NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Naldemedine for treating opioid-induced constipation

1 Recommendations

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

Why the committee made these recommendations

The treatment of opioid-induced constipation depends on whether the opioid is the only cause of the constipation (pure opioid-induced constipation) or if there are other contributing factors (mixed aetiology constipation). Treatment may include a peripherally acting mu-opioid receptor antagonist (PAMORA) alone. But, more commonly a PAMORA and a conventional laxative are used together. Naldemedine is an oral PAMORA for adults after previous laxative treatment.

The clinical evidence shows that naldemedine increases the frequency of bowel movements compared with no treatment and other PAMORAs.

The cost-effectiveness evidence includes naldemedine in several clinical scenarios, for both pure opioid-induced constipation and mixed aetiology constipation. In all scenarios, the most likely cost-effectiveness results are within what NICE normally considers an acceptable use of NHS resources. Therefore, naldemedine is recommended for opioid-induced constipation after laxative treatment.

Issue date: April 2020

2 Information about naldemedine

Marketing authorisation indication

2.1 Naldemedine (Rizmoic, Shionogi) has a marketing authorisation in the UK for 'the treatment of opioid-induced constipation in adult patients who have previously been treated with a laxative'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price of a 28-tablet pack of naldemedine is £41.72 (excluding VAT; BNF online, accessed March 2020). The cost of a course of treatment depends on the duration of opioid-induced constipation needing treatment. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Shionogi, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

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

- Combination standard laxatives are recommended for mixed aetiology constipation, when initial laxative therapy has been tried (see technical report, issue 1, page 14).
- 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 (see technical report, issue 1, page 14).

- 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 now clear (see technical report, issue 2, page 15).
- 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 (see technical report, issue 3, page 16).
- 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 (see technical report, issue 5, page 19).

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 11, page 25), and took these into account in its decision making. It discussed the following issues, including issues 4 and 6 from the technical report, which remained unresolved after the technical engagement stage.

New treatment option

People with opioid-induced constipation would welcome a new treatment option

3.1 Opioid receptors are present in the gastrointestinal tract. When opioids bind to these receptors they can disrupt normal gastrointestinal function, usually resulting in opioid-induced constipation. Treatment for opioid-induced constipation could be a single treatment with a peripherally acting mu-opioid receptor antagonist (PAMORA) such as oral naloxegol or subcutaneous methylnaltrexone. But, it more commonly involves a combination of a PAMORA and a conventional laxative. Naldemedine is an alternative oral PAMORA taken as a single daily dose. The clinical expert explained that opioid-induced constipation is very common in people with non-cancer and cancer pain, and continues regardless of the

type of opioid used. The expert estimated that over 80% of patients with cancer pain will have opioid-induced constipation, while the prevalence is likely to be lower in patients with non-cancer pain. The clinical expert also highlighted that in clinical practice, many patients taking a 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. The clinical expert said that 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. The committee concluded that people with opioid-induced constipation would welcome a new treatment that improves their constipation symptoms and quality of life.

Comparators

There are several relevant comparators including no treatment, laxatives, naloxegol and methylnaltrexone

3.2 The clinical expert confirmed that all relevant comparators had been included in the key subpopulations modelled by the company (see section 3.4, table 1). The clinical expert explained that the available PAMORAs are subcutaneous methylnaltrexone and oral naloxegol. The committee was informed that methylnaltrexone is primarily used to treat severe cases of constipation when a response is needed quickly, before switching to an oral treatment. The comparators included:

- naloxegol for people with opioid-induced constipation
- methylnaltrexone for people with opioid-induced constipation and cancer pain
- laxatives for people with mixed aetiology constipation
- no treatment for people with opioid-induced constipation or mixed aetiology constipation.

The committee also discussed the value of conventional laxatives in managing opioid-induced constipation. The clinical expert explained that because of the way opioids cause constipation and the way conventional laxatives work, there is very little evidence to support the use of conventional laxatives for treating opioid-induced constipation. The committee concluded that all relevant comparators had been included in the correct subpopulations' analyses.

