Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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Delta House 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman: Professor Jonathan G Fox

lubiprostone, 24 micrograms soft capsules (Amitiza®) SMC No. (977/14)

Sucampo Pharma Europe Ltd

04 July 2014

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission:

lubiprostone (Amitiza®) is not recommended for use within NHS Scotland.

Indication under review: the treatment of chronic idiopathic constipation and associated symptoms in adults, when response to diet and other non-pharmacological measures (e.g. educational measures, physical activity) are inappropriate.

In patients with chronic idiopathic constipation, lubiprostone increased the weekly frequency of spontaneous bowel movements when compared with placebo. Patients treated with lubiprostone reported improved symptom scores for stool consistency, straining and constipation severity compared with patients who received placebo.

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

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

For the treatment of chronic idiopathic constipation and associated symptoms in adults, when response to diet and other non-pharmacological measures (e.g. educational measures, physical activity) are inappropriate.

Dosing Information

One 24 micrograms capsule taken orally twice daily. A course of treatment for constipation with lubiprostone is two weeks.

In patients with moderate or severe hepatic impairment (Child-Pugh classification B or C), the initial dose should be 24 micrograms once daily, and can be titrated to 24 micrograms twice daily according to tolerance and response.

Product availability date

December 2013

Summary of evidence on comparative efficacy

Lubiprostone is a prostone which activates chloride channels located on the apical membrane of the intestine. It enhances chloride-rich intestinal fluid secretion which increases intestinal motility and alleviates symptoms associated with constipation without affecting electrolyte concentration in the serum.[1] In recent times, the definition of constipation has become more specifically defined from the traditional reduced stool frequency to incorporate other symptoms such as stool consistency, sense of incomplete evacuation and straining at stool.

The company has requested that SMC considers lubiprostone when positioned for use in patients with chronic idiopathic constipation (CIC) in whom treatment with standard laxatives have failed to provide adequate relief.

Two identically designed, multi-centre, randomised, double-blind, placebo-controlled phase III studies were conducted in the United States (SC0131 [n=242] and SC0232 [n=237]).[2,3] The studies recruited adults with a history of chronic idiopathic constipation (≥ 6 months) defined as <3 spontaneous bowel movements (SBM) per week and one of the following additional symptoms with at least a quarter of bowel movements: straining, sensation of incomplete evacuation, very hard and/or hard stools.

Following a two-week baseline period, patients were randomised in blocks of four to either lubiprostone 24 micrograms or matching placebo twice daily for four weeks. Lifestyle and diet was to be kept stable during the study. Rescue medication (bisacodyl suppository followed by phosphate enema if ineffective) permitted outwith the 48 hours prior to initial dose and during the first week of treatment was indicated in patients requesting relief and who had not experienced a bowel movement for at least three consecutive days. Other concomitant prescribed or over-the-counter constipation medicines were not permitted during the study with the exception of fibre supplements in patients who had been taking these for at least three months prior to screening.

Bowel movements and symptoms were recorded in a patient daily diary. The primary outcome was the frequency of SBM in the first week analysed in the intention-to-treat (ITT) population, with last observation carried forward (LOCF) to impute missing data. In both studies, patients treated with lubiprostone had a significantly greater mean number of SBM when compared with placebo during week 1 (see Table 1).

Secondary outcomes included the frequency of SBM during weeks 2-4, percentage of patients with SBM within 24 hours after first study drug, the need for laxative rescue, symptom scores of stool consistency, straining, abdominal bloating and discomfort, and overall constipation severity. A responder analysis was conducted in which a full response was defined as a SBM frequency ≥4/week, without the use of rescue medication, excluding those who dropped out due to lack of efficacy.

Results relating to SBM frequency are presented in table 1. During the second treatment week, there was no significant difference between the treatment groups in the proportion of patients requiring laxative rescue in SC0131[4] and in SC0232. Symptom scores for stool consistency, straining and constipation severity were statistically significantly improved in patients treated with lubiprostone compared with placebo in both studies. Mean abdominal bloating and discomfort scores tended to be lower in the lubiprostone groups compared with placebo, although statistical significance was not consistently demonstrated. Significantly greater proportions of patients in the lubiprostone groups had a SBM within 24 hours of their first dose compared with placebo (57% and 61% versus 37% and 31%, respectively).

