National Institute for Health and Care Excellence

Technology Appraisal

Lubiprostone for the treatment of chronic idiopathic and opioid induced constipation

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Association of Coloproctology of Great Britain and Ireland	Yes. Treatment of chronic constipation which has failed normal laxatives is a difficult secondary and tertiary care problem. It is also expensive. New drugs should be considered on an individual basis	Comment noted. The remit has been split to reflect the two different indications for lubiprostone. Lubiprostone will be appraised within the boundaries of the marketing authorisation for both chronic idiopathic constipation and opioid-induced constipation.
	Sucampo Pharma Europe	We agree that there is a need for a Technology Appraisal. In addition, we believe that cost effectiveness and utility analyses for the two indications may well differ in important aspects, which would be challenging to be addressed in a MTA. We believe that two STAs are preferable because there is some urgency to produce guidance for the treatment of CIC in adults. Lubiprostone is already approved for treatment of CIC in the UK. In fact, we strongly believe that the novel mechanism of action of the compound, will allow patients to benefit from a truly innovative therapy and to offer treating physicians an important additional option addressing an unmet medical need in CIC making it a priority issue. We have over 6 years worth of real world evidence for the safe use of lubiprostone in adults. In the absence of UK based guidance, the World Gastroenterology Organisation guideline for treatment is available that recommends the use of lubiprostone for treatment with Grade I, Level A evidence	Comment noted. The remit has been split to reflect the two different indications for lubiprostone. Lubiprostone will be appraised within the boundaries of the marketing authorisation for both chronic idiopathic constipation and opioid-induced constipation.

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		[http://www.worldgastroenterology.org/assets/export/userfiles/05_constipation.pdf]; Accessed 20 February 2013. For the population of patients suffering from OIC related to chronic non-cancer pain for which we will seek approval for lubiprostone, there is urgency in a STA as there is well-expressed unmet medical need in this patient population as no treatment is formally approved at this point in time. Again, based on the unique and novel mechanism of action of lubiprostone, not interfering with the analgesic effects of opioids and based on its longterm safety record, we strongly believe lubiprostone will serve a high unmet medical need in the population of non-cancer related OIC suffers.	
	Norgine Pharmaceuticals	In Norgine's view it is appropriate and essential to carry out an MTA of the treatment of constipation, irrespective of underlying cause. Constipation is a very common problem and consumes a substantial amount of health resources (1,2). The treatment received by patients remains mixed at best with many patients being treated with multiple agents. Some of the currently available treatments have a stronger evidence base than others. Despite this, no patient treatment pathway exists. This Technology Appraisal presents an opportunity for a comprehensive review of all available therapies, including a revisit of previous STAs and CGs such as: - Methylnaltrexone for the treatment of opioid-induced bowel dysfunction in advanced illness or palliative care - Suspended June 2009 - Prucalopride for the treatment of chronic constipation in women - TA211 (which is due for review in Oct 2013) - Constipation in children and young people - CG 99 (which is due for review in May 2013) It is Norgine's recommendation that a treatment algorithm / treatment pathway be clearly defined to enable clinicians and patients to make appropriate decisions in the management of constipation. Reference:	Comment noted. The requests for conducting a MTA including all the interventions available for constipation and for a clinical guideline, as it was agreed that there is no clear treatment pathway for constipation, were discussed at the scoping workshop and noted in the report to the Department of Health.

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		1. American Gastroenterological Association Technical Review on Constipation (Gastroenterology 2013;144:218–238) 2. Efficacy and Safety of Traditional Medical Therapies for Chronic Constipation: Systematic Review (Am J Gastroenterol 2005;100:936-971)	
	TMC Pharma Services	Appropriate, especially for the area of Chronic Idiopathic Constiptation (CIC) as the prevalance is relatively high in the UK (4-20%) and guidance on clinical vs cost effectiveness would be useful.	Comment noted. The remit has been split to reflect the two different indications for lubiprostone. Lubiprostone will be appraised within the boundaries of the marketing authorisation for both chronic idiopathic constipation and opioid-induced constipation.
	Royal College of Nursing	Yes	No action required
	The British Pain Society	We believe this is an appropriate topic to bring to NICE for guidance. From the perspective of the BPS, we are aware and concerned that the number of patients on long term opioid therapy for pain (non-cancer as well as cancer) is increasing. The chronic adverse effects of opioids are significant and amongst these, opioid-induced constipation is often overlooked, but can be very troublesome for patients. The NICE guidance on opioids in palliative care (No 140) and its associated NICE pathway did not, in our view, resolve the problems of how to deal with longterm complications of opioid therapy such as constipation.	Comment noted. It was agreed at the scoping workshop that there is no clear treatment pathway for constipation. A request for a clinical guideline on constipation was noted in the report to the Department of Health.
	British Society of Gastroenterology	Yes	No action required
	Healthcare Improvement Scotland	It would be appropriate to review this topic, although it would be better to do more general reviews of the management of idiopathic constipation and opiate-induced constipation in order to provide clearer guidance as to which of the plethora of treatments available would be most appropriate and cost effective.	Comment noted. It was agreed at the scoping workshop that there is no clear treatment pathway for constipation. A request for a

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			clinical guideline on constipation was noted in the report to the Department of Health.
Wording	Association of Coloproctology of Great Britain and Ireland	Yes - comparable to prucalopride	No action required
	Sucampo Pharma Europe	Lubiprostone for the treatment of chronic constipation in adults is the wording recommended by MHRA.	Comment noted. The remit has been split to reflect the two different indications for lubiprostone. Lubiprostone will be appraised within the boundaries of the marketing authorisation for both chronic idiopathic constipation and opioid-induced constipation.
	Norgine Pharmaceuticals	No, the wording of the remit does not reflect the issues that NICE should consider. The following is Norgine's suggested wording for the title of this appraisal 'To appraise the clinical and cost effectiveness of all available treatment options for constipation; when dietary management options and non pharmacological measures (e.g. educational measures, physical activities) are inappropriate or have proven inadequate'. Please see rationale in our response to the section above.	Comment noted. The requests for conducting a MTA including all the interventions available for constipation, and for a clinical guideline were discussed at the scoping workshop It was agreed that there is no clear treatment pathway for constipation. These points were noted in the report to the Department of Health.
	TMC Pharma Services	Current Draft Remit wording suggests that Lubiprostone is licenced for use in CIC and Opioid Induced Constipation. The current MHRA approved indication seems to be only for CIC.	Comment noted. The remit has been split to reflect the two different indications for

