Surrey Heartlands Integrated Care System Area Prescribing Committee (APC)
Integrated Care Partnerships (ICPs) (Surrey Downs, Guildford & Waverley, North West Surrey, East Surrey (as part of the CRESH system) & associated partner organisations.

NICE Technology Appraisals: Local implementation

NICE TA Guidance	Naldemedine for treating opioid-induced constipation (TA 651)		
Available at	https://www.nice.org.uk/guidance/ta651		
Date of issue	30 September 2020	**Implementation deadline**	30 December 2020

Medicine details	
Name, brand name	Naldemedine (Rizmoic)
Manufacturer	Shionogi
Licensed indication	Rizmoic is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative (Oct 2020)
Formulation	Film Coated Tablet 200 micrograms (Oct 2020)
Usual dosage	200 micrograms (one tablet) daily
NICE recommended dosage/schedule	N/A

Disease and potential patient group	
Brief description of disease	A very common side effect experienced by patients taking opioids is constipation. Constipation is defined as • Infrequent bowel movements (typically three times or fewer per week) • Difficulty during defecation (straining during more than 25% of bowel movements or a subjective sensation of hard stools), or the sensation of incomplete bowel evacuation Opioid-induced constipation (OIC) may present immediately when a patient takes the opioid, or it may present gradually during opioid therapy. In association with constipation, patients may also develop other GI side effects like nausea, vomiting, bloat, abdominal pain, and straining. Many patients who develop constipation following opioids stop the drug therapy because they simply cannot tolerate the adverse effects on the GI tract. Once constipation to opioids has developed, the relief with treatment is slow and does not always result in optimal relief from constipation[1]
Potential patient numbers per 100,000	OIC is experienced by 40% to 60% of patients without cancer receiving opioids. Over 80% of patients with cancer pain experience OIC. The prevalence of opioid-induced constipation is not known. However, in England in 2010 there were over 17 million prescriptions for opioid items. In 2010-11 there were 57,506 hospital admissions due to constipation in England, and in 2011, there were 57 deaths registered in England and Wales due to constipation[2].

SUMMARY

NICE recommendation

Naldemedine is recommended, within its marketing authorisation, as an option for treating opioid-induced constipation in adults who have had laxative treatment.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

1. Combination standard laxatives are recommended for mixed aetiology constipation, when initial laxative therapy has been tried.

2. Opioid-induced constipation often happens at the same time as other causes of constipation (mixed aetiology constipation) in people with both non-cancer and cancer pain. In these circumstances, naldemedine is suitable for managing the opioid-induced component of mixed aetiology constipation.

3. Laxative-inadequate response is an artificial definition not used in clinical practice and has been removed from the treatment pathway. The company positioning of naldemedine in the relevant subgroups in the treatment pathway is clear.

4. Rescue medication should be included in both the naldemedine and comparator groups. Cost-effectiveness analyses include the intention-to-treat (ITT) population and can be considered relevant for decision making.

5. The results of the COMPOSE trials can be generalised to England. Naldemedine is likely to be equally effective in people with non-cancer and cancer pain who have opioid-induced constipation[1]

Cost implications*

Cost of product:

£543.85 per year

Alternative treatments and cost per patient (per year / per month as appropriate)

Other NICE recommended products:

Treatment	Regimen	Treatment cost/year (£)[3]
Naloxegol (TA 345)	25 mg taken orally once daily (12.5 mg for people with renal insufficiency)	671.60
Methylnaltrexone (4 months of treatment)	Subcutaneous injection, every 2 days.	1,284.05
Naloxone-oxycodone	25 mg/10 mg taken orally every 12 hours	1,103.08

These treatments are for use if other laxatives have failed, see below

Options not reviewed by NICE but used in standard practice:

As per local guidelines, agreed previously by APC and follow CKS guidance- https://surreyccg.ressystems.net/PAD//Content/Documents/2/Management%20of%20chronic%20constipation%20in%20adult%202019%20final.pdf

Treatment	Regimen	Treatment cost/year (£)[3]
Senna+Macrogol	Senna 7.5mg max dose 2 tablets ON + macrogol 2 sachets OD	£76.37
Bisacodyl	Max 2 tablets OD	£23.83

Impact to patients

OIC is very common in people with non-cancer and cancer pain, and continues regardless of the type of opioid used. Ineffective response to treatment with stimulant laxatives and stool softeners can lead to faecal impaction resulting in unplanned hospital care.

Many patients taking a Peripherally-Acting Mu-Opioid Receptor Antagonists (PAMORA)have mixed aetiology constipation and so need a combination treatment to target the different causes of constipation. For some patients the burden of opioid-induced constipation on quality of life is greater than the pain that needs an opioid. This often means patients stop opioid treatment.

In 2018-19, 211 people a day were admitted to hospital in England for constipation[4]. This admissions data represents an increase of 16% on 2014-15 and a rise of 7.7% on 2017-18. Initiation of appropriate and effective laxatives can ensure that constipation is managed effectively in primary care and reduce the need for unplanned hospital care.

