/809) p<0.001
Eluxadoline 75mg, % composite responder, (n)	23.4 (100/426) p=0.112	30.4 (116/382) p=0.001	26.7 (216/808) p<0.001
Placebo, % composite responder, (n)	19.0 (81/427)	20.2 (77/381)	19.5 (158/808)

p-values for active treatment versus placebo.

In the subgroup of patients that had not achieved an adequate response with previous loperamide use in the 12 month before the start of the study (22%, 541/2,428), those patients treated with eluxadoline 75mg and 100mg had a statistically significant higher percentage of composite responders when compared with the placebo group (26.8%, 31.6% and 17.5% respectively). Similar results were shown with eluxadoline 100mg in the subgroup that had prior adequate symptom control with loperamide in the previous 12 months.[5]

IBS-Quality of Life (IBS-QoL) is composed of 34 items, scored from one to five. Responders were defined by at least a 14-point improvement in total score from baseline. For IBS-3002 there was no statistically significant difference in response between placebo and either eluxadoline group. Across all the time points, differences ranged from 3 to 5%.[3] Other important secondary outcomes are presented in table 2.

Table 2. Important secondary outcomes from week 1 to 26.[3, 6]

Study	IBS-3001			IBS-3002		
	Eluxadoline 100mg	**Eluxadoline 75mg**	**Placebo**	**Eluxadoline 100mg**	**Eluxadoline 75mg**	**Placebo**
Abdominal pain responders, %, (n)	46.5 (198/426) p=0.36	45.2 (193/427) p=0.58	43.3 (185/427)	50 (191/382) p=0.15	47.5 (181/381) p=0.45	44.8 (171/382)
Stool consistency responders, %, (n)	34.0 (145/426) p=0.001	28.1 (120/427), p=0.19	24.1 (103/427)	39.8 (152/382) p<0.001	34.4 (131/381) p<0.001	23.6 (90/382)
Adequate relief responders %, (n)	49.5 (211/426) p=0.005	45.7 (195/427), p=0.097	40.0 (171/427)	53.7 (205/382) p=0.006	52.8 (201/381) p=0.013	43.7 (167/382)
Global symptom responders %, (n)	37.1 (158/426) p=0.14	36.3 (155/427) p=0.22	32.3 (138/427)	43.2 (165/382) p=0.012	45.1 (172/381) p=0.002	34.3 (131/382)

p-values for active treatment versus placebo.

The company also included a meta-analysis in the submission with results for the primary outcome in line with those of the pooled analysis.[4]

IBS-2001 was a phase II, dose finding study, similar in design to IBS-3001 and IBS-3002, with a primary efficacy assessment at four weeks. Although the results did not show conclusive superiority over placebo in terms of the primary outcome of composite response, EMA was satisfied that the study showed "trending results" for the 100mg dose.[3 7]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

Pooled safety data from IBS-3001 and IBS-3002 studies show all adverse event rates of 56% (450/808) in the placebo group and 59% (986/1,666) in the eluxadoline group (75mg and 100mg pooled). Serious adverse event rates in these same groups were 3% (24/808) and 4.5% (75/1,666) respectively. In IBS-3001 9.5% (81/855) of patients in the pooled eluxadoline group and 3.7% (16/427) of patients in the placebo group discontinued treatment due to an adverse event. The corresponding results in IBS-3002 were 7.9% (60/764) for eluxadoline and 5.0% (19/382) in the placebo group. There were no concerns regarding opioid addiction or withdrawal.[4]

Gastrointestinal adverse events were most common and these would be expected considering the disease being treated and eluxadoline pharmacology. The following common adverse events occurred in the pooled IBS-3001 and IBS-3002 studies in the eluxadoline and placebo groups respectively; constipation (8% versus 2.5%), nausea (7.7% versus 5.1%), abdominal pain (6.5% versus 4.1%), vomiting (4.1% versus 1.4%), abdominal distension (2.6% versus 1.6%), flatulence (2.9% versus 1.6%), increased level of alanine aminotransferase (2.6% versus 1.5%), and cardiac events (1.7% and 1%). Severe constipation occurred in less than 1% of patients treated with eluxadoline and there were no serious complications in the placebo group.[1] Treatment discontinuation due to constipation occurred in 1.1% for eluxadoline 75mg, 1.7% for eluxadoline 100mg and 0.2% for placebo.[4]