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			lubiprostone. Lubiprostone will be appraised within the boundaries of the marketing authorisation for both chronic idiopathic constipation and opioid-induced constipation.
	The British Pain Society	Yes	No action required
	British Society of Gastroenterology	Yes	No action required
	Healthcare Improvement Scotland	Yes	No action required
Timing Issues	Association of Coloproctology of Great Britain and Ireland	Not urgent	Comment noted
	Sucampo Pharma Europe	NICE have approached us to discuss a HTA following horizon scanning activities. We agree this is a priority issue and there is some urgency and need for a STA.	Comment noted. The remit has been split to reflect the two different indications for lubiprostone.
	Norgine Pharmaceuticals	Norgine considers this appraisal to be urgent and essential as there are an increasing number of licensed treatments becoming available, with a potentially high impact on NHS budget but no clear guidance on the optimum treatment pathway. This lack of clarity ultimately leads to inappropriate prescribing and wastage of scarce resources, a problem which has been recognised by the inclusion of laxatives in the April 2012 [Version4.2] update of the 'NPC's Key therapeutic topics – Medicines management options for local implementation'. This is, therefore, a good opportunity for NICE to provide much needed support to the NHS in making appropriate treatment choices for patients	Comment noted. It was agreed at the scoping workshop that there is no clear treatment pathway for constipation. A request for a clinical guideline on constipation was noted in the report to the Department of Health.

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		suffering from constipation.	
	TMC Pharma Services	Low Urgency	Comment noted
	The British Pain Society	It is important but cannot be regarded as 'urgent', especially as other aspects of conventional opioid prescribing and its complications still need to be addressed.	Comment noted. It was agreed at the scoping workshop that there is no clear treatment pathway for constipation. A request for a clinical guideline on constipation was noted in the report to the Department of Health.
	British Society of Gastroenterology	This is an issue which is important as there is a sizeable unmet need in the treatment of chronic constipation. In additon, as the use of opiates increases, so does the problem of the side effect of constipation. As a result, it would be suggested that the appraisal be completed as soon as possible. It is not urgent but should be addressed in the course of the next 6 months	Comment noted. The remit has been split to reflect the two different indications for lubiprostone.
	Healthcare Improvement Scotland	Not of the highest priority as other treatments are already available for these problems.	Comment noted.
Additional comments on the draft remit	Sucampo Pharma Europe	By carrying out a STA in CIC we would benefit patients by improving patient choice and patient safety in the treatment of CIC. For OIC, alternative medical treatments are not available to the treatment group. We have significant post marketing data for both indications.	Comment noted. The remit has been split to reflect the two different indications for lubiprostone.
	Norgine Pharmaceuticals	None	No action required
	TMC Pharma Services	No Additional Comments	No action required

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	British Society of Gastroenterology	No	No action required

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Association of Coloproctology of Great Britain and Ireland	Only small amounts available. The cost, success group and comparison with prucalopride would be useful	Comment noted. Prucalopride is listed as a comparator in the scope for chronic idiopathic constipation in the comparators section for people for whom treatment with prucalopride is indicated.
	Sucampo Pharma Europe	The information is considered adequate. However, we would like to state that the two proposed comparators for OIC in non-cancer related pain do not have a current licence to treat such patients.	Comment noted. Comparators in the scope should constitute established clinical practice. In some instances comparators may include treatments which are used off-label for an indication. Clinical experts commented that peripheral mu-opioid antagonists such as methylnaltrexone and naloxone-oxycodone are used to treat opioid-induced constipation, after oral laxatives have been ineffective, and therefore should be included as comparators in the scope.
	Norgine Pharmaceuticals	The draft scope as it is currently written (title, background and comparators) does not sufficiently reflect the needs of NHS patients and clinicians in terms of the need for proper guidance which ensures the most appropriate treatments for constipation are used in a cost effective and stepwise approach.	Comment noted. It was agreed at the scoping workshop that there is no clear treatment pathway for constipation. A request for a clinical guideline on constipation was noted in the report to the Department of Health.
	TMC Pharma Services	OK	No action required
	Royal College of	Other agents are used as prokinetics such as erythromycin	Comment noted. It was agreed at the scoping

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	Nursing	and gastrograffin. These are not included.	workshop that these were not relevant comparators.
	The British Pain Society	The background does not clearly separate out the two issues of 'chronic constipation' and 'opioid-induced constipation'. The defintion given for the former (symptoms for at least a quarter of the time for at least six months) may be reasonable for the general population. However it is inappropriate for opioid-induced constipation, especially for cancer patients. In these cases, constipation that is present for even two weeks may cause substantial distress and lead to unecessary hospital or hospice admissions for some patients who may be near the end of life. The statement that 'Approximately 32,000 people receive strong opioids (for cancer and non-cancer pain) in England' seems to be an under-estimate to us. The large majority of patients who die in the UK with cancer have received strong opioids in the last weeks of life. Furthermore, there are over one million cancer 'survivors', many of who will also be on opioids including strong opioids for original cancer-related and treatment-related pain. We wonder if there is a '0' missing from the cited figure. The statements about oral laxatives and rectal measures (suppositories and enemas) make no reference to the fact that the evidence base for nearly all of these products available in the UK is almost non-existent. Indeed, the recommendations in the recent NICE guidance on strong opioids with respect to managing constipation were based on 'expert opinion'. Also, there is no reference to the risks of rectal measures, eg electrolyte disturbances in the elderly with phosphate enemas.	Comment noted. The remit and scope have been split to reflect the two different indications for lubiprostone. Two different background sections have been written. The background section of the scope aims to give a brief and clear definition of the spectrum of disease relevant to the new technology. Complete details related to the disease will be included in the appraisal. The epidemiological data in the scope has been amended to reflect that the figure shown in the draft scope referred only to people receiving strong opioids (for cancer and non-cancer pain) in a palliative care setting in England. It is expected that the prevalence for opioid-induced constipation in people with chronic non-cancer pain would be considerably higher. The background section in the scope has been amended accordingly.

