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SMC2242

naldemedine 200 micrograms film-coated tablets (Rizmoic®)

Shionogi BV

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

naldemedine (Rizmoic®) is accepted for use within NHSScotland.

Indication under review: For the treatment of opioid induced constipation (OIC) in adult patients who have previously been treated with a laxative.

Naldemedine compared to placebo significantly improved the spontaneous bowel movement response rate in patients with opioid induced constipation and either non-cancer or cancer pain.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of opioid induced constipation (OIC) in adult patients who have previously been treated with a laxative.[1]

Dosing Information

The recommended dose of naldemedine is 200 micrograms (one tablet) to be taken orally once daily. Naldemedine can be used with or without other laxatives, and can be taken with or without food.[1]

Naldemedine can be taken at any time of the day; however, it is recommended that it be taken at the same time each day. Alteration of the analgesic dosing regimen is not required. Naldemedine must be discontinued if treatment with opioids is discontinued.[1]

Product availability date

October 2019

Summary of evidence on comparative efficacy

Naldemedine is an antagonist of the mu-, delta-, and kappa-opioid receptors. It functions as a peripherally acting mu-opioid receptor antagonist within the enteric nervous system of the gastrointestinal tract. Naldemedine acts by decreasing the constipating effects of opioids without reversing the centrally mediated effects of opioids.[1]

Evidence supporting the efficacy and safety of naldemedine comes from COMPOSE-1 and COMPOSE-2, which were identical, phase III, double-blind, randomised, placebo-controlled, parallel-group studies. Patients aged 18 to 80 years with chronic non-cancer pain, who were taking opioids for at least 3 months at a stable total daily dose ≥30mg morphine equivalent for ≥1 month with experience of OIC were included. Patients were either not taking laxatives or agreed to discontinue any laxative before the 14-day screening period. Patients were included if they had experienced ≤4 spontaneous bowel movements (SBMs), defined as a bowel movement occurring without the use of rescue laxative medication in the previous 24 hours, within the 14-day screening period, ≤3 SBMs in any given week, and at least one bowel symptom (straining, lumpy/hard stools, sensation of incomplete evacuation/blockage) in at least 25% of bowel movements (BMs). Patients were also required to have at least 78% compliance with daily completion of electronic diary entries in the 14-day screening period.[2]

Patients were randomised equally to receive double-blind naldemedine 200 micrograms orally once per day (COMPOSE-1: n= 273 COMPOSE-2: n= 276) or placebo (COMPOSE-1: n=272; COMPOSE-2: n=274) for 12 weeks. Regular laxative use was not permitted throughout the treatment period. Rescue laxative therapy was initiated if a patient did not have a BM for any period of 72 hours during the treatment period. During the study, opioid doses were managed by the treating physician, and breakthrough medication (non-opioid and opioid) was allowed.

Randomisation was stratified by average total daily opioid dose (30 to 100mg and >100mg equivalents of oral morphine).[2]

The primary outcome was the proportion of responders, defined as those having ≥3 SBMs per week and an increase from baseline of ≥1 SBM per week for that week (a positive response week) for ≥9 weeks out of the 12-week treatment period and ≥3 of the last 4 weeks of the 12-week treatment period. Proportion of responders was assessed in the intention-to-treat population (ITT) which included all randomised patients.[2] In COMPOSE-1 and COMPOSE-2, the proportion of responders was significantly higher in the naldemedine groups than in the placebo groups. The results are presented in Table 1.

Post-hoc analyses defining the study population as inadequate response to laxatives (LIR) and adequate response to laxatives (non-LIR) patient groups showed consistent efficacy in both groups when data from COMPOSE-1 and 2 were pooled.[3]

Table 1. Primary outcome results of COMPOSE-1 and COMPOSE-2 (ITT population).[2]

	COMPOSE-1		**COMPOSE-2**	
	naldemedine 200mcg (n=273)	placebo (n=272)	naldemedine 200mcg (n=276)	placebo (n=274)
Responders	130	94	145	92
Response rate	48%	35%	52%	34%
Difference (95% CI)	13% (4.8% to 21%) p=0.002		19% (11% to 27%) p<0.001	