A key benefit of a PAMORA is that patients can have a normal stool, while those taking conventional laxatives often experience a continual back and forth of being constipated and then having diarrhoea. This is a huge burden for both patients and carers in terms of continually managing bowel function
Unlike naloxegol, naldemedine can be taken either with or after food.
Patients may experience abdominal pain, vomiting and diarrhoea, severe persistent symptoms should be reported to their GP.
Patients should be aware of opioid withdrawal symptoms and report this to their GP as soon as possible.

Impact to primary care prescribers

The addition of this product onto formulary and guidelines would offer another option for treatment of OIC. It is licensed to be able to use with other laxatives for the management of other underlying causes of constipation.
GPs can initiate therapy if the patient has failed on other laxatives. The GP would need to monitor patient for success of treatment at regular intervals, and treatment should be stopped as soon as opioid therapy is stopped.

No dose adjustment is required in renal impairment, however, due to the limited therapeutic experience in patients 75 years old and older, naldemedine therapy should be initiated with caution in this age group.

Cases of gastrointestinal perforation have been reported in the post-marketing setting, including fatal cases, when naldemedine was used in patients who were at an increased risk of gastrointestinal (GI) perforation, (e.g. diverticular disease and underlying malignancies of the gastrointestinal tract or peritoneal metastases).
Naldemedine must not be used in patients with known or suspected GI obstruction or in patients at increased risk of recurrent obstruction, due to the potential for GI perforation.
Caution with regards to the use of naldemedine should be exercised in patients with any conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g. peptic ulcer disease, Ogilvie's syndrome, malignancy of the GI tract, Crohn's disease). The overall benefit risk for each patient should be taken into account. Patients should be monitored for

the development of severe, persistent or worsening abdominal pain. If obstruction or perforation are suspected, naldemedine must be discontinued
Abdominal adverse reactions (e.g. abdominal pain, vomiting and diarrhoea) have been reported with Rizmoic. Patients should be advised to report severe, persistent or worsening symptoms to their physician. In cases of severe diarrhoea or abdominal pain, the patient should be monitored and treated for dehydration using rehydration and appropriate treatment as needed.
Caution should be exercised with regards to opioid withdrawal. Patients should be advised to discontinue naldemedine and to contact their physician if opioid withdrawal occurs[5].

Impact to secondary care

Effective management of drug induced constipation could reduce the number of patients requiring unplanned hospital care as a result of severe chronic constipation. It is unlikely that this medication would be initiated in secondary care.
There will be some patients who may still experience inadequate bowel movement with naldemedine and they would need referral to a specialist.

Impact to CCGs

The current option for OIC is naloxagol (Moventig®). Naldemedine is cheaper and it is also licensed for use with other laxatives being used to treat other underlying causes of constipation.

Implementation

In order to ensure implementation the current guidance would need to be amended to offer a choice of either naloxagol or naldemedine (see appendix 1 attached).
An update would be put in medicines management newsletter to inform prescribers of the new therapy.
There is no current need to switch patients, this would be an option for treatment of OIC in new patients and for those where current laxative therapy is not achieving optimum bowel movement. Naldemedine should be used in caution for patients over the age of 75. The dose does not need to be adjusted for renal impairment and therapy with naldemedine should be discontinued once opioid therapy has stopped.

Please explain what will need to happen to ensure implementation within 90 days of publication.
Consider need for starting criteria, monitoring parameters, stopping criteria
Place in therapy – current guidelines need updating / new guidelines or pathway required
Any possible deprescribing or decommissioning?
Any barriers to implementation locally?
Is there a cohort of patients that will need special consideration e.g. transition patients?
How does this treatment link to documents already on the prescribing advisory database?
Will there need to be other documents reviewed and if so how do they need to be updated?
Consider timescales (within 3 months,6 months etc.?)

Recommendation to APC

PbRe: Y/N

Colour classification guidelines

Recommended traffic light status (see attached guidelines):

GREEN

References:

1. https://www.nice.org.uk/guidance/ta651/resources/naldemedine-for-treating-opioidinduced-constipation-pdf-82609193616325
2. https://www.sps.nhs.uk/medicines/naldemedine/
3. https://www.nhsbsa.nhs.uk/sites/default/files/202009/Drug%20Tariff%20October%202020.pdf
4. https://bowelinterestgroup.co.uk/wp-content/uploads/2020/07/Cost-of-Constipation-2020.pdf
5. https://www.medicines.org.uk/emc/product/10816/smpc
6.

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Declaration of Interest:

XXXX

Date: XXXX

Reviewed by:

Name, Designation, Organisation

Declaration of Interest:

XXXX

Date: XXXX

VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
v.1	*02/11/20*	*Mandeep Bhogal*	*Draft*	*Out for consultation*
v.2	*20/11/20*	*Mandeep Bhogal*	*Draft*	*With Comments*