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		These may have accounted for some of the 103 deaths registered in 2010 as due to constipation. The listing of prucalopride and methylnatrexone as 'prokinetics' is pharmacologically incorrect.	
	British Society of Gastroenterology	No additional comments – appears to be appropriate. Background given but more details would have helped	Comment noted. The background section of the scope aims to give a brief and clear definition of the spectrum of disease relevant to the new technology. Complete details related to the disease will be included in the appraisal.
	Healthcare Improvement Scotland	No concerns	No action required
	AstraZeneca	AstraZeneca agree with the definitions of both chronic and opioid induced constipation (OIC) in the background section (par 1 and 2) but suggest that it is necessary to provide more information about the differences between the conditions particularly in relation to the underlying pathophysiology. Please also see our comments in the 'population' section below.	Comment noted. The remit and scope have been split to reflect the two different indications for lubiprostone. Two different background sections have been written. The background section of the scope aims to give a brief and clear definition of the spectrum of disease relevant to the new technology. Complete details related to the disease will be included in the appraisal.
The technology/ intervention	Association of Coloproctology of Great Britain and Ireland	Yes	No action required
	Sucampo Pharma Europe	The information is considered adequate.	No action required
	Norgine Pharmaceuticals	The draft scope focuses on one treatment option (lubiprostone) within the identified therapy area. As mentioned above (and to	Comment noted. The requests for conducting a MTA including all the interventions available for

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		ensure a proper MTA review), as there is currently no overarching guidance in the management of constipation, it is essential that all available treatment options be included within the remit, title, scope, background information and supporting information for this Technology Appraisal.	constipation, and for a clinical guideline was discussed at the scoping workshop. It was agreed that there is no clear treatment pathway for constipation. These discussions have been noted in the report to the Department of Health.
	TMC Pharma Services	Yes, and this section clearly states the current licenced indication, unlike the initial draft remit paragraph.	Comment noted. No action required
	The British Pain Society	The statement 'Lubiprostone has a UK marketing authorisation….in adults when response to diet and non-pharmacological treatments are inappropriate' does not make sense. Perhaps it should state 'when response to diet has failed' or 'when dietary measures and non-pharmacological treatments are inappropriate'. Basically dietary measures, non-pharmacological and pharmacological interventions are three distinct categories.	Comment noted. Lubiprostone will be appraised within the boundaries of the marketing authorisation for both chronic idiopathic constipation and opioid-induced constipation.
	British Society of Gastroenterology	Yes	No action required
	Healthcare Improvement Scotland	Yes	No action required
Population	Association of Coloproctology of Great Britain and Ireland	Yes	No action required
	Sucampo Pharma Europe	We agree with the treatment population	No action required
	Norgine Pharmaceuticals	In Norgine's view, constipation (regardless of cause or underlying condition) should be the focus of this Technology Appraisal.	Comment noted. The population in the scope is determined by the therapeutic indications specified in the marketing authorisation of the intervention and the clinical evidence available.

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	TMC Pharma Services	Yes	No action required
	Royal College of Nursing	Pregnant women, patients who have undergone previous bowel resection.	Comment noted. It was agreed at the scoping workshop that there will be no evidence available for these specific groups.
	The British Pain Society	We find it strange that only patients with 'chronic non-cancer pain with opioid-induced constipation' are identified. We believe that cancer patients with OIC should also be included in the scope. It is not clear to us where in the patient pathway lubiprostone may be placed - should it only be used after failure of 'standard' oral laxative therapy, or could it be used firstline in suitable patients?	Comment noted. The population in the scope is determined by the therapeutic indications specified in the marketing authorisation of the intervention and the clinical evidence available. It was noted at the scoping workshop that the trials are only in people with 'chronic non-cancer pain with opioid-induced constipation'. NICE guidance will be produced in line with the final marketing authorisation for lubiprostone. If people with cancer-pain opioid induced constipation are included in the marketing authorisation, then the manufacturer will be encouraged to include evidence for this patient population in their submission. The licensed indication for lubiprostone in chronic idiopathic constipation does not restrict its use to only when previous laxative therapy has failed. If the evidence allows, patients for whom previous treatment with laxatives has been unsuccessful in providing adequate relief will be considered as a subgroup.
	British Society of Gastroenterology	Yes. Populations have been defined. Both idiopathic and opioid related constipation to be considered different groups. There should be clear exclusion criteria eg. patients with pelvic outlet obstructive defaecatory problems	Comment noted. The remit and scope have been split to reflect the two different indications for lubiprostone. The population in the scope is determined by the therapeutic indications specified in the marketing authorisation of the intervention and

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			the clinical evidence available. It was agreed at the scoping workshop that there is no evidence to support that patients with pelvic outlet obstructive defaecatory problems should be excluded from the patient population.
	Healthcare Improvement Scotland	It is appropriate to consider idiopathic and opioid-induced constipation separately. I do not have expertise in the management of idiopathic constipation. For opioid-related constipation, NICE guidelines are that laxative treatment should be prescribed for all patients initiating strong opioids. For this population lubiprostone should be considered only if laxative therapy is not tolerated or incompletely effective.	Comment noted. The remit and scope have been split to reflect the two different indications for lubiprostone. The population in the scope is determined by the therapeutic indications specified in the marketing authorisation of the intervention and the clinical evidence available. If the evidence allows, patients for whom previous treatment with laxatives has been unsuccessful in providing adequate relief will be considered as a subgroup.
	AstraZeneca	AstraZeneca does not consider it appropriate to include a population with both adults with chronic idiopathic constipation and adults treated for chronic non-cancer pain with opioid induced constipation (OIC). We believe these populations need to be reviewed as separate topics. While OIC and chronic idiopathic constipation share similar signs and symptoms, it is important to note that they can differ interms of clinical presentation(1)and do differ in terms of diagnosis and underlying pathophysiology. Chronic idiopathic constipation is diagnosed when a person is experiencing constipation symptoms, but no specific cause for the problem can be identified. For diagnosis, constipation symptoms need to be present at least two days a week for at least three months.OIC is defined as <3 spontaneous bowel movements (SBM) per week and typically begins within 1 week following initiation of opioid therapy.(2) More importantly, the underlying pathophysiology is different: OIC is caused specifically by	Comment noted. The remit and scope have been split to reflect the two different indications for lubiprostone.