CI = confidence interval

A hierarchical statistical testing strategy was applied in each study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Secondary outcomes in COMPOSE-1 and COMPOSE-2 included change in the frequency of SBMs per week from baseline to the last 2 weeks of the treatment period and from baseline to week 1 of the treatment period, change in the frequency of complete spontaneous bowel movement (CSBM), defined as a SBM with the feeling of complete evacuation, per week from baseline to the last 2 weeks of the treatment period, and change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the treatment period. In both studies, statistically significant differences in favour of naldemedine were reported for all specified secondary outcomes (Table 2).[2]

Table 2. Key secondary results of COMPOSE-1 and COMPOSE-2 (ITT population).[2, 3]

	COMPOSE-1		COMPOSE-2	
	naldemedine 200mcg (n=273)	placebo (n=272)	naldemedine 200mcg (n=276)	placebo (n=274)
Change in the frequency of SBMs per week from baseline to the last 2 weeks of the treatment period (least square mean) [SE]	3.4 [0.2]	2.1 [0.2]	3.6 [0.2]	2.2 [0.2]
- Least square mean difference (95% CI)	1.3 (0.8 to 1.8) p<0.001		1.4 (0.9 to 1.9) p<0.001	
Change in the frequency of SBMs per week from baseline to week 1 of the treatment period (least square mean) [SE]	3.5 [0.2]	1.4 [0.2]	3.9 [0.2]	1.7 [0.2]
- Least square mean difference (95% CI)	2.1 (1.6 to 2.6) p<0.001		2.2 (1.6 to 2.7) p<0.001	
Change in the frequency of CSBM per week from baseline to the last 2 weeks of the treatment period (least square mean) [SE]	2.5 [0.2]	1.6 [0.2]	2.8 [0.2]	1.6 [0.2]
- Least square mean difference (95% CI)	1.0 (0.5 to 1.5) p<0.001		1.2 (0.7 to 1.6) p<0.001	
Change in the frequency of SBMs without straining per week from baseline to the last 2 weeks of the treatment period (least square mean)	1.5 [0.1]	0.7 [0.1]	1.8 [0.2]	1.1 [0.2]
- Least square mean difference (95% CI)	0.7 (0.3 to 1.1) p<0.001		0.8 (0.3 to 1.2) p=0.0011	

CI= confidence interval; CSBM= complete spontaneous bowel movement; SBM= spontaneous bowel movement; SE= standard error

In COMPOSE-1, 2, and 3, the patient assessment of constipation symptoms (PAC-SYM) and the patient assessment of quality of life (PAC-QOL) questionnaires were completed at baseline, week 2, 4 and 12 (plus week 24, 36, and 52 for COMPOSE-3). Improvements in PAC-SYM and PAC-QOL scores of greater than 0.8 and 1 respectively are deemed clinically relevant.[3] In COMPOSE-1, 2 and 3, patients receiving naldemedine 200micrograms experienced greater improvements from baseline to week 12 compared with placebo in PAC-SYM and PAC-QOL scores: mean change from baseline to week 12 in PAC-SYM overall score (naldemedine group) = -0.93, -1.01, and -1.11 (least squares mean) respectively; mean change from baseline to week 12 in PAC-QOL overall score (naldemedine group) = -0.93, -1.08, and -1.19 (least squares mean).[3, 5-7]

COMPOSE-3 was a randomised, double-blind, placebo-controlled, parallel-group, phase III study that examined the long-term efficacy of naldemedine (200micrograms once daily orally) versus placebo for 52 weeks in a population of 1,246 patients (623 patients in each group) with chronic non-cancer pain who were on a stable opioid regimen and diagnosed with OIC. Patients had no more than 4 SBMs total over the 14-consecutive-day qualifying period, as well as no more than 3 SBMs in a given week of the qualifying period. Patients on a stable laxative regimen at screening

could continue this treatment during the study. Laxative therapy was provided for patients who required laxatives (as a stable regimen or as rescue) during the screening and treatment periods.[3, 9]

Efficacy outcomes were secondary outcomes in COMPOSE-3, and included change in frequency of bowel movements from baseline, measured at 12, 24, 36 and 52 weeks and quality of life outcomes. The study demonstrated an increase in the frequency of bowel movements in the naldemedine group compared with placebo, with a treatment difference of 1.3 BMs per week at week 12. This difference was sustained through Week 52.[3, 9] Patients in the naldemedine group had a greater improvement from baseline in the mean overall PAC-SYM score over time than patients in the placebo group. Secondary efficacy outcomes were analysed for the subgroup of patients on or not on a stable laxative regimen. For patients on a stable laxative regimen, a greater change in the frequency of BMs per week from baseline to week 12 was found for naldemedine compared with placebo; treatment difference of 1.2 BMs per week. This difference was sustained through Week 52.[3]