Response in the COMPOSE trials

Naldemedine is clinically effective compared with placebo and there are more clinical benefits for patients than considered in the trials

3.3 The company submission included 4 pivotal randomised trials (COMPOSE-1, -2 -3 and -4) and 3 supportive open-label safety studies (COMPOSE-5, -6 and -7). The primary outcome for COMPOSE-1, -2 and -4 was the proportion of people who had spontaneous bowel movements. For COMPOSE-3, the primary outcome was measures of treatment-emergent adverse events. The proportion of people who had spontaneous bowel movements was significantly greater in the naldemedine arm compared with placebo for COMPOSE-1, -2 and -4:

- COMPOSE-1: naldemedine 48%, placebo 35%, percentage change 13.0% (95% confidence interval [CI] 4.8 to 21.2).
- COMPOSE -2: naldemedine 53%, placebo 34%, percentage change 18.9% (95% CI 10.8 to 27.0).
- COMPOSE-4: naldemedine 71%, placebo 34%, percentage change 36.8% (95% CI 23.7 to 49.9).

The committee discussed the response rates in the COMPOSE trials and noted that there was response in both the naldemedine and placebo groups. The clinical expert explained that pure opioid-induced constipation should respond to a PAMORA (including naloxegol and methylnaltrexone). Because the response rates in the COMPOSE trials were not 100%, this suggests that patients having naldemedine had

mixed aetiology constipation. The expert explained that many other factors other than opioid use can contribute to constipation. These include gastrointestinal pathology, other medications including antiemetics and painkillers, level of mobility and diet. These causes of constipation would not respond to a PAMORA and in some cases would not respond to a conventional laxative. The clinical expert also explained that the frequency of bowel motions is not as important to patients as other symptoms of opioid-induced constipation such as bloating, straining and incomplete evacuations, which affect the patient's quality of life. Opioids may also affect other functions in the gut, causing symptoms such as nausea and gastroparesis. The expert explained that PAMORAs not only increase the frequency of bowel movements but also help to manage these other side effects of opioids. The committee concluded that the increase in quality of life for people whose constipation had a response to naldemedine compared with placebo includes relief of other opioid-induced symptoms, which may be directly or indirectly related to constipation. It also concluded that naldemedine is more clinically effective compared with placebo and there are more clinical benefits for patients than considered in the trials.

Subpopulations included in the economic model

The key subpopulations (0 to 4) reflect the clinical pathway in NHS practice and were relevant for decision making

3.4 The committee considered several key subpopulations revised by the company after clarification stage and after technical engagement. The committee agreed that subpopulations 1 to 4 reflect the clinical pathway in NHS practice (see table 1 below).

Table 1: Key subpopulations modelled by the company

Subpopulation	Intervention	Comparator	Source
0: OIC, patients with non-cancer pain	Naldemedine with or without a rescue laxative	Placebo with or without a rescue laxative	COMPOSE-1 and COMPOSE-2 (ITT)
1: OIC and mixed aetiology constipation, patients with non-cancer pain	Naldemedine with or without a laxative and with or without a rescue laxative	Placebo with or without a laxative and with or without a rescue laxative	COMPOSE-3 (ITT)
2: mixed aetiology constipation, patients with non-cancer pain	Naldemedine plus stable laxative with or without a rescue laxative	Placebo plus stable laxative with or without a rescue laxative	COMPOSE-3 (ITT stable laxative subgroup)
3: OIC, patients with non-cancer pain	Naldemedine with or without a rescue laxative	Naloxegol with or without a rescue laxative	ITC from Luthra et al. 2018
4: OIC, patients with cancer pain	Naldemedine with or without a rescue laxative	Methylnaltrexone (SC) with or without a rescue laxative	ITC based on COMPOSE-4 and Bull et al. 2015

Abbreviations: OIC, opioid-induced constipation; ITT, intention-to-treat analysis; ITC, indirect treatment comparison; SC, subcutaneous injection.

The committee discussed the clinical plausibility of the various subpopulations modelled by the company. The clinical expert confirmed that the key subpopulations 0 to 4 reflected NHS practice. The clinical expert explained that standard practice in England often involves patients starting therapy with a conventional laxative, which will often remain as part of the treatment regimen in both pure opioid-induced constipation and mixed aetiology constipation. When there is a poor response, a PAMORA would be considered in addition to the conventional laxative, and response to therapy would be monitored. The experience of the clinical expert indicated varying NHS practice, and limited use of the NICE technology appraisal guidance on naloxegol for treating opioid-induced constipation . The committee agreed that subpopulations 0 to 4 reflected naldemedine in clinical practice and were relevant for decision making.

