National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Methylnaltrexone bromide for treating opioid-induced constipation

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

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Royal College of Nursing	This is an appropriate topic to be reviewed.	Comment noted. No action required.
	TMC Pharma Services Ltd	Opioid induced constipation (OIC) seems to be without NICE recommended treatments/specific guidelines. It can be confused with chronic idiopathic constipation however it is separate condition with different cause and requiring a different treatment pathway.	Comment noted. No action required.
Wording	Royal College of Nursing	Yes.	Comment noted. No action required.
	TMC Pharma Services Ltd	Appropriate wording.	Comment noted. No action required.
Timing Issues	TMC Pharma Services Ltd	A NICE recommended treatment for OIC should be a priority for NICE. Opioids are increasingly used for the management of chronic severe pain of non-malignant origin. A meta-analysis found that 41% of patients suffered from opioid-induced constipation after 8 weeks of therapy. *(Kalso E, et al. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain 2004;112:372–380.)* Additionally, patients with opioid-induced constipation report significant increases in physician visits and sickness-related absence from work,	Comments noted. No action required.

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		compared with opioid users who do not experience constipation. *(Ford A, et al. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: Systematic review and meta-analysis. The American journal of gastroenterology 2013;108(10):1566-1574)*	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	Royal College of Nursing	Strong opioid therapy is used for the 'management' not 'treatment' of pain. Definition of constipation omitted.	Comment noted; scope amended accordingly.
	TMC Pharma Services Ltd	Appropriate wording	Comment noted. No action required
The technology/ intervention	TMC Pharma Services Ltd	Suggest to include the following: The EMA CHMP has recently adopted a positive opinion recommending an extension to the existing indication for Relistor™ (methylnaltrexone bromide) for the **treatment of opioid-induced constipation (OIC) when response to laxative therapy has not been sufficient in adult patients, aged 18 years and older.** (Ref EMA/CHMP/249216/2015 23rd April 2015).	Comment noted; scope amended accordingly.
Population	Royal College of Nursing	The proposal states that it will explore the use of Methylnaltrexone for opioid induced constipation but this is significantly broader than opiod induced constipation in patients receiving opioids for palliative care. The population needs to be tightened.	Comment noted. The scope was written prior to the granting of the extended marketing authorisation when the new wording was not known. The population has been amended to

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			reflect new indication.
	TMC Pharma Services Ltd	Methylnaltrexone is indicated for the treatment of opioid-induced constipation when response to laxative therapy has not been sufficient in adult patients, aged 18 years and older and therefore the population in the scope should reflect this as NICE guidance will only be issued within the products' marketing authorisation. We recommend the population should be described as " Adults with opioid-induced constipation who have had an inadequate response to laxative therapy" Typically this should be after the use of oral stimulant/softener/osmotic laxatives or combinations of such therapies, but prior to rectal interventions (e.g. enemas, suppositories).	Comment noted. The population has been amended to reflect new indication.
Comparators	Royal College of Nursing	Oral naloxone is omitted. Need to be more specific about combination therapy for the treatment of opiod induced constipation e.g. the concurrent use of stimulants and faecal softeners. The combination of oxycodone and naloxone is for treatment of pain and prophylaxis of constipation not treatment of constipation. Other oral treatments are used for opiod induced hyperalgesia including but not limited to gastrografin.	Comments noted. Naloxone (including oral naloxone) was listed under the second bullet in the comparators listed in the table in the scope. It was agreed at the scoping workshop that the combination of oxycodone and naloxone is an appropriate comparator for the subgroup already receiving oxycodone. The scope has been amended accordingly.