COMPOSE-4 was a double-blind, randomised, placebo-controlled, parallel-group study in Japan comparing naldemedine (200 micrograms orally once daily) to placebo for 2 weeks for the treatment of OIC in chronic cancer pain. The primary outcome was the proportion of SBM responders during the 2-week treatment period, defined as patients with ≥3 SBMs per week and an increase from baseline of ≥1 SBM per week. The proportion of SBM responders was significantly greater in the naldemedine group compared to placebo: 71% versus 34%, p<0.001. Naldemedine 200micrograms did not demonstrate significant improvements from baseline to week two compared to placebo in both patient reported outcomes of PAC-SYM and PAC-QOL.[4]

The submitting company presented three indirect treatment comparisons (ITCs) in their submission to support the economic analysis: a published network meta-analysis (NMA) (referred to as “Luthra 2019”), a Bucher ITC versus naloxegol (ITC 1), and a naïve unadjusted ITC versus methylnaltrexone (ITC 2). Luthra 2019 compared naldemedine with the following in adult patients with OIC: placebo, methylnaltrexone, naloxone, alvimopan, naloxegol, bevenopran, lubiprostone, prucalopride, naronapride, velusetrag, linaclotide or plecanatide for a minimum of 2 weeks. A total of 27 studies were included and outcomes included failure to respond to therapy, adverse events as a result of therapy, and individual adverse events such as diarrhoea, abdominal pain, nausea, or reversal of analgesia. In ITC 1, naldemedine was indirectly compared with naloxegol 25mg in adult patients with OIC who had cancer or chronic non-cancer pain and were receiving an opioid regimen. This population also had an inadequate response to laxative treatment. Four studies were included in the analysis: COMPOSE-1, COMPOSE-2, KODIAC-04, and KODIAC-05.[2, 10] Outcomes included response rate at week 4 (defined as ≥3 SBMs in ≥3 of 4 weeks) and response rate at week 12 (defined as ≥3 SBMs per week). In ITC 2, naldemedine was indirectly compared with subcutaneous methylnaltrexone. The study population used for this ITC was all cancer patients randomised to naldemedine 200 micrograms in COMPOSE-4 versus the subcutaneous methylnaltrexone group in a randomised placebo controlled study.[4, 11] The only outcome reported for this analysis was difference in reduction of SBMs at week 2.

The submitting company concluded that the results of Luthra 2019 were generally positive for naldemedine, however due to limitations of the NMA the results were largely not incorporated into the economic analysis. In ITC 1, no significant differences between naldemedine and naloxegol 25mg were reported at week 4 and week 12 in terms of response rates. Similarly, in ITC 2, the company stated that no significant difference was observed when naldemedine was compared with methylnaltrexone.

Summary of evidence on comparative safety

Overall the European Medicines Agency (EMA) concluded that the safety of naldemedine was demonstrated by showing consistent results in both the inadequate response to laxatives and non-inadequate response to laxatives subgroups. COMPOSE-3 was a 52 week, phase III safety study, the results of which are discussed in detail below. Information on the methods and efficacy results can be found in the comparative efficacy section. Other naldemedine studies that assessed safety as secondary outcomes, namely COMPOSE-1, 2, and 4, reported similar rates of adverse events. The EMA noted that the adverse event profile of naldemedine is similar between cancer and non-cancer patients.[3]

At data cut off June 2015, the duration of treatment was 52 weeks in both the naldemedine and placebo groups. Over half of patients in the naldemedine group (66% [413/623]) and placebo group (66% [413/623]) completed the treatment period. Treatment emergent adverse events (AEs) were reported by 68% (425/621) in the naldemedine group and 72% (446/619) in the placebo group and were considered treatment-related in 24% and 20% of patients in the respective groups. Study discontinuation as a result of treatment emergent AEs was reported in 6.3% (39/621) in the naldemedine group and 5.8% (36/619) in the placebo group. AEs were considered serious in 9.7% (60/621) of the naldemedine group and 12% (73/619) in the placebo group. Study discontinuation as a result of serious treatment emergent AEs was reported in 1.1% (7/621) in the naldemedine group and 1.9% (12/619) in the placebo group.[9]