There were 5 cases of pancreatitis, all of which occurred in eluxadoline groups, and were possibly associated with Sphincter of Oddi spasm. Previous cholecystectomy, with previous bile-duct related disease and high alcohol intake are consider risk factors for Sphincter of Oddi spasm and pancreatitis. Eluxadoline is contraindicated in patients at risk of Sphincter of Oddi dysfunction or pancreatitis.[3]

Summary of clinical effectiveness issues

IBS is thought to affect 10% to 20% of the population. It most commonly affects patients in the age range of 20 to 30 years old, and women are twice as likely to be affected as men.[8] Patients may have a significant IBS related negative impact on their quality of life.[9] In addition to dietary and lifestyle interventions, antispasmodics (such as mebeverine) and the antimotility agent loperamide are commonly used for the treatment of IBS-D associated pain and diarrhoea respectively. Off-label use of tricyclic antidepressants (TCAs), such as low dose amitriptyline can be trialled in patients not achieving an adequate response or unable to tolerate these first line options. Other treatment options, following TCAs include; cognitive behavioural therapy, hypnotherapy, probiotics and other off-label medicines such as selective serotonin reuptake inhibitors, ondansetron and rifaximin.[9-11] Eluxadoline is a first in class medicine. Clinical experts consulted by SMC considered that there is an unmet need in this therapeutic area, namely for patients who failed treatment with existing therapies. The submitting

company has requested that SMC considers eluxadoline when positioned for use in patients who have not responded adequately, or cannot tolerate all other suitable treatment options, including loperamide, antispasmodics, and antidepressants. It is unknown if the population in the key studies, IBS-3001 and IBS-3002 reflects this positioning.

In the pooled data for the two phase III studies, IBS-3001 and IBS-3002, a significantly higher proportion of patients allocated to eluxadoline 100mg and 75mg achieved the composite clinical response compared with placebo following 26 weeks of treatment. Composite responders required a ≥30% reduction in worst abdominal pain from baseline for ≥50% of the days assessed, and on the same days to have a stool consistency score <5 using the Bristol stool scale (scores 1 to 7).[4] The results for pain response were not statistically significant, but the results for secondary outcomes assessing stool consistency, IBS-D global score response and adequate relief of IBS symptoms all showed evidence of improvement for eluxadoline versus placebo.[3]

The study outcome relied on patient reported outcomes and patient reported symptoms. These are important and relevant to patients but consistency of reporting of these outcomes over time may be highly variable. The studies' inclusion criteria selected patients with more persistent symptoms than the definition of IBS-D outlined in the Rome III criteria. In terms of stool consistency response, patients achieving a BSS score of five were not considered responders but this score is not considered diarrhoea. There was no significant difference in abdominal pain response between placebo and both eluxadoline doses in either IBS-3001 or IBS-3002 studies.[3] Abdominal pain is considered a major driver for IBS patients to seek help from healthcare services.[12] This non-significant difference was combined with the significant difference seen in the stool consistency measure to provide the significant primary composite outcome. Some symptoms experienced by patients with IBS-D were not accounted for in the primary outcome. Patients were not tested for bile acid malabsorption, which is commonly misdiagnosed as IBS-D, and is estimated to account for one third of those diagnosed with IBS-D.[3]

Eluxadoline would provide another treatment option for patients with IBS-D intolerant to or unresponsive to all other suitable treatment options, including loperamide, antispasmodics, and antidepressants. Clinical experts consulted by SMC considered that the place in therapy of eluxadoline is following the failure of existing options. Twice daily continuous dosing may provide less flexibility and be more burdensome than other treatments which can be used as required for "waxing and waning" symptoms.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing eluxadoline to no treatment, for the treatment of IBS-D. The company positioned eluxadoline for use in adults with IBS-D who have not responded adequately to, or cannot tolerate, all other suitable treatment options. The time horizon used in the analysis was five years.

A Markov model was submitted consisting of two sub components i.e. a continuer and discontinuer component. Each component comprised of eight health states, defined according to a patients IBS-QoL total score change and daily pain score. Patients on either eluxadoline or no treatment enter the model in the poorest/worst health state IBS-QoL 1 with pain not improved and transition through the model according to treatment specific transition probabilities. A stopping rule was implemented at 4 weeks to capture a lack of treatment efficacy. Discontinuation was determined based on whether the patients' symptoms were adequately relieved. Patients discontinuing at 4 weeks were assumed to revert back to their baseline utility and only incurred disease related costs. Patients responding at 4 weeks could discontinue throughout the duration of the model based on persistence data from the pooled phase II and phase III studies.[4 7]