Indirect treatment comparisons

The indirect treatment comparisons for subpopulations 3 and 4 are relevant for decision making

3.5 The company submission did not include any direct evidence comparing naldemedine with any of the active comparators (naloxegol and methylnaltrexone). It included the results from an indirect treatment comparison comparing naloxegol with naldemedine (relative risk [RR] 0.79 [95% CI 0.63 to 0.99]) which informed subpopulation 3, based on an independent publication by Luthra et al. (2018). Also, the company included the results from an indirect treatment comparison comparing methylnaltrexone with naldemedine (RR 0.88 [95% CI 0.71, 1.06]). This informed subpopulation 4, based on the COMPOSE-4 trial and a randomised controlled trial by Bull et al. (2015). The company did not provide the methods used to combine the data from the trials in the indirect treatment comparison for subpopulation 4 after technical engagement. The company also highlighted that they did not have the input data for the indirect treatment comparison used to inform subpopulation 3. Therefore, the ERG was unable to assess the appropriateness of the indirect treatment comparison analyses or verify the results. After technical engagement, the ERG did several probabilistic sensitivity analyses and concluded that the uncertainty in the indirect treatment comparisons were unlikely to have a large effect on the cost-effectiveness results. For subpopulation 4, the ERG noted that methylnaltrexone is much more expensive than naldemedine. So, even if methylnaltrexone was much more effective, naldemedine would still be cost effective. The clinical expert noted that as subpopulations 3 and 4 did not include a direct comparison of these PAMORAs with naldemedine, it was difficult to determine whether there was a true difference between treatments. The committee concluded that any uncertainty was likely to have a small effect on the cost-effectiveness results for these subpopulations. It therefore considered that the indirect treatment

comparisons for subpopulations 3 and 4 were relevant for decision making.

Assumptions in the economic model

Stopping treatment for constipation that does not respond is an appropriate assumption in the model

3.6 The company's economic model structure was based on the model considered in NICE's technology appraisal guidance on naloxegol. This consisted of a decision-tree structure for the first cycle followed by a Markov-structure from the second cycle onwards. Patients enter the Markov model at either opioid-induced constipation or non-opioid-induced constipation (when having treatment) health states, with a cycle length of 4 weeks and time horizon of up to 5 years. The company made several structural assumptions in their economic model, based on the NICE technology appraisal guidance on naloxegol, including for stopping treatment. Patients were assumed to stop treatment with naldemedine if their constipation had not responded by week 4 or had responded but they then experienced a reoccurrence of opioid-induced constipation. After stopping treatment, people whose constipation had not responded were assumed to not resume treatment across the 5-year time horizon of the economic model. The committee discussed loss of treatment response and the clinical likelihood of having only 1 possibility of response to naldemedine. The clinical expert explained that patients with pure opioid-induced constipation often develop mixed aetiology constipation, meaning response to a PAMORA may reduce. However, the clinical expert explained that for people with pure opioid-induced constipation, a PAMORA should not stop working and people should not develop a tolerance. Any loss of efficacy is normally because of a change in the patient's underlying condition rather than because of the PAMORA itself. The committee discussed the effect of assuming that treatment would be stopped on the estimates of cost effectiveness. It noted that the company had modelled naldemedine across various time horizons between 1 and

5 years. For most subpopulations, the incremental cost-effectiveness ratios (ICERs) increased slightly with a shorter time horizon. The ERG also noted that their clinical expert confirmed the appropriateness of assuming that treatment would be stopped for people whose constipation does not respond, or those who lost response. The committee recognised that stopping treatment for constipation that stops responding to naldemedine is plausible in clinical practice and is an appropriate assumption for the model.

Extrapolation of treatment response

Choice of survival distribution has a minimal effect on the ICERs for each subpopulation

3.7 The company submission included the probabilities for loss of treatment response to naldemedine, which were based on extrapolated time-to-event data from the relevant trials (see section 3.4, table 1). The company did not explore the clinical plausibility of their preferred parametric curves to model loss of treatment response at the clarification stage or after technical engagement. Instead, it highlighted that for all subpopulations, the choice of survival distribution has a minimal effect on the ICERs for each subpopulation. The ERG agreed with the choice of parametric curve in the company submission for subpopulations 1 to 4 but concluded that the Gompertz model was more appropriate for subpopulation 0. This was based on clinical opinion, which suggests that loss of response is likely to plateau at a certain level. The committee was aware that the choice of the curve has a minimal effect on the ICERs for all the subpopulations. It agreed that, while the clinical plausibility of the time-to-event curves is not known and that it would have been helpful for the company to provide this information, the effect on the ICERs is likely to be small.