		SC0131		SC0232	
		Lubiprostone (n=120)	Placebo (n=122)	Lubiprostone (n=119)	Placebo (n=118)
Primary outcome					
Mean SBM frequency	Base line	1.37	1.47	1.3	1.5
	Wk 1	5.69*	3.46	5.89**	3.99
Secondary outcomes* **					
SBM, mean frequency	Wk 2	5.06	3.18	4.96	3.55
	Wk 3	5.25	2.84	5.56	3.36
	Wk 4	5.30	2.91	5.37	3.46
Responder analysis, % full response	Wk 1	65	43	72	49
	Wk 2	58	36	58	43
	Wk 3	56	29	61	36
	Wk 4	58	28	60	39

Table 1: Primary and selected secondary outcomes for pivotal studies.[2,3]
*p=0.0001, **p<0.0001, *** p<0.05 for each secondary outcome (lubiprostone versus placebo); SBM = spontaneous bowel movement.

A post-hoc analysis was performed in a subgroup of the pooled population of the two studies who had used constipation medication during the last 90 days. These patients were considered refractory to other constipation medicines.[5,6] This sub-group consisted of 265/479 (55%) of patients in the two studies, with baseline symptom scores and SBM frequency similar to the full studies' populations.[11] Full responder rates were significantly higher in the lubiprostone than placebo groups: for weeks 1 to 4 ranged from 53% to 67% in the lubiprostone group and 32% to

47% in the placebo group. Lubiprostone patients tended to score their SBM as looser than placebo patients, and with less straining.

A study of similar design to the pivotal studies was conducted in Japanese adults with CIC.[7] Patients were randomised to either lubiprostone 24 micrograms (n=62) or placebo (n=62) twice daily for four weeks. The primary endpoint, change from baseline in SBM frequency at week 1, was significantly greater in the lubiprostone than the placebo group, 3.7 versus 1.3 respectively, p<0.001. This study also measured health-related quality of life using SF-36 and the Irritable Bowel Syndrome-Quality of Life measure (Japanese version). There was no significant difference between the treatment groups in the change in SF-36 or IBS-QOL-J scores after four weeks treatment.

Three open-label, single-arm observational studies provide evidence for long-term efficacy of lubiprostone when taken on an "as required" basis by patients up to 48 weeks. In all the studies SBM frequency as well as accompanying symptoms improved from baseline.[8]

Summary of evidence on comparative safety

No comparative safety data are available. Refer to the summary of product characteristics for details of adverse effects.

A significantly higher proportion of lubiprostone patients experienced adverse events in SC0131 compared with placebo (70% versus 51%).[3] In SC0232, the proportion of patients experiencing adverse events was significantly greater in the lubiprostone group compared with placebo (55% versus 35%).[9] Rates of discontinuation from the pivotal studies due to adverse events were greater in the lubiprostone groups compared with placebo (7.5% versus 0.8% and 13% versus 0.8%). Treatment-related adverse events were experienced by 51% versus 21% and 43% versus 16% of lubiprostone and placebo patients respectively in the two studies.[2,3]

The most common treatment-related adverse events were: nausea (lubiprostone 32% and 21% of patients, placebo 3.3% and 4.2% of patients), headache (lubiprostone 12% and 5% versus placebo 5.7% and 2.5%), abdominal pain (5.0% and 6.7% versus 0.8% and 4.2%), flatulence (5.8% versus 0.8% in both studies), dizziness (5.8% and 5.0% versus 0.8% in both studies) and diarrhoea (5.0% and 3.4% versus 1.6% and 0%).[2,3]

No safety data were presented for the subgroup of the population who had received previous laxatives.

Summary of clinical effectiveness issues

The company has requested that SMC considers lubiprostone when positioned for use in patients with CIC in whom treatment with standard laxatives have failed to provide adequate relief.