The most common treatment emergent AEs were gastrointestinal disorders with 17% (104/621) in the naldemedine group and 11.3% (70/619) in the placebo group experiencing these AEs. The most commonly reported gastrointestinal disorder was diarrhoea, with 11% (68/621) in the naldemedine group compared to 5.3% (33/619) in the placebo group. Other treatment emergent AEs in the naldemedine versus placebo groups include abdominal pain with 8.2% (51/621) versus 3.1% (19/619); nausea with 7.9% (49/621) versus 5.7% (35/619) and vomiting in 6.0% (37/621) versus 3.1% (19/619). Treatment emergent AEs of possible opioid withdrawal were reported in 2.4% (15/621) of the naldemedine group versus 0.6% (4/619) in the placebo group.[9]

Summary of clinical effectiveness issues

Chronic non-cancer pain and cancer related pain are highly prevalent and often treated with opioids. Opioid use is associated with a number of adverse events, the most common being OIC. Research suggests that around 40% to 50% of individuals taking opioids for chronic pain will experience OIC and in cancer related pain this prevalence is thought to be as high as 70% to 85%. Clinical experts consulted by SMC suggested that in non-cancer pain, OIC should be treated by reducing / stopping opioids where possible. If that is not possible, OIC can currently be managed with laxatives such as stool softeners and/or stimulant laxatives. However, these may have a limited effect and patients often report dissatisfaction with and poor adherence to laxative treatment. At present, two other peripherally-acting opioid antagonist treatments are available in Scotland for OIC. Naloxegol is approved for use in individuals who have had an inadequate response to laxatives (SMC 1106/15) and subcutaneous methylnaltrexone is currently approved for use in the palliative care setting when response to usual laxative therapy has not been sufficient (SMC 518/08).[8, 12]

Naldemedine has been shown to be effective in treating OIC in both cancer pain and non-cancer pain populations across several studies. In COMPOSE-1 and 2, a significantly larger proportion of SBM responders were seen in the naldemedine group compared with placebo after 12 weeks, with treatment differences of 13% and 19% respectively. Longer-term data from the 52 week COMPOSE-3 study was also supportive. In cancer pain patients, evidence of efficacy came from COMPOSE-4, which showed a treatment difference with placebo of 37% in SBM response rate after 2 weeks of treatment, and longer-term data was collected in COMPOSE-5. Post-hoc subgroup analysis of the LIR and non-LIR populations showed consistent results.[3]

In COMPOSE-1, 2, and 3, patients receiving naldemedine experienced greater improvements from baseline to week 12 compared with placebo in PAC-SYM total score and improvements were also noted in the PAC-QOL from baseline to week 12. However it is not clear what proportions of patients in the studies achieved clinically meaningful improvements in PAC-SYM (>0.8) or PAC-QOL (>1). In patients with cancer chronic pain (COMPOSE-4), naldemedine did not demonstrate significant improvements from baseline to week 2 compared with placebo in PAC-SYM or PAC-QOL, suggesting that constipation may have little influence on the overall quality of life for cancer patients. Patient reported outcomes are regarded as highly relevant for OIC by the EMA.[3, 5-7, 13]

The clinical evidence presented in support of naldemedine is subject to some limitations. Firstly, the treatment period of COMPOSE-4 was limited to 2 weeks instead of 4 weeks as recommended by EMA guidelines. However, the EMA felt this was acceptable due to the efficacy demonstrated in the non-cancer population, the strict outcomes evaluated, and the supportive 12-week study (COMPOSE-5). A further limitation of COMPOSE-4 and COMPOSE-5 was that the studies were solely conducted in Japan, which poses a potential issue with regards to generalisability to the Scottish population. Relatively low baseline mean total daily opioid doses in the cancer studies

may also limit the findings, and may help to explain the difference in treatment effect observed in COMPOSE-1 and 2 compared with COMPOSE-4.[3]

A further limitation in the evidence presented for naldemedine is the lack of data for patients who take more than 400mg of morphine (or equivalent) per day. A small number of patients (<5%) in the COMPOSE-1 and 2 studies had baseline daily opioid doses >400mg morphine (or equivalent). The EMA considered that the number of patients in COMPOSE-4 taking high doses of opioid were lower than had been previously reported for relevant Western populations. As a competitive antagonist, there will be an upper limit to the efficacy associated with naldemedine 200 micrograms daily. Consequently, the summary of product characteristics advises that there is limited experience in patients treated with opioid doses higher than 400mg morphine (or equivalent).[3]