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		binding to mu-receptors in the GI tract which inhibits normal bowel activity. OIC is unlikely to improve over time it must be anticipated, monitored, and addressed throughout opioid treatment.(3) We also suggest more clarity in terms of defining the patient population, specifically in relation to whether the technology is to be appraised in a patient population in whom there has been a sub optimal response to laxatives and who then respond to the technology under review. References: (1) Am J Gastroenterol advance online publication, 9 November 2010; doi: 10.1038/ajg.2010.431 (2) Rome Foundation. Rome III Disorders and Criteria. Rome Foundation 2011: Available from: http://www.romecriteria.org/criteria/. (3) Benyamin et at. Pain Physician. 2008;11:s105-s120. http://www.painphysicianjournal.com/2008/april/2008;11;S105-S120.pdf	The population in the scope is determined by the therapeutic indications specified in the marketing authorisation of the intervention and the clinical evidence available. If the evidence allows, patients for whom previous treatment with laxatives has been unsuccessful in providing adequate relief will be considered as a subgroup.
Comparators	Association of Coloproctology of Great Britain and Ireland	Yes	No action required.
	Sucampo Pharma Europe	For CIC our population is males as well as females however the suggested comparator has a narrower therapeutic window and is for the treatment of females only.	Comment noted. The comparators in the scope for lubiprostone for treating chronic idiopathic constipation have been amended. Prucalopride is specified as a comparator for people for whom treatment with prucalopride is indicated. Comparators in the scope should constitute established clinical practice. In some instances comparators may include treatments which are used off-label for an indication. Clinical experts

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		For OIC related to chronic non-cancer pain it should be noted that all of the suggested pharmaceutical comparators do not have a current license. For OIC in chronic non cancer pain there is no clinically established pharmaceutical comparator. We have evidence that suggests the use of lubiprostone in OIC for chronic non cancer pain in the non-palliative setting.	commented that peripheral mu-opioid antagonists such as methylnaltrexone and naloxone-oxycodone are used to treat opioid-induced constipation, after oral laxatives have been ineffective, and therefore should be included as comparators in the scope.
	Norgine Pharmaceuticals	The current list of comparators does not cover all treatment options within this therapy area. It is our view that the following drugs should be the comparators: Bulk-forming laxatives [Ispaghula, Methylcellulose, Sterculia] Stimulant laxatives [Bisacodyl, Docusate, Glycerol, Senna, Sodium picosulfate, Dantron] Faecal softeners [Arachis oil, Liquid paraffin] Osmotic laxatives [Lactulose, Macrogols, Magnesium salts, Phosphates, Sodium citrate] Peripheral opioid-receptor antagonists [Methylnaltrexone] 5HT4-receptor agonists [Prucalopride]	Comment noted. Following discussions at the scoping workshop the comparators in the scopes have been amended to include oral laxatives as relevant comparators for lubiprostone for treating chronic idiopathic and opioid induced constipation. Comparators in the scope should constitute established clinical practice. In some instances comparators may include treatments which are used off-label for an indication. Clinical experts commented that peripheral mu-opioid antagonists such as methylnaltrexone and naloxone-oxycodone are used to treat opioid-induced constipation, after oral laxatives have been ineffective, and therefore should be included as comparators in the scope.
	TMC Pharma Services	Comparators need to widened in both areas to include first line treatments such as osmotic, bulk forming and stimulant laxatives as they are the most direct comparators for initiation after diet and non-pharmacologicals.	Comment noted. Following discussions at the scoping workshop the comparators in the scopes have been amended to include oral laxatives as relevant comparators for lubiprostone for treating chronic idiopathic and opioid induced constipation.
	Royal College of	No - Should also include the range of laxatives that are	Comment noted.

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	Nursing	currently used to treat chronic constipation i.e. Movicol, lactulose which both have a similar action re softening the stools etc and stimulant laxatives such as senna	Following discussions at the scoping workshop the comparators in the scopes have been amended to include laxatives as relevant comparators for lubiprostone for treating chronic idiopathic and opioid induced constipation.
	The British Pain Society	For patients with opioid-induced constipation, we find it strange that the UK licensed oxycodone-naloxone combination product (Targinact) is not included. We also feel that current oral laxatives such as bulking agents, stool softeners and bowel stimulants should all be included as comparators, not just the rectal measures. Some patients prefer not to use longterm medications for constipation and so we believe that comparators should include dietary measures alone, or no laxatives.	Comment noted. Comparators in the scope should constitute established clinical practice. In some instances comparators may include treatments which are used off-label for an indication. Clinical experts commented that peripheral mu-opioid antagonists such as methylnaltrexone and naloxone-oxycodone are used to treat opioid-induced constipation, after oral laxatives have been ineffective, and therefore should be included as comparators in the scope. Following discussions at the scoping workshop the comparator sections in the scopes have also been amended to include oral laxatives as relevant comparators for lubiprostone for treating chronic idiopathic and opioid induced constipation.
	British Society of Gastroenterology	Yes. I would consider prucalopride as the best alternative care. Comparison should be of like with like and should be with laxatives, Prucalopride and other appropriate drugs	Comment noted. Following discussions at the scoping workshop the comparators in the scopes have been amended to include oral laxatives as relevant comparators for lubiprostone for treating chronic idiopathic and opioid induced constipation. The comparators section in the scope for lubiprostone for treating chronic idiopathic constipation has been amended. Prucalopride is specified as a comparator for people for

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			whom treatment with prucalopride is indicated
	Healthcare Improvement Scotland	Laxatives haven't been suggested as a comparator treatment. This is presumably because the market is considered to be those for whom laxatives are not tolerated or not effective, but this needs to be clarified.	Comment noted. Following discussions at the scoping workshop the comparators in the scopes have been amended to include oral laxatives as relevant comparators for lubiprostone for treating chronic idiopathic and opioid induced constipation.
	AstraZeneca	The following comments relate to the indication of Opioid Induced Constipation (OIC) There are no guidelines for the treatment for opioid induced constipation and no national picture for how opioid induced constipation is currently treated. The clinical guideline (CG140) for opioids in palliative care gives the following recommendations for managing constipation: 1.1.17 Inform patients that constipation affects nearly all patients receiving strong opioid treatment. 1.1.18 Prescribe laxative treatment (to be taken regularly at an effective dose) for all patients initiating strong opioids. 1.1.19 Inform patients that treatment for constipation takes time to work and adherence is important. 1.1.20 Optimise laxative treatment for managing constipation before considering switching strong opioids. With the lack of national guidelines, no NICE approved treatments and such variance in the treatment pathway at a local level, we consider it difficult to define the standard treatments in which the technology should be compared. Please find below some comments in relation to the suggested comparators mentioned in the scope Methylnaltrexone	Comment noted. Following discussions at the scoping workshop the comparators in the scope for lubiprostone for treating opioid-induced constipation has been amended. Comparators in the scope should constitute established clinical practice. In some instances comparators may include treatments which are used off-label for an indication. Clinical experts commented that peripheral mu-opioid antagonists such as methylnaltrexone and naloxone-oxycodone are used to treat opioid-induced constipation, after oral laxatives have been ineffective, and therefore should be included as comparators in the scope. The appraisal of methylnaltrexone was terminated as the manufacturer did not provide an evidence submission. NICE has been unable to make any recommendations on the use of this technology. Please see: http://publications.nice.org.uk/methylnaltrexone-for-treating-opioid-induced-bowel-dysfunction-in-people-with-advanced-illness-ta277 Consultees considered that prucalopride was