Lubiprosotone is the first of a new class of medicines for constipation. Furthermore, its marketing authorisation covers use in men, in whom there are no licensed treatment options when laxatives have failed to provide adequate relief. A relevant comparator may be prucalopride, which is licensed for use in women in whom laxatives have failed to provide

adequate relief. Prucalopride has not been accepted for use in NHS Scotland by SMC. NHS Scotland Primary Care prescribing data suggest there is very low-level usage.[10]

There are a number of limitations to the available evidence. The primary outcome in the pivotal studies, frequency of spontaneous bowel movements, is a patient-reported outcome for CIC; however, there are additional symptoms that, depending on the individual, may be of greater importance e.g. feelings of incomplete evacuation, straining, stool consistency. Lubiprostone treatment was associated with clinically significant improvements in SBM weekly frequency and improvements in symptom scores for straining and stool consistency when compared with placebo.

In the two pivotal phase III studies,[2,3] there was a higher drop-out rate in the lubiprostone groups, attributable predominantly to discontinuation due to adverse events. LOCF was used to impute missing data and in the responder analysis patients who dropped out were marked as non-responders only if the reason was lack of efficacy.

The study populations did not specifically represent the proposed positioning of lubiprostone as suggested by the company. As a proxy for the proposed patient population, post-hoc sub-group analyses of the pooled patient populations of the two pivotal studies were conducted. The sub-group comprised patients with documented use of constipation medication within 90 days of study entry and represented 55% of the studies' ITT populations. It is not clear if adequate trials of laxatives were taken in this sub-group of patients and whether they reflected a refractory population.

The marketing authorisation recommends treatment courses of two weeks with no advice on re-treatment frequency.[1] Data for usage beyond four weeks is uncontrolled so the treatment effect in the long-term is uncertain. The summary of product characteristics notes that treatment over 12 months was well tolerated, with decreased abdominal bloating, abdominal discomfort and constipation severity.[1]

To support the proposed positioning and economic case, the company presented an adjusted indirect comparison (Bucher method) of lubiprostone and prucalopride with placebo the common comparator. Several outcomes were compared, related to common symptoms of chronic idiopathic constipation (SBM frequency, consistency and degree of straining) assessed over four weeks of treatment. Due to variations in the outcomes measured between the lubiprostone and prucalopride studies, individual patient-level data were used from the lubiprostone phase III study program to enable comparison with prucalopride. The limited data available only allowed comparison of patients with chronic idiopathic constipation and not in patients with inadequate response to laxatives.

The results of the indirect comparison suggest that lubiprostone and prucalopride treatment was associated with similar increases in SBM frequency, and similar proportions of patients with an increase of at least one SBM/week from baseline. There was no significant difference between the treatments for SBM with no straining, but patients taking lubiprostone were less likely to have "severe" or "very severe" straining. There was no difference between the treatments for stools of "hard" or "very hard" consistency, but prucalopride was more likely to lead to SBM of "normal" consistency.

A weakness of the analysis stemmed from the differences between the studies' inclusion criteria, specifically their definition of CIC. Patients in the lubiprostone studies were recruited on

the basis of SBM frequency, whereas the prucalopride studies used complete SBM (which incorporated feelings of complete evacuation).

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing lubiprostone with two comparators: prucalopride and current care. Current care was assumed to consist of immediate referral to investigations and invasive procedures, which included stoma surgery, sacral neuromodulation and biofeedback. The patient group in the economic evaluation was patients with CIC where all laxative options have failed and investigations such as colonoscopies and invasive treatment for constipation are being considered. The company stated that currently there are no SMC-accepted drug treatment options for patients with CIC once all laxative options have been exhausted. Prucalopride is not recommended by SMC, but is recommended by NICE and the company argued that it is used to treat patients with CIC in Scotland.

A Markov model was used with a two year time horizon which included the following five health states: treatment (where patients were on treatment with lubiprostone or prucalopride), investigations/invasive procedures, resolved, unresolved and death. It was assumed that all patients who failed treatment would be referred to an outpatient appointment with a gastroenterologist and the majority of patients would undergo a colonoscopy. Following this, some patients were assumed to undergo invasive procedures and then move to the 'resolved' or 'unresolved' health states. The cycle length in the model was two weeks as this is the duration of the initial course of treatment with lubiprostone, after which response is measured. A stopping rule was included in the model whereby treatment with lubiprostone was only continued after the initial two week treatment period if patients had ≥ 3 SBM per week and there was no use of rescue medication in the previous week. A similar stopping rule was included for patients receiving prucalopride but was applied at week four in line with the prucalopride licence.

