

## National Institute for Health and Clinical Excellence

## Methylnaltrexone for the treatment of opioid-induced bowel dysfunction in advanced illness or palliative care

## Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Wyeth	<p>We do not believe that is appropriate to refer this topic to NICE for appraisal as it does not appear to meet the Department of Health criteria for topic selection. Although the topic relates to government health priorities in End of Life Care, it does not meet any of the other conditions set by the Department of Health in terms of promotion of the best possible improvement in public health, wellbeing and/or patient care and the reduction in health inequalities. Further, we do not believe that NICE will add value by issuing guidance on this topic, in line with the criteria specified by the Department of Health.</p> <p>The burden of disease relating to opioid-induced constipation in patients with advanced illness who are receiving palliative care is low. In 2007, the National Horizon Scanning Centre estimated there were approximately 4,000 palliative care patients in England and Wales with laxative-resistant opioid-induced constipation. This estimate is in line with Wyeth's own estimates of 2,000 - 6,000 eligible patients. Given the low patient numbers, and the acute nature of the condition, the aggregate health benefit across the NHS as a whole is likely to be small in comparison to other technologies which have a wider target patient population, and/or a greater impact on health. The budgetary impact of methylnaltrexone is anticipated to be low (Wyeth estimates suggest a maximum budgetary impact of between £500,000 and £1,500,000 per annum in England and Wales, assuming that all eligible patients are treated, which is of course unlikely). It could therefore be argued that a drug with such a small impact on population health and NHS budgets does not merit the investment in resources associated with a NICE appraisal.</p>	The Department of Health referred the topic as part of the 18 <sup>th</sup> wave.

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	Wyeth	Palliative Care has been defined by the World Health Organisation as follows: ' ... the active, holistic care of patients with advanced, progressive illness. Management of pain and other symptoms and provision of psychological, social and spiritual support is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families.' These characteristics are considered in detail in the NICE clinical guideline on Improving Supportive and Palliative Care for Adults with Cancer (2004). Given the uniquely holistic nature of palliative care, and the complex combinations of underlying conditions, symptoms and polypharmacy which vary from patient to patient, it is unclear how a NICE technology appraisal could be implemented in this environment.	As above
	RCN	<p>As this is a unique product within the field we do not feel it is appropriate to examine this drug but if it has to be examined it should be dealt with as a clinical guideline rather than a Health Technology appraisal. The rationale for guideline development is that at the moment there are no nationally recognised guidelines for the management of OIC. Constipation that is not recognised or treated effectively in palliative care may result in considerable distress both for the patient and carer. This could also lead to an unnecessary admission of the patient into hospital or hospice. It is important to differentiate this group of patients from patients who have long standing problems with constipation so that they receive an appropriate and rapid diagnosis and management regime.</p> <p>We feel in these circumstances with the increasing focus on end of life care strategies and preferred place of care that clinical guidelines would thus address use of this drug more appropriately.</p>	The topic was referred as a technology appraisal.
Wording	Wyeth	If the appraisal were to proceed, the draft remit/appraisal objective should reflect the likely marketing authorisation of methylnaltrexone in the UK. Therefore we suggest the following: To appraise the clinical and cost effectiveness of methylnaltrexone within its licensed indication for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care when response to usual laxative therapy has not been sufficient.	Scope amended to reflect marketing authorisation

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Timing Issues	Wyeth	<p>The proposed appraisal is considered to be low priority in terms of urgency (see above comments on Appropriateness).</p> <p>A phase IV randomised placebo-controlled trial with sites in the United Kingdom is due to commence in May 2008, with results anticipated during 2010/11. This study will use the licensed doses of methylnaltrexone and includes various endpoints which would be relevant for a NICE technology appraisal and which were not studied in the original clinical trial programme (EQ-5D, constipation-related quality of life, resource use).</p>	Noted
Additional comments on the draft remit		None	

**Comment 2: the draft scope**

Section	Consultees	Comments	Action
Background information	Wyeth	<p>The analgesic effect of opioids is predominately through central opioid receptors. Peripheral mu-opioid receptors are partially responsible for bowel motility.</p> <p>Suggest amending "bowel moment" to "bowel movement".</p> <p>It may be important to mention that laxatives are not effective in all patients. When patients do not respond to laxatives, it is usual to move on to rectal interventions such as suppositories and enemas. In a small proportion of patients, unresolved constipation may result in faecal impaction and manual evacuation of faeces may be necessary.</p>	Suggestions have been incorporated where appropriate
	RCN	<p>Within this we feel that constipation should be defined for this client group. Constipation is defined using the ROME criteria but these do not relate explicitly to OIC which is rather different to idiopathic or functional constipation. It is important to differentiate the type of constipation so that patient receives appropriate diagnosis and management</p>	The scope mentions that this treatment is for opioid-induced constipation