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		AstraZeneca UK understand that an appraisal of Methylnaltrexone for the treatment of opioid-induced bowel dysfunction in advanced illness or palliative care was referred in July 2008 and the current review status is 'in progress'. http://guidance.nice.org.uk/TA/Wave18/24 Methylnaltrexone is a subcutaneous injection which is indicated only for patients with advanced illness in palliative care. It is the only prescription treatment option available specifically for OIC. Although it offers a therapeutic option in the treatment of OIC, the indication is limited and the mode of application often is unaccepted in patients and leads to reduced compliance. Due to the limited label, AstraZeneca considers that methylnaltrexone (subject to NICE Appraisal) may be an appropriate comparator only for a subgroup of patients, who suffer from advanced diseases, receive palliative care, and have inadequate response to laxatives Prucalopride Prucalopride is indicated for the treatment of chronic constipation in women for whom other laxatives have not given adequate relief. Despite the differences in pathophysiology between the two conditions, OIC and chronic constipation, and prucalopride‘s limited label in women, AstraZeneca accepts that prucalopride may be an appropriate comparator only in the potential situation of 'off label' usage in the treatment of OIC. Rectal interventions e.g. suppositories and enemas AstraZeneca considers rectal interventions e.g. suppositories and enema as an appropriate choice of comparator which may include the combination of laxatives as rescue intervention. Surgical Treatment The background information describes surgical treatments as an option for people for whom laxitives have failed to provide adequate relief. We would not consider bowel surgery an appropriate comparator in OIC. Bowel surgery would be a very	only a relevant comparator for the population with chronic idiopathic constipation. Consultees considered that surgical options were only used ‘last line’ and therefore are not relevant comparators for either scope.

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		last line treatment after you had tried and failed everything else possible	
Outcomes	Association of Coloproctology of Great Britain and Ireland	Yes	No action required
	Sucampo Pharma Europe	The defined outcomes are appropriate apart from the outcome for pain. The 'pain' outcome should be redefined as 'abdominal discomfort'. We have 'abdominal discomfort' as an endpoint for both CIC and OIC indications. Wellbeing measures are also available in addition to HRQOL.	Comment noted. Following discussions at the scoping workshop the outcomes sections in the scopes have been amended. It was agreed at the workshop that pain defined as abdominal discomfort is already covered by symptoms of constipation and has been removed. Wellbeing was also considered to be covered by symptoms of constipation and health related quality of life and has not been included as an outcome measure in the scopes.
	Norgine Pharmaceuticals	Yes	No action required
	TMC Pharma Services	Should also specifically include need for manual evacuations and enemas.	Comment noted. Following discussions at the scoping workshop the outcomes sections in the scopes have been amended. It was agreed at the workshop that the use of rescue medication or interventions is a relevant outcome measure.
	Royal College of Nursing	No. Suggest including the Bowel Function Index as a validated objective assessment tool.	Comment noted. No action required. It was noted at the workshop that The Bowel Function Index assesses the symptoms of constipation. It was agreed to also include sense of complete evacuation as an outcome measure.
	The British Pain	We believe that the scope should try to identify evidence based	Comment noted. It was noted at the workshop

Section	Consultees	Comments	Action
	Society	on standardised validated bowel outcome measures, such as the Bowel Function Index and PAC-SYM. The use of Bristol Stool Chart would also be expected. It is not clear to us what will be covered by the term 'response rate' as an outcome. The scope will need to define what the response relates to (bowel functioning, frequency, comfort, patient satisfaction and preference etc). We would expect to see in the list of outcomes the following - ease of bowel movement; sense of complete evacuation; aspects relating to dignity and privacy, especially for patients in hospital who receive rectal interventions in multi-bay hospital wards. While we agree that health-relatd quality of life is an important outcome measure, we would expect that appropriate tools are used. For instance, the EQ-5D would not be sensitive enough.	that The Bowel Function Index and PAC-SYM assess the symptoms of constipation. Following discussions at the workshop the outcomes sections in the scopes have been amended. Response rate was considered to be covered by frequency of spontaneous bowel movements and it has been removed from the outcomes lists. Sense of complete evacuation has been included as a relevant outcome measure. The clinical outcome measures would usually be expected to have an impact on survival or health related quality of life and be able to be translated into QALYs for the evaluation of cost effectiveness (Section 2.2.6 of the Guide to the methods of technology appraisals). http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
	British Society of Gastroenterology	Yes, most of them should do so. One would also like to define what the duration of the response is.	Comment noted. Following discussions at the scoping workshop the outcomes sections in the scopes have been amended. Response rate was considered to be covered by frequency of spontaneous bowel movements and it has been removed from the outcomes lists.
	Healthcare Improvement	• Frequency of defecation – this is an appropriate outcome. • Time to bowel movement - this is less important if the drug is	Comment noted. Following discussions at the scoping workshop the outcomes sections in