There is no experience with naldemedine for the treatment of constipation induced by partial opioid mu-agonists (for example buprenorphine).[3]

Clinical experts consulted by SMC felt that naldemedine would likely be used in cases where standard interventions were not achieving an adequate response. Therefore, analysis of the LIR subgroup may be the most representative of treatment effects in practice. However, these analyses should be interpreted with caution given that they were performed post-hoc, and were not powered to detect differences. Treatment effects were similar for the LIR and the non-LIR subgroups (SBM responders 16.2% and 15.6% respectively).[3]

Naldemedine has not been directly compared to relevant comparators in Scotland, namely naloxegol and methylnaltrexone. As described in the comparative efficacy section, the company presented three ITCs to address this uncertainty. Luthra 2019 had the following limitations: 25mg and 12.5mg naloxegol treatment groups were combined in this analysis; only 11 out of 27 studies were at low risk of bias, which may have resulted in an overestimation of treatment effect; the vast majority of studies included in the analysis were based in secondary and tertiary care, limiting the generalisability of the results to patients being treated for OIC in primary care; quality of life outcomes were not assessed. Despite these limitations, the conclusion that naloxone and naldemedine appear to be the most efficacious treatments for OIC seems credible.

The limitations associated with ITC 1 (naldemedine versus naloxegol) were as follows: pooled data from the COMPOSE and KODIAC studies broke randomisation, and the analysis was at risk of confounding and selection bias; possible clinical heterogeneity in the form of differences in mean total daily doses of opioids at baseline between the COMPOSE and KODIAC studies; and important potential treatment effect modifiers such as weight, prior laxative use, and chronic pain conditions were not compared; information on the baseline characteristics of the LIR subpopulations used in the analysis is lacking; choice of week 12 outcome was questionable as the primary outcome of all included studies was not reported; safety and quality of life outcomes were not assessed. Overall, despite the limitations, the claim that there is no statistically significant difference between naldemedine and naloxegol seems reasonable.

ITC 2 had the following limitations: ITC 2 was a naïve unadjusted comparison, which negates randomisation and does not account for heterogeneity; there was substantial methodological and clinical heterogeneity; of particular note were the differences in number of patients with a primary diagnosis of cancer, mean total daily dose of opioid at baseline, and the mean number of BMs/week at baseline, definitions of OIC, outcomes used for the analysis, location of the studies (Japan versus multinational); differences in placebo rates between studies support the idea that the study populations were heterogeneous; the differences in the route of administrations between oral naldemedine and subcutaneous methylnaltrexone may have contributed; difference in patient population (stable cancer patients versus palliative patients). Due to the substantial limitations of ITC 2, the submitting company's conclusions on the comparison of naldemedine with methylnaltrexone in patients with advanced illness are highly uncertain.

Summary of comparative health economic evidence

The submitting company presented a range of cost-utility analyses to assess the cost effectiveness of naldemedine in a range of populations and versus different comparators, as described in table 3 below:

Table 3: Populations and comparators presented in the economic analysis

Scenario	Population	Comparator
0	non-cancer pain and OIC, previously treated with a laxative	No treatment
1 Base case	non-cancer pain and OIC	Second line laxative monotherapy
2	mixed aetiology constipation (including OIC) when combined with existing laxative therapy	Combination laxative therapy
3	OIC with previous inadequate response to laxatives	Naloxegol
4	advanced illness	Subcutaneous methylnaltrexone (MNTX)
5	cancer related pain and OIC	No treatment

Following clarification, the company stated that scenario 1 should be considered the base case analysis, but that scenarios 2 and 3 may also represent potentially relevant populations. Scenarios 0 and 5 may be considered less relevant as no treatment as a comparator is unlikely for these patients. The comparative clinical evidence for Scenario 4 was very unreliable so this comparison is unlikely to be reliable. The results in the DAD will, therefore, focus on Scenarios 1, 2 and 3.

The economic analysis was based on a model that combined a decision-tree structure for the first 4 weeks with a Markov structure for the subsequent 4-weekly cycles up to a time horizon initially presented by the submitting company of 5 years. This was later extended to 20 years in a request for further sensitivity analysis given the potential for treatment over extended durations. The Markov structure was made up of health states for OIC, non-OIC (on treatment), non-OIC (untreated), and death. The decision tree aspect of the model made use of treatment response

data to determine the proportion of patients who entered the model in either the OIC state or the non-OIC (on treatment) state. The Markov structure then models the transitions from non-OIC (on treatment) to the OIC state (i.e. loss of response, at which point treatment is discontinued), the transitions between OIC and non-OIC (untreated), and transitions from any state to death.