By applying regression analysis to the phase II study,[7] the company identified IBS-QoL and pain improvement (based on total score change) to have the highest impact on patient utility. As such these outcomes were considered to be the primary determinant of QoL within the model. The global symptom score (GSS) was also considered to be a key determinant of QoL, however this was excluded from the model due to the added complexity it would cause. Due to the lack of long term data, the model extrapolated treatment efficacy based on 'last observation carried forward' i.e. transition matrices from week 24 to week 28 were used from week 28 onwards. In relation to treatment discontinuation, the proportion of patients adequately relieved at 4 weeks was estimated to be 56.2% and 41.7% in the eluxadoline and no treatment arms respectively, based on the pooled phase III studies. It is worth noting that the model assumes patients in the eluxadoline arm who discontinue treatment after 4 weeks (based on persistence data) retain a 25% incremental QoL life benefit compared to the no treatment arm, via a difference in distribution of patients across health states. In the base case analysis long term treatment persistence was estimated by fitting log normal distributions to available Kaplan Meier data (in both treatment arms). The log normal function was selected based on goodness of fit statistics and visual inspection.

Medicine acquisition costs were included in the analysis. The cost per cycle of eluxadoline was adjusted to account for compliance and persistence using data from the pooled IBS-2001, IBS-3001 and IBS-3002 studies. By cycle 13 (1 year) 86.3% of patients in the eluxadoline arm were assumed to be treatment- compliant, with 40.6% expected to remain on treatment. Disease- related resource use was included in the model based on whether or not a patient experienced adequate relief from disease symptoms. Resource use including, GP visits, inpatient visits, outpatient visits, A&E attendances, CT scan, ultrasound, colonoscopy, sigmoidoscopy, endoscopy and X-ray was captured via an IBS-D questionnaire which was completed by eight gastroenterologists. The cost associated with pancreatitis was included in the economic model.

Utility values were derived from the phase II study.[7] Quality of life values were elicited from patients using the EuroQoL-5 Dimensions (EQ-5D) at baseline, 4 weeks, 8 weeks and 12 weeks. Values were adjusted using a UK tariff (attained from UK general population). The economic model does not use treatment specific utility values. The incremental quality adjusted life year (QALY) gain associated with eluxadoline therefore stems from the difference between patient distributions across health states within the continuer component of the model.

The key base case results and sensitivity analyses relevant to the population SMC was asked to consider are presented in the tables below. Due to a number of uncertainties surrounding modelled assumptions, the combined analyses presented in Table 4 may represent a more appropriate base case analysis.

Table 3: Base case results

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost-effectiveness ratio (ICER) £
no treatment	7,416	3.231	-	-	-
Eluxadoline	7,938	3.337	522	0.106	4,958

QALY = quality adjusted life year, ICER = incremental cost-effectiveness ratio

Table 4: Scenario analyses for eluxadoline versus no treatment

Parameter varied	ICER
Resource use data from alternative published literature (Fisher et al base case resource use)	£11,063
Removal of 25% eluxadoline benefit for discontinuers	£6,337
A 50% reduction in the proportion of patients (continuing treatment in the eluxadoline arm) that move in to the IBS-Qol 4 with pain improved health state at 6 months	£10,702*
Utility values estimated using phase III mapped utility data	£5,734*
Combined scenario analysis which assumes the following - Gompertz parametric curve used to model persistence after 4 weeks for no treatment arm - 0% eluxadoline relative benefit for discontinuers - Extrapolation of transition probabilities using the average 4 weekly transitions - Resource use for inadequate responders based on alternative published literature (Fisher et al base case resource use) - Utility values estimated using phase III mapped utility data	£20,652*
Combined scenario analysis which assumes the following - Gompertz parametric curve used to model persistence after 4 weeks for treatment arm - 0% eluxadoline relative benefit for discontinuers - Extrapolation of transition probabilities using the average 4 weekly transitions - Resource use for inadequate responders based on alternative published literature (Fisher et al base case resource use) - Utility values estimated using phase III mapped utility data -A 50% reduction in the proportion of patients (continuing treatment in the eluxadoline arm) that move in to the IBS-Qol 4 with pain improved health state at 6 months	£30,606*

*Analysis provided on request

There were a number of weaknesses with the analysis which included the following;

- There is some uncertainty surrounding the use of total change from baseline score in IBS-QoL and daily pain within the economic analysis, given that the primary outcomes were IBS-QoL and improvement in pain response.