Section	Consultees	Comments	Action
	Scotland	to be used in the long term rather than just as rescue medication. • Response rate – this isn't defined and I'm not sure what it means in this context • Symptoms of constipation – this is an important outcome • Pain – this is essentially the same as symptoms of constipation and health-related quality of life so could be removed • Use of rescue medication – this is also essentially the same as symptoms of constipation and health-related quality of life so could be removed • Adverse effects of treatment – this is an important outcome • Health-related quality of life – this is also an important outcome	the scopes have been amended. Time to bowel movement, response rate and pain have been removed from the outcomes list as they are considered to be covered by other outcomes already specified in the list. It was agreed that the use of rescue medication or interventions is a relevant outcome measure.
	AstraZeneca	AstraZeneca considers the outcome measures as appropriate outcomes for the proposed health technology appraisal.	Comment noted. No action required.
Economic analysis	Association of Coloproctology of Great Britain and Ireland	Yes	No action required
	Sucampo Pharma Europe	No comment	No action required
	Norgine Pharmaceuticals	None	No action required
	TMC Pharma Services	OK	No action required
	The British Pain Society	The proposed use of QALY and ICER is appropriate for chronic constipation and posibly opioid-induced constipation in non-cancer pain patients. However, we do not think the QALY/ICER measures are appropriate for evaulating cost	Comment noted. No action required. The reference case states that cost-effectiveness analysis is the preferred form of economic evaluation. This seeks to establish whether

Section	Consultees	Comments	Action
		effectiveness in the cancer population. Many of these patients may only be on strong opioids for weeks to months, but these are weeks and months in the last year of life and the distress caused by constipation is unduly large in comparison to the cost of relieving it. Thus, a hospital admission arising from opioid-induced constipation occuring once in 5 years for a chronic pain patient may be 'reasonable', but would be quite unacceptable for a cancer patient who has just weeks to live. The economic analysis should include the costs associated with need for nursing visits and interventions (especially suppositories and enemas); reduction in frequency of faecal impaction that may necessitate a hospital or hospice admission.	differences in cost between options can be justified in terms of changes in health effects. Health effects should be expressed in terms of QALYs (Section 5.2.11 of the Guide to the methods of technology appraisal). The economic analysis section in the scope states the potential impact on resource costs and savings for the NHS and personal social services (PSS) that would be expected from the introduction of the technology and that will be assessed during the appraisal. (Section 2.2.7 of the Guide to the methods of technology appraisal) http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
	British Society of Gastroenterology	No comment. Advise about this would be helpful from the health statisticians about how long the analysis needs to be done for to get meaningful data	Comment noted. No action required
	Healthcare Improvement Scotland	I don't have the expertise to comment on this section.	No action required.
	AstraZeneca	AstraZeneca agrees with NICE that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs and outcomes between the technologies being compared	Comment noted. No action required
Equality and Diversity	Association of Coloproctology of Great Britain and Ireland	No issues	Comment noted. No action required
	Sucampo Pharma	We do not think any change is required.	Comment noted. No action required

Section	Consultees	Comments	Action
	Europe		
	Norgine Pharmaceuticals	None	Comment noted. No action required
	TMC Pharma Services	No comments	No action required
	The British Pain Society	We are aware that prucalopride has a UK license only for females with chronic constipation. We trust that the scope for lubiprostone will look at the evidence in both males and females.	Comment noted. No action required
	British Society of Gastroenterology	Appropriate for the gropus it is being proposed for. However as mentioned there need to be clear guidelines as to which groups need excluding eg obstructive problems, neurological problems etc.	Comment noted. It was agreed at the scoping workshop that there is no evidence to support that these patient groups should be excluded from the overall patient population.
	Healthcare Improvement Scotland	The analysis shouldn't raise any equality issues.	Comment noted. No action required
Innovation	Association of Coloproctology of Great Britain and Ireland	Small subsection of constipated patients may have improvement in quality of life	Comment noted. No action required
	Sucampo Pharma Europe	Lubiprostone works through a unique mechanism of action which therefore offers patients an alternative choice in treatment and physicians an important alternative choice in their therapeutic armamentarium. Many patients that were studied for CIC were refractory to current standard of care and lubiprostone offered significant health related benefits. Evidence of the use of lubiprostone from studies with patients	Comment noted. If the evidence allows, people for whom previous therapy with laxatives has failed to provide adequate relief will be considered as a subgroup. Consultees considered that no other subgroups would require special consideration.

Section	Consultees	Comments	Action
		with hepatic and renal impairment is available. The US label has been changed and has removed the need for a negative pregnancy test before use. Substantial real world data is available from post marketing studies that show cases longer term safe use of lubiprostone. A recent investigator-sponsored clinical trial strongly suggests lubiprostone to be safe and effective in constipation related to Parkinson's disease (Ondo et al. Placebo controlled trial of lubiprostone for constipation associated with Parkinson Disease. Neurology 2012;78:1650-1654. Recent preclinical studies suggest an additional beneficial effect of treatment on the intestinal microbiome (Keely et al. Activated fluid transport regulates bacterial-epithelial interactions and significantly shifts the murine colonic microbiome. Gut Microbes 2012;3:250-260; Musch et al. Lubiprostone decreases mouse colonic inner mucus layer thickness and alters intestinal microbiota. Dig Dis Sci 2013 Jan 18: Epub ahead of print). None of these aspects will be included in the QALY calculation.	
	Norgine Pharmaceuticals	Lubiprostone offers a new mechanism of action. However, Norgine does not consider lubiprostone to be innovative in its potential to make a significant and substantial impact on health-related benefits. A new mechanism of action does not necessarily translate into superior efficacy. This was demonstrated by a recent study conducted by Norgine which showed, that when compared head to head in a controlled environment, MOVICOL is at least as effective as prucalopride in female patients with constipation who are resistant to treatment with laxatives, and has fewer side effects. This highlights the need for new treatments to be compared against	Comment noted. The requests for conducting an MTA including all the interventions available for constipation, and for a clinical guideline was discussed at the scoping workshop. It was agreed that there is no clear treatment pathway for constipation. These discussions have been noted in the report to the Department of Health.