The key clinical data required for the model were the proportion of patients who respond to treatment initially; the probability of losing response over time; and the probabilities of transitioning between OIC and non-OIC (untreated) and the reverse. The key source of these data for naldemedine in each of the alternative scenarios came from the COMPOSE studies. These studies were also used to inform the comparators, with the exception of the response rates for naloxegol and methylnaltrexone, which were both estimated through indirect treatment comparisons (ITCs), as described above.

For the transition probabilities from non-OIC (on treatment) to OIC, survival curves were fitted to the relevant data from the COMPOSE studies, to extrapolate beyond the study period up to the time horizon. The company determined the best fitting survival function to be the log-normal distribution in all scenarios. For the comparisons with naloxegol and methylnaltrexone, the company performed ITCs to estimate response ratios and these were applied as hazard ratios to the relevant baseline naldemedine curve.

To estimate the probability of transitioning to the non-OIC (untreated) from the OIC state and to the OIC state from the non-OIC (untreated) state, the submitting company used the placebo group data from the COMPOSE studies and justified this as representing untreated patients. The company calculated rates of transition based on the period between the classification of a patient's constipation status at the initial response at 4 weeks (or first follow-up time) and the next 4 weeks (or next follow-up time).

Utilities were not collected in the COMPOSE studies – only non-preference-based measures of health-related quality-of-life (HRQoL). Namely, the SF-36 generic health questionnaire and the PAC-QOL disease-specific questionnaire. To inform the model the submitting company used utilities from NICE TA345 for naloxegol, which provided utilities directly elicited using the EQ-5D-3L. TA345 provided utilities that were both treatment- and health-state specific, as well as some that were just health-state specific. The company used the former for all main alternative scenarios, with values of 0.642 for non-OIC treated with naldemedine, 0.613 for non-OIC for the comparator or no treatment, and 0.553 for the OIC health state. Separate scenario analyses were performed on each of the main scenarios with alternative approaches for utility estimation used. These included the use of mapped EQ-5D-3L data from both the SF-12 (subset of the SF-36) data from the COMPOSE studies, and the use of the health-state specific utilities from TA345.

The main costs in the analysis related to the costs of the treatment and comparators, the costs of treating grade 3 and 4 adverse events (on the basis of a GP appointment) and costs associated with being in the OIC states of the model (to include inpatient, outpatient and primary care costs).

The latter were estimated from the company's Clinical Practice Research Datalink (CPRD) analysis; no specific costs were attached to the non-OIC states.

The key results presented by the submitting company are reported in table 4.

Table 4. Base case results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER pairwise (£/QALY)
Scenario 1 (Company's base case)	1,280	2.771	392	0.04393	8,929
Scenario 2	1,702	2.804	780	0.08347	8,967
Scenario 3	1,143	2.818	95	0.03746	2,781
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted					

The company provided a range of sensitivity and scenario analyses. The results demonstrated greatest sensitivity in the ICERs to the estimation of utility values as shown in tables 5 and 6.

Table 5. Health state specific utilities using EQ-5D from TA345

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER pairwise (£/QALY)
Scenario 1 (Company's base case)	1,245	2.811	369	0.01902	19,394
Scenario 2	1,656	2.823	749	0.03827	19,557
Scenario 3	1,112	2.861	104	0.01040	10,016
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

Table 6. Health state specific utilities mapped from SF-12 data from COMPOSE trials

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER pairwise (£/QALY)
Scenario 1 (Company's base case)	1,245	2.296	369	0.01598	23,172
Scenario 2	1,656	2.306	749	0.03216	23,240
Scenario 3	1,112	2.338	104	0.00874	12,072
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

The submitting company responded to requests for further sensitivity analyses and provided three key additional scenario analyses. One analysis assumed equal efficacy for each treatment group for Transition A (loss of response: moving from non-OIC-on-treatment to OIC) i.e. the only treatment benefit was the initial response to treatment. The second scenario extended the time horizon to 20 years, and the third scenario removed the costs of the OIC health state as these were likely to be overestimated in comparison to the assumed zero cost for the non-OIC health state. The results of these scenarios for the base case (Scenario 1) are given in Table 7.