For the comparison with prucalopride, the source of the clinical data was the indirect comparison. Based on the results of the indirect comparison, lubiprostone was assumed to have a greater effect on increasing the number of SBMs with a relative risk of 1.12 applied in the model. However, this result was not statistically significant. The effectiveness of invasive procedures was based largely on assumption, which was then tested in the sensitivity analysis. Trial data on the proportion of patients who continued treatment were combined with longer-term US prescription data to estimate the probability of remaining on treatment for patients who qualified to continued treatment beyond the stopping rule. This analysis showed that by the end of year 1 around 12% of patients remained on treatment.

Quality of life data were collected in two of the open-label, single-arm observational studies using the SF-36 questionnaire but were not used in the base case analysis. Instead, utility values were taken from a published US study which looked at the change in quality of life of CIC patients using EQ-5D. Patients who responded to treatment had a utility value of 0.9 compared with 0.83 for non-responders. For the initial treatment period before the stopping rule, the utility value applied was estimated for each arm based on an average of responders and non-responders according to the proportion who responded to treatment. This resulted in a slightly higher utility value for patients in the lubiprostone arm (0.89 vs 0.87).

Drug costs of lubiprostone and prucalopride were included. Both treatments were assumed to be initiated during a GP or consultant outpatient appointment. Subsequent treatment for patients who did not respond to drug treatment was assumed to consist of invasive procedures such as stoma surgery, sacral neuromodulation or biofeedback. Rescue medication was also included but use was assumed to be the same for prucalopride and lubiprostone arms. Other costs included the cost of a telephone consultation to assess response to treatment and costs of invasive procedures included as part of current care. Other disease management costs, such as GP, hospital visits and lab tests, were included according to whether patients had resolved CIC or unresolved CIC.

In the base case analysis, the submitting company estimated that the cost per quality-adjusted life-year (QALY) of lubiprostone compared with current care was £24,958 with an incremental cost of £336 and a QALY gain of 0.0135. A range of sensitivity analysis was conducted which indicated the results were most sensitive to changes in the utility values and the efficacy of current care.

For the comparison with prucalopride, lubiprostone was estimated to be dominant with estimated savings of £54 and a QALY gain of 0.0002. In the sensitivity analysis lubiprostone remained the dominant treatment or was less costly but also less effective in the majority of scenarios.

The following weaknesses were noted:

- The comparison with prucalopride is less relevant as it is not recommended by SMC and is not widely used in Scotland. Therefore, the comparison with current care is the relevant analysis. However, some concerns were raised that the invasive procedures included as part of current care in the model are unlikely to reflect how these patients would be treated in clinical practice as other options, such as manual evacuation, would be considered first. The efficacy of current care (which consisted of biofeedback, stoma surgery and sacral neuromodulation) was based on assumption only and is therefore uncertain. This was tested in the sensitivity analysis where the cost per QALY increased to £45k when 100% efficacy of current care was assumed.
- Quality of life data were collected in the open-label studies using the SF-36 questionnaire, which can then be mapped to EQ-5D data to estimate utility values. However, the utility values used in the base case analysis were taken from a separate published study. The results were sensitive to the utility values, with the cost per QALY vs current care increasing to £66k when utility values based on the trial data were used. The company argued there were limitations with the SF-36 data and therefore the utility values used in the base case were more robust. However, it should be noted that the difference between responders and non-responders based on the SF-36 data was more conservative and comparable to the utility gain applied to responders in other submissions for similar conditions.
- The results were also sensitive to the discontinuation rate applied in the model. The company argued that the base case approach may be conservative and therefore provided additional sensitivity analysis using an alternative approach based on extrapolation of the trial data. This resulted in a much higher proportion of patients remaining on treatment at the end of year 1 (38%) and lowered the cost per QALY below £20k. However it was considered that this approach may result in an underestimation of the discontinuation rate in practice.