Utility values in the economic model

The ICERs are sensitive to treatment-specific utility values and it is acceptable to include these in the economic model

3.8 The EQ-5D was not used in the COMPOSE trials, and so utility values from NICE's technology appraisal guidance on naloxegol were used. The company used treatment-specific utilities for the non-opioid-induced constipation (when having treatment) health state in the base case. The ERG noted that each health state should be homogeneous enough that the utility does not differ between different treatments. Therefore, it would have preferred a refined Markov model to which health state-specific utility values could be applied. The ERG's clinical expert did not expect differences in quality of life between people having naldemedine or naloxegol. The committee was aware that the ICER was sensitive to assuming treatment-specific utilities. Using health state-specific utilities increased the company's base case ICERs for subpopulations 0, 1 and 2 to £28,131, £27,484 and £15,020 per quality-adjusted life year (QALY) gained, respectively. The ERG noted that while it was not ideal to use treatment-specific utilities, the non-opioid-induced constipation (when having treatment) health state was probably quite heterogeneous in terms of spontaneous bowel movements. The committee agreed that using treatment-specific utilities was reasonable based on the approach in NICE's technology appraisal guidance on naloxegol, and on the clinical expert opinion that naldemedine would improve a range of opioid-induced side effects, in addition to increases in spontaneous bowel movements seen in the COMPOSE trials. The committee noted that the company's model may not have captured these additional health benefits of naldemedine, and therefore accepted the use of treatment-specific utilities in the economic model.

Cost-effectiveness estimates

The most plausible ICER is likely to be below £20,000 per QALY gained for all subpopulations

3.9 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Because of the uncertainty in the indirect treatment comparisons and the impact on the choice of utility values, the committee agreed that an acceptable ICER would be below £20,000 per QALY gained. The committee recognised that the company's cost-effectiveness estimates for naldemedine using treatment-specific utility values were below £20,000 per QALY gained for all subpopulations (see table 2 below) and considered this to be a cost-effective use of NHS resources.

Table 2 Naldemedine cost-effectiveness results for key subpopulations

Subpopulation	Incremental costs	Incremental QALYs	ICER (per QALY gained)
Subpopulation 0	£275.11	0.022	£12,556
Subpopulation 1	£838.46	0.067	£12,489
Subpopulation 2	£788.59	0.083	£9,462
Subpopulation 3	£73.72	0.02	£3,649
Subpopulation 4	-£3,356	0.014	Naldemedine is dominant (it is more effective and costs less than comparators)

The ICERs in table 2 have been calculated using incremental costs and QALYs from the company's economic model.

The committee noted that the use of health state-specific utilities increased the ICERs for some of the subpopulations above this range, but that these were still under £30,000 per QALY gained. The committee was also persuaded that using health state-specific utilities did not capture all the broader benefits of treatment with naldemedine as highlighted by the clinical expert. If these were taken into account, the ICERs were likely to be under £20,000 per QALY gained. The committee was reassured by the results of the ERG's probabilistic sensitivity analysis for subpopulation 1. This indicated that naldemedine had probabilities of being cost effective of 74.8% and 86.3% at £20,000 and £30,000 per QALY gained, respectively. The committee agreed that treatment with naldemedine will likely result in an ICER below £20,000 per QALY gained compared with the relevant comparators for all the subpopulations.

Other factors

There are no equality issues relevant to the recommendations

3.10 No equality/social value judgement issues were identified.

The benefits of naldemedine are captured in the cost-effectiveness analysis

3.11 The company considered naldemedine to be innovative because of its permanent binding capacity and higher receptor affinity compared with other PAMORAs. The committee agreed that these were important benefits of naldemedine. But, it concluded that it had not been presented with evidence of any additional benefits that could not be captured in the QALYs.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions,

local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has opioid-induced constipation and the doctor responsible for their care thinks that naldemedine is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Selby
Chair, appraisal committee
March 2020

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C. Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a

conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Anita Sangha
Technical lead

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ISBN: [to be added at publication]