## Appendix C - Summary form

Section	Consultees	Comments	Action
The technology/ intervention	Wyeth	Methylnaltrexone is a selective antagonist at peripheral mu-opioid receptors. Wyeth have applied for a marketing authorisation for opioid-induced constipation in patients with advanced illness who are receiving palliative care and who have had an insufficient response to usual laxatives. It is difficult to identify 'standard therapy' for opioid-induced constipation in palliative care. Methylnaltrexone is used in addition to patients' existing usual laxative regimens.	Noted
Population	Wyeth	Adults with advanced illness who are receiving palliative care, with opioid induced constipation who have not had a sufficient response to usual laxatives. Methylnaltrexone may be of particular benefit to those patients who are unable to receive oral laxatives, e.g. patients with head and neck tumours.	The scope has been updated with definition of the population according to the marketing authorisation.
	RCN	We feel this definition should make explicit reference to the fact that palliative care does not just relate to cancer patients and those with long term chronic conditions may also require opioids i.e. advanced illness in both malignant and chronic conditions	Population described according to the marketing authorisation.
Comparators	Wyeth	As methylnaltrexone will be used in addition to standard laxatives, the appropriate comparator is a treatment sequence to manage opioid-induced constipation in those patients who have not had a sufficient response to usual laxative therapy, with or without methylnaltrexone. The treatment sequence should include rectal interventions.	Included – see updated scope
	RCN	This is a unique product so there are, to our knowledge, no comparators. Additionally circumstances for the treatment of constipation are different within palliative care patients. Although a step wise approach to the treatment of constipation may normally be adopted for management in constipation in this case other drugs may not be effective.	See comparators in the updated scope

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Outcomes	Wyeth	Response to intervention measured as the proportion of patients who experience a bowel movement (responder or non-responder, not frequency). Frequency is an inappropriate metric as there is no consensus on "normal" frequency of bowel movement in palliative patients. Time to bowel movement Effect on pain medication	Outcomes included – see updated scope
	RCN	We feel these outcomes should also reflect more qualitative measures that reflect national policy such as end of life care and preferred place of stay. Managing this problem may result in individuals being able to stay at home to die rather than being admitted into hospital or hospice.	Outcomes included – see updated scope
Economic analysis	Wyeth	Wyeth acknowledges the usefulness of the reference case and the presentation of the results in terms of incremental cost per quality-adjusted life year. Due to the difficulties in accurately capturing benefit in terms of cost per quality-adjusted life year in an acute setting and in a palliative patient population it may be appropriate to consider alternative ways of representing the value of methylnaltrexone.	Consideration will be given to alternative approaches to economic analysis over and above the reference case
	RCN	We feel that cost effectiveness of a treatment being used in palliative care cannot be measured in terms of incremental costs per quality-adjusted life year.	Consideration will be given to alternative approaches to economic analysis over and above the reference case
Equality considerations	Wyeth	Consideration should be given to whether the use of a cost per QALY could be considered discriminatory in a palliative population who have limited capacity to demonstrate QALY gains relating to opioid-induced constipation in view of their short life expectancy and poor background quality of life.	Consideration will be given to alternative approaches to economic analysis over and above the reference case.
Other considerations	RCN	We feel this should be considered as a clinical guideline not HTA	Agreed that this will be an appraisal

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Questions for consultation	Wyeth	The inclusion criteria for the clinical trials of methylnaltrexone should be used to define patients with advanced illness who are receiving palliative care, namely patients with a terminal disease such as incurable cancer or end-stage AIDS with a life-expectancy of 1 - 6 months.  We do not believe that there are any subgroups of patients in whom the technology is expected to be more clinically effective and/or more cost effective.	Noted
Additional comments on the draft scope.		None	

**Comment 4: Regulatory issues**

Section	Consultees	Comments	Action
Remit	Wyeth	The anticipated marketing authorisation of methylnaltrexone in the UK will have the following indication: The treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care who have not had a sufficient response to usual laxative therapy	Noted
Current or proposed marketing authorisation	Wyeth	Indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care who have not had a sufficient response to usual laxative therapy.	Noted

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

1. NHS Quality Improvement Scotland
2. Royal College of Anaesthetists
3. Royal Pharmaceutical Society
4. Welsh Assembly Government