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	TMC Pharma Services Ltd	We propose that oral laxatives such as stimulant/softener/osmotics are not suitable comparators, as in clinical practice it is likely that for OIC, methylnaltrexone bromide will be used after these agents, should they be ineffective in clinical practice. It is also proposed that the combination product of oxycodone/naloxone is not a suitable comparator as the primary indication for this product is analgesia and would mean an "opioid switch" for any patients not receiving oxycodone as their primary opioid therapy, should they remain constipated. Instead we propose the comparators to be: • Rectal interventions (e.g. suppositories and enemas) • Naloxegol (subject to ongoing NICE appraisal)	Comments noted. The issue of whether laxatives are an appropriate comparator was explored at the scoping workshop. Following the scoping workshop it was agreed that oral laxatives should not be included as a comparator and that the following wording should be added to the 'Other considerations' section of the table in the scope: '*If evidence allows the following subgroup will be considered: adults for whom previous treatment with more than one oral laxative has been unsuccessful in providing adequate relief.'* It was also discussed at the scoping workshop that the combination of oxycodone and naloxone is an appropriate comparator

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			for the subgroup already receiving oxycodone. The scope has been amended accordingly.
Outcomes	Royal College of Nursing	Include signs of constipation. Time to first bowel action after intervention. Include upper gastro-intestinal effect of grastro-oesophageal reflux. Include duration and frequency of treatment. Pain - needs to be more specific. Directly related to intervention e.g. bowel distention pain? or reversal of opioid induces analgesia? or anorectal pain on bowel opening?	Comments noted. It was agreed at the scoping workshop to include the outcome, time to first bowel action after intervention and agreed that adverse events should state an example such as reversal of opioid induced analgesia. The scope has been amended accordingly. Attendees further agreed that the outcome, pain, was all-encompassing and that for the purposes of the scope it was not necessary to define the specific types of pain. No action required.
	TMC Pharma Services Ltd	We would recommend including the following additional outcomes • Use of rescue medication or interventions	Comment noted. Attendees at the scoping workshop

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		• Effects on analgesic efficacy • Responder rates • Time to first post dose laxation • Discontinuation rates	agreed to include the use of rescue medication or interventions, the effects of analgesic efficacy will be added as an example of 'adverse effects', response rates, and time to first bowel action after intervention. The scope has been amended accordingly.
Economic analysis	TMC Pharma Services Ltd	Appropriate wording. It is anticipated any health economic model developed would adhere to the NICE reference case.	Comment noted. No action required.
Equality and Diversity	TMC Pharma Services Ltd	Appropriate wording	Comment noted. No action required
Innovation	Royal College of Nursing	The publication of guidance would raise the profile of this treatment which is rarely used outside of the acute hospital and hospice setting. Yes. A significant reduction in constipation related symptoms including distress. Case reports.	Comments noted. The company and other consultees will be able to fully describe why it considers rmethylnaltrexone bromide to be innovative in their evidence submissions, which will then be considered by the Appraisal Committee

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	TMC Pharma Services Ltd	Yes. Methylnaltrexone bromide is a selective antagonist of opioid binding at the μ-receptor. In vitro studies have shown methylnaltrexone bromide to be a μ-opioid receptor antagonist (inhibition constant [Ki] = 28 nM), with 8-fold less potency for kappa opioid receptors (Ki = 230 nM) and much reduced affinity for delta opioid receptors. As a quaternary amine, the ability of methylnaltrexone bromide to cross the blood-brain barrier is restricted. This allows methylnaltrexone bromide to function as a **peripherally acting mu-opioid antagonist** in tissues such as the gastrointestinal tract, without impacting opioid-mediated analgesic effects on the central nervous system.	Comments noted. The company and other consultees will be able to fully describe why it considers methylnaltrexone bromide to be innovative in their evidence submissions, which will then be considered by the Appraisal Committee
Other considerations	Royal College of Nursing	Measure of distress.	Comment noted. This will be considered under the outcome measure 'quality of life'.
Questions for consultation	Royal College of Nursing	Double blinded randomised controlled trials (RCTs). Hopefully placebo controlled.	Comment noted. No action required.
Additional comments on the draft scope	Royal College of Nursing	The draft scope confuses the licensed indication opioid induced constipation in palliative care with the opioid induced constipation. This needs to be clarified in the title in the context of the marketing authorisation.	Comment noted. The scope was written prior to the granting of the extended marketing authorisation when the new wording was not known. The population has been amended to reflect the new indication.

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

AstraZeneca
Department of Health
Resolution Chemicals