Section	Consultees	Comments	Action
		established standard treatments rather than placebo (3). As mentioned in above sections, there are many agents used in the treatment of constipation but there is limited clinical evidence on which to judge the comparative efficacy of individual therapies (4). There have been some reviews which have looked at selected treatments. For instance, a systematic review by Lee Robichaud et al indicated that polyethylene glycol (PEG) is better than lactulose in outcomes of stool frequency per week, form of stool, relief of abdominal pain and the need for additional products and went on to recommend that PEG should be used in preference to lactulose in the treatment of chronic constipation (5). Another example is a recent technical review by the American Gastroenterological Association which compared efficacy and graded the quality of evidence for pharmacological therapies for constipation. The review rated PEG and osmotic and stimulant laxatives as having high quality evidence compared to moderate quality of evidence for newer treatments such as lubiprostone and prucalopride (1). A proper comparative review of the clinical and cost effectiveness of lubiprostone alongside other available therapies is therefore essential so as to fully determine their place in the treatment pathway for the management of constipation.	
		Reference: 1. American Gastroenterological Association Technical Review on Constipation (Gastroenterology 2013;144:218–238) 2. Efficacy and Safety of Traditional Medical Therapies for Chronic Constipation:	

Section	Consultees	Comments	Action
		Systematic Review (Am J Gastroenterol 2005;100:936-971) 3. Movicol® (PEG 3350 + Electrolytes) or Prucalopride in the treatment of Chronic Constipation: A head-to-head comparison in a controlled environment. M. Halphen, R. Cinca , D. Chera, H. J. Gruss (Abstract presented at UEGW 2012 and manuscript accepted for publication in APT on 19/02/2013.) 4. MeReC Bulletin Vol.21 No.02. Jan 2011 5. Lactulose versus polyethylene glycol for chronic constipation. Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus Polyethylene Glycol for Chronic Constipation. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD007570 DOI: 10.1002/14651858.CD007570.pub2.	
	TMC Pharma Services	The mode of action is somewhat innovative, but do not consider this a "step change" in the management of constipation. Particularly, the comparison to basic osmotic laxatives needs to be considered that also increase fluid in the gut albeit by different mechanism.	Comment noted. Following the discussions at the scoping workshop the comparators in the scopes have been amended to include oral laxatives as relevant comparators for lubiprostone for treating chronic idiopathic and opioid induced constipation.
	Royal College of Nursing	Unsure as not aware of its current use in clinical practice	Comment noted. No action required
	The British Pain Society	Lubiprostone is the only drug for constipation in the UK which works with this mode of action on chloride ion channels and therefore does represent an innovative technology.	Comment noted. No action required
	British Society of Gastroenterology	Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a ‘step-change’ in the management of the condition? Yes Do you consider that the use of the technology can result in	Comment noted. No action required

Section	Consultees	Comments	Action
		any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? No Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. The outcomes measures as defined in the draft scope would be appropriate. Yes. This is a problem area which affects a lot of patients and a new technology which helps would be most welcome Most of the outcome data and the QALY calculations would be most useful	
	Healthcare Improvement Scotland	It will be useful to have a new therapeutic option with a new mechanism of action as it may be helpful for the people in whom this condition is not adequately managed with current treatment options.	Comment noted. No action required
Other considerations	Sucampo Pharma Europe	The treatment of constipation in the disabled population should be considered.	Comment noted. It was agreed at the scoping workshop that people with disabilities would not require special considerations.
	Norgine Pharmaceuticals	Please see comments above	See response to the innovation section above
	TMC Pharma Services	No comments	No action required
	Royal College of Nursing	There is some apparent concern regarding the use of lubiprostone during pregnancy Also the issue of lubiprostone in overdose - this could be considered a high risk in some members of the population who self medicate and increase their laxative medication if they consider the dose prescribed is not effective enough - patients would need to be advised accordingly	Comment noted. It was agreed at the scoping workshop that there was unlikely to be any evidence for the use of lubiprostone during pregnancy. If the evidence allows the following subgroup will be considered: people for whom previous treatment with laxatives has been unsuccessful in providing adequate relief.

Section	Consultees	Comments	Action
	British Society of Gastroenterology	No comment	No action required
Questions for consultation	Association of Coloproctology of Great Britain and Ireland	Is it a different group of patients who will respond than those taking prucalopride	Comment noted. It was agreed at the scoping workshop that prucalopride should be a comparator for people with chronic idiopathic constipation in whom prucalopride was indicated.
	Sucampo Pharma Europe	No comment	No action required
	Norgine Pharmaceuticals	- Laxatives as well as other available therapies should be considered as comparators - Norgine is in support of NICE's intention to appraise this technology through its Multiple Technology Appraisal (MTA) Process as this will yield the most value to NHS clinicians and patients.	Comment noted. Following discussions at the scoping workshop the comparators in the scopes have been amended to include oral laxatives as relevant comparators for lubiprostone for treating chronic idiopathic and opioid induced constipation. The requests for conducting an MTA including all the interventions available for constipation, and for a clinical guideline was discussed at the scoping workshop. It was agreed that there is no clear treatment pathway for constipation. These discussions have been noted in the report to the Department of Health
	TMC Pharma Services	First/second line agents (as mentioned above) should be the relevant comparators and hence invasive procedures such as manual evacuation, enemas or surgery should be considered as appropriate comparators.	Comment noted. Following discussions at the scoping workshop the comparators sections in the scopes have been amended to include laxatives as relevant comparators for lubiprostone for treating chronic idiopathic and opioid induced constipation. It was agreed at the workshop that rectal interventions (e.g. suppositories and enemas) are relevant comparators for lubiprostone for

Section	Consultees	Comments	Action
			treating opioid-induced constipation. It was agreed at the scoping workshop that surgery is not a relevant comparator for lubiprostone.
	The British Pain Society	The BPS hopes that there is clearer distinction made in the final scope between the three entities of: chronic constipation, OIC in chronic non-cancer pain and OIC in cancer pain. We also look for greater clarification on the the place that lubiprostone may have on the patient pathway, eg firstline treatment or only after other treatments have failed.	Comment noted. The remit has been split to reflect the two different indications for lubiprostone. The license indication for lubiprostone does not restrict its use only when previous laxative therapy has failed. Lubiprostone will be considered as first line treatment for chronic idiopathic and opioid-induced constipation. If the evidence allows, the subgroup of patients for whom previous treatment with laxatives has been unsuccessful in providing adequate relief will be considered.
	British Society of Gastroenterology	A detailed plan with excluding and including criteria, patient demographics and groups studied, the drug information and key studies done etc need to be made available	The scope defines the issues of interest as clearly as possible. Full details of the clinical evidence will be presented during the appraisal of the technology.
Additional comments on the draft scope.	Norgine Pharmaceuticals	From Norgine's experience and interaction with healthcare professionals, there is a clear need for development of an optimum treatment pathway / algorithm for the management of constipation. We believe this will serve as a useful tool/ reference for NHS clinicians managing patients with constipation.	Comment noted. It was agreed at the scoping workshop that there is no clear treatment pathway for constipation. A request for a clinical guideline on constipation was noted in the report to the Department of Health.
	TMC Pharma Services	Bearing in mind a single current licenced indication (CIC), this could be dealt with via STA as opposed to MTA	Comment noted. The remit has been split to reflect the two different indications for lubiprostone, and two STAs have been proposed.
	Royal College of	Where on the patient pathway is this medication being	The licensed indication for lubiprostone does