- There is some uncertainty surrounding the modelled treatment effect associated with the eluxadoline treatment arm. Based on a review of the treatment specific transition matrices, a high proportion of eluxadoline patients who continue on treatment transition into the health state with the highest quality of life benefit (IBS-QoL 4 with pain improvement) relatively early, compared to those in the no treatment arm. For example, at six months, approximately 17.7% of patients in the eluxadoline arm enter this health state, while only 9.9% of patients in the comparator arm transition to this state. This differential in treatment efficacy may lack plausibility given that a significant difference in terms of IBS-QoL and pain response at certain time points was not demonstrated between eluxadoline and no treatment within the phase III IBS studies.[4] In order to explore uncertainty surrounding this assumption the company was asked to provide a scenario analysis whereby the proportion of patients in the eluxadoline arm (in the IBS-QoL 4 with pain improved health state at 6 months) was reduced by 50%. Based on this analysis the incremental QALY gain associated with eluxadoline decreased to 0.049 (from 0.106 in the base case). This resulted in an increased ICER (see Table 4).
- A 25% health benefit for patients discontinuing eluxadoline after 4 weeks was included in the model. The benefit is applied to the eluxadoline arm only, via the distribution of patients across the modelled health states based on last observation prior to discontinuation. The company justified the inclusion of this benefit based on opinion of two IBS clinicians, however there are no existing data to support this assumption. Therefore the scenario analysis which removes this health benefit may represent a more plausible ICER.
- For the extrapolation of persistence data in the no treatment arm, the Gompertz curve appeared to provide a better fit to the Kaplan-Meier data based on goodness of fit statistics. The use of this curve after year one, indicates that most patients plateau i.e. no longer discontinue. The company state that this plateauing effect does not appear to be clinically plausible, however this effect may have some clinical plausibility as patients are likely to continue to receive support i.e. implementing dietary and lifestyle advice over time.
- There is some uncertainty surrounding the base case utility values as these were derived from short term (12 week) phase II study data.[7] For completeness the company was asked to provide a revised analysis whereby disease-specific quality of life data captured within the IBS-3001 and IBS-3002 studies were mapped to EQ-5D values. The ICER was not overly sensitive to this analysis (see Table 4).
- Based on a review of previously published resource use estimates within similar health technology assessments for IBS-constipation, resource use estimates for inadequate responders (and subsequently no treatment) appear to be overestimated. For instance, the model assumes that inadequate responders will utilise sigmoidoscopy, colonoscopy and endoscopy resources, however in practice patients are likely to have received these exams prior to treatment initiation. As such the scenario analysis which uses Fisher et al (base case estimates) may reflect a more appropriate resource use estimates.

Due to the uncertainties outlined above the economic case has not been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and carer involvement

No patient group submission was received.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published its latest diagnosis and treatment guidelines for IBS in England and Wales in February 2015 (CG61). This guideline recommends diet and lifestyle changes as the first step in treatment for patients with IBS. Pharmacological therapy is recommended depending on the severity of predominant symptoms. For patients with IBS-D, first-line treatment recommendations are antispasmodics and the anti-motility agent loperamide. Antidepressants are recommended as second-line treatment if loperamide or antispasmodics have not helped. Referral for psychological therapies such as cognitive behavioural therapy and hypnotherapy are recommended for those patients who have not responded to pharmacological treatment after 12 months. [13]

NICE CG61 supersedes the guideline published by the British Society of Gastroenterologists (BSG) in 2007. This BSG guideline, the American Gastroenterology Association IBS guideline from 2014 and the World Gastroenterology Organisation Global guidelines for IBS from 2015 provide similar recommendations to NICE CG 61 for first and second line treatment of IBS-D, but they also list antibiotics, such as rifaximin, 5-HT receptor antagonists and probiotics as treatment options.[9 14 15]

Additional information: comparators

Non-pharmacological therapy and medicines used off-label.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
eluxadoline	100mg twice daily (or 75mg twice daily for patients unable to tolerate 200mg/day)	£1,147

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eMC dm&d on 28 September 2017.

Additional information: budget impact

The submitting company estimated there would be 8,796 patients eligible for treatment with eluxadoline in year 1 rising to 13,363 patients in year 5. The estimated uptake rate was 1% in year 1 (88 patients) and 12% in year 5 (1,604 patients).

The gross impact on the medicines budget was estimated to be £48k in year 1 rising to £875k in year 5. As no medicines were assumed to be displaced the net medicines budget impact is equivalent to the gross impact.

References

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6. **Commercial in Confidence*

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This assessment is based on data submitted by the applicant company up to and including 17 November 2017.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.