The base case cost per QALY versus current care is relatively high and is associated with considerable uncertainty. The results are particularly sensitive to changes in the efficacy

assumptions and using the utility values derived from the trial-based data. Due to these weaknesses, the economic case has not been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

There are no UK or European guidelines in relation to the management of chronic idiopathic constipation in adults.

Additional information: comparators

Prucalopride is not recommended for use in NHS Scotland by SMC, but there is some use in small numbers of patients.

Bulk-forming laxatives (ispaghula husk, sterculia and methylcellulose) and osmotic laxatives (lactulose and macrogols) may be used regularly over long periods, with stimulant laxatives (bisacodyl, senna, docusate and sodium picosulfate) used in shorter courses on an as required basis.

Cost of relevant comparators

Drug	Dose Regimen	Cost per day (£)	Cost per two-week course (£)	Cost per year (£)
Lubiprostone	**24 micrograms orally twice daily**	**1.91**	**30**	**695**
Prucalopride	1mg or 2mg orally once daily	1.38 to 2.13	19 to 30	502 to 775
Macrogol 3350	One to three sachets orally daily in divided doses	0.18 to 0.53	3 to 7	66 to 193
Methylcellulose	1,500mg to 3,00mg orally twice daily	0.17 to 0.35	2 to 5	62 to 127
Sterculia	One to two sachets orally once or twice daily	0.10 to 0.38	1 to 5	36 to 138
Docusate	100mg to 500mg orally daily in divided doses	0.07 to 0.35	1 to 5	25 to 127
Lactulose	15mL orally twice daily and adjusted to response.	0.20	3	73
Bisacodyl	5mg to 20mg orally at night	0.04 to 0.15	1 to 2	15 to 55
Sodium picosulfate	5mg to 10mg orally at night	0.07 to 0.15	1 to 2	25 to 55
Ispaghula husk	One sachet twice daily	0.11	2	40
Senna	15mg to 30mg orally at night	0.05 to 0.10	1	18 to 36

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 30 April 2014 except lubiprostone (from company submission). Two pack sizes of lubiprostone are available; daily and annual costs calculated from 56-capsule pack; and two-week course calculated from 28-capsule pack.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 9,763 in year 1 and 9,976 in year 5, with an estimated market share of 2% in year 1 and 10% in year 5.

The gross medicines budget impact was estimated to be £94k in year 1 and £480k in year 5. As no other medicines were assumed to be displaced, the net medicines budget impact is the same as the gross.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1) Sucampo Pharma Europe Ltd. Summary of product characteristics – AMITIZA 24 micrograms soft capsules. www.medicines.org.uk (Last updated 01 October 2013)
2) Johanson JF, Morton D, Geenen J & Ueno R. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. American Journal of Gastroenterology 2008; 103: 170-7.
3) Barish CF, Drossman D, Johanson JF & Ueno R. Efficacy and safety of lubiprostone in patients with chronic constipation. Digestive Diseases and Sciences 2010; 55: 1090-7.
4) *Commercial in Confidence*
5) Panas RM, Dodds D, Scott CB & Ueno R. Lubiprostone initiates improvement in constipation symptoms in refractory patients. Poster presented at Gastro (UEGW/WCOG) conference, London, 21 to 25 November 2009.
6) Panas RM, Joswick T, Lichtlen P et al. PTH-195 Lubiprostone treatment improves constipation and related symptoms in patients refractory to other constipation therapies. Gut 2013; 62: A291
7) Fukudo S, Hongo M, Kaneko H et al. Lubiprostone improves not only spontaneous bowel movement but also quality of life in patients with chronic idiopathic constipation: phase III randomized, double-blind, and placebo-controlled study and long-term treatment study in Japan. (Abstract) Gastroenterology 2011; 140: S-616
8) Medicines and Healthcare product Regulatory Agency. Amitiza 24 microgram soft capsules (PL 21341/0003) UKPAR. www.mhra.gov.uk (Accessed 07 April 2014)
9) *Commercial in Confidence-*
10) ISD Scotland. Prescription Cost Analysis 2012 to 2013. www.isdscotland.org [Accessed 12 May 2014].
11) *Commercial in Confidence*

This assessment is based on data submitted by the applicant company up to and including 13 June 2014.

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

Drug 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.