Section	Consultees	Comments	Action
	Nursing	considered? Is it being considered as first line or only if traditional treatments have failed?	not restrict its use only when previous laxative therapy has failed. If the evidence allows, patients for whom previous treatment with laxatives has been unsuccessful in providing adequate relief will be considered as a subgroup.
	British Society of Gastroenterology	No additional comments.	No action required

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Shire Pharmaceuticals

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Lubiprostone for treating opioid induced constipation in people with chronic, non-cancer pain

Response to consultee and commentator comments on the provisional matrix of consultees and commentators

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Add NHS England	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. NHS England has been added to the matrix of consultees and commentators under 'Others'.

2.	Add Health Research Authority	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Health Research Authority has been added to the matrix of consultees and commentators under 'Relevant research groups'.
3.	Add Public Health England	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Public Health England has been added to the matrix of consultees and commentators under 'Associated Public Health groups'.

4.	Add Public Health Wales NHS Trust	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Public Health Wales NHS Trust' has been added to the matrix of consultees and commentators under 'Associated Public Health groups'.
5.	Add the British Society of Paediatric Gastroenterology, Hepatology and Nutrition	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. British Society of Paediatric Gastroenterology, Hepatology and Nutrition has been added to the matrix of consultees and commentators under 'Professional Groups'.

6.	Add NHS Richmond CCG	NICE Secretariat		Added	Our process requires the involvement of two CCG's. Therefore NHS Richmond CCG is now included.
7.	Add NHS North Staffordshire CCG	NICE Secretariat		Added	Our process requires the involvement of two CCG's. Therefore NHS North Staffordshire CCG is now included.
8.	Add Association for Palliative Medicine should be included	The British Pain Society		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. The Association for Palliative Medicine has been added to the matrix of consultees and commentators under 'Professional Groups'.

9.	Add ERIC - Education and Resources for Improving Childhood Continence	Norgine Pharmaceuticals Ltd		Not included	This appraisal is for use in adults only. Therefore ERIC has not been added to the Matrix.
10.	Add PromoCon	Norgine Pharmaceuticals		Not included	PromoCon has been added to the Matrix under 'Patient/carer groups' please refer to point 18.
11.	Add PromoCon	Royal College of Nursing		Added	PromoCon has been added to the Matrix under 'Patient/carer groups' please refer to point 18.
12.	Add Parkinson's Society	SUCAMPO		Not included	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria, they have not been added to the Matrix of consultees and commentators'

13.	Add MS Society	SUCAMPO		Not included	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria, they have not been added to the Matrix of consultees and commentators'
14.	Add Cancer Research UK	SUCAMPO		Not included	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria, they have not been added to the Matrix of consultees and commentators'
15.	Add International Foundation for Functional Gastrointestinal disorders	SUCAMPO		Not included	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria, they have not been added to the Matrix of consultees and commentators'
16.	Add CORE charity	SUCAMPO		Not included	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria, they have not been added to the Matrix of consultees and commentators'

17.	Add SCOPE	SUCAMPO		Not included	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria, they have not been added to the Matrix of consultees and commentators'
18.	Add PromoCon	PIP		Added	PromoCon provides a national service, working as part of Disabled Living, Manchester to improve the life for all people with bladder or bowel problems by offering product information, advice and practical solutions to both professionals and the general public

19.	Remove The British Society of Paediatric, Gastroenterology, Heptology and Nutrition	NICE Secretariat		Removed	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria. The British Society of Paediatric, Gastroenterology, Heptology and Nutrition has not been included in the matrix of consultees and commentators.
20.	Add Actavis UK	NICE Secretariat		Added	Actavis UK has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators
21.	Add Bells healthcare	NICE Secretariat		Added	Bells healthcare has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators

22.	Add Ecolab UK	NICE Secretariat		Added	Ecolab UK has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators
23.	Add Optima Consumer Health	NICE Secretariat		Added	Optima Consumer Health has been identified as a comparator manufacturer for the appraisal topic and has been included in the matrix of consultees and commentators
24.	Remove Chemidex Pharma	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Chemidex Pharma has not been included in the matrix of consultees and commentators.

25.	Remove ConvaTec	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; ConvaTec has not been included in the matrix of consultees and commentators.
26.	Remove Crawford Pharmaceuticals	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Crawford Pharmaceuticals has not been included in the matrix of consultees and commentators.
27.	Remove DDSA Pharmaceuticals	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; DDSA Pharmaceuticals has not been included in the matrix of consultees and commentators.

28.	Remove G&G Vitamins	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; G&G Vitamins has not been included in the matrix of consultees and commentators.
29.	Remove Health Aid	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Health Aid has not been included in the matrix of consultees and commentators.
30.	Remove Health+Plus	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Health+Plus has not been included in the matrix of consultees and commentators.
31.	Remove Lanes Health	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Lanes Health has not been included in the matrix of consultees and commentators.

32.	Remove Merck Consumer Healthcare	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Merck Consumer Healthcare has not been included in the matrix of consultees and commentators.
33.	Remove Mylan UK	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Mylan UK has not been included in the matrix of consultees and commentators.
34.	Remove Novartis Pharmaceuticals	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Novartis Pharmaceuticals has not been included in the matrix of consultees and commentators.

35.	Remove Procter & Gamble Health and Beauty Care	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Proctor & Gamble Health and Beauty Care has not been included in the matrix of consultees and commentators.
36.	Remove Seven Seas	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Seven Seas has not been included in the matrix of consultees and commentators.
37.	Remove Typharm	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Typharm has not been included in the matrix of consultees and commentators.

38.	Remove Virtual Generics	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Virtual Generics has not been included in the matrix of consultees and commentators.
39.	Remove Watson Pharmaceuticals	NICE Secretariat		Remove	This organisation's interests are not directly related to the appraisal topic and as per our inclusion criteria; Watson Pharmaceuticals has not been included in the matrix of consultees and commentators.