Table 7. Additional requested analyses for Scenario 1 population

Modelled scenario	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER pairwise (£/QALY)
Equal efficacy for Transition A	1,280	2.771	422	0.037	11,478
20-year time horizon	3,159	8.094	489	0.057	8,570
No health state costs for OIC	816	2.771	455	0.044	10,357
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

The submitting company also provided an analysis using the Luthra *et.al* network meta-analysis (NMA), this resulted in a reduced ICER for Scenario 3 of £2,009 per QALY.

Key weaknesses of the submitting company's economic analyses are as follows:

- The economic analyses were based on post-hoc subgroup analyses which broke randomisation. No economic analysis was performed based on the ITT population of the COMPOSE-1 and -2 studies. As noted in the clinical effectiveness section above, there are concerns about the robustness of the comparative evidence base versus methylnaltrexone and the ability to estimate benefits of naldemedine over this comparator.
- As can be seen from the sensitivity analyses, the ICERs were sensitive to the use of alternative methods to populate the utility values in the model. As noted, the base case used values from a NICE assessment of naloxegol and included a both a treatment-specific benefit and health- state benefit. The treatment-specific advantage was justified by the company on the basis of responders on naldemedine having more SBMs per week than a responder on placebo and also that a similar approach was used in other SMC submissions in this disease area. .
- Risk ratios of response were assumed to be equivalent to HRs and applied to baseline survival curves to estimate the comparator Transition A probabilities for Scenarios 3 and 4. This analysis is unreliable. Further to this, the assumed HRs were applied to log-normal survival functions, which do not allow for proportional hazards.
- Following the New Drugs Committee meeting, the company provided some additional scenario analysis on request. These analyses were to account for the combined impact of using non-treatment specific utility values, removing costs from the OIC state and an adjustment to the calculation of the half-cycle correction in the model. The impact from combining these aspects was to increase the ICERs. For example, the ICER for Scenario 1 increased to £17,713 but it should be noted that this analysis derived the utility scores from a mapping of PAQ-SYM data rather than using either set of values referred to in the sensitivity analyses in tables 5 and 6 above. The difference in utility values between OIC and the non-OIC health state in this combined analysis was larger than that assumed in the values from the NICE appraisal underpinning the analysis in table 5.
- The time horizon of 5 years in the company's base case is short in comparison to the maximum opioid usage in the company's CPRD analysis but it was helpful that the company provided an analysis over a longer time horizon.

Despite these issues, the economic case was demonstrated.

Summary of patient and carer involvement

No patient group submission was received.

Additional information: guidelines and protocols

The management of OIC falls under several multidisciplinary areas, and therefore is covered across multiple guidelines.[14-17] Opioids are most commonly prescribed in the chronic pain, palliative care and cancer pain settings. In Scotland there are no specific guidelines for the management of OIC, however the recent Scottish Intercollegiate Guidelines Network (SIGN) 'managing chronic pain' makes reference to constipation as an adverse event however, it makes no specific recommendations for management.[17]

Within the UK the National Institute for Health and Care Excellence (NICE) guidance titled 'Palliative care for adults: strong opioids for pain relief' (CG140) recommends laxatives be taken regularly at an effective dose, yet the guidance makes no specific recommendations to a particular medicine.[15]

In 2018, the European Society for Medical Oncology (ESMO) published clinical practice guidelines titled 'Diagnosis, assessment and management of constipation in advanced cancer' where the focus was on constipation in oncology patients, yet they refer to OIC. The guideline examined the evidence and made the following recommendations: individuals prescribed opioids, who do not have a pre-existing contraindication of diarrhoea, be prescribed concomitant laxatives; with osmotic and stimulant laxatives being the preferred option. In patients where previous laxatives were not effective, the guideline makes specific recommendations to introduce methylnaltrexone and naloxegol. With methylnaltrexone recommended for restricted use in the palliative care setting and naloxegol recommended in patients who had poor outcomes with previous laxative therapy. While the guideline makes no specific recommendation to prescribing naldemedine they do review the literature and find that in patients treated with 0.4mg they experience a higher rate of adverse events (for example diarrhoea) in the intervention group compared with placebo and that individuals had a better outcome when prescribed 200 micrograms.[14]

Additional information: comparators

Naloxegol, methylnaltrexone (palliative setting).

Additional information: List price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Naldemedine	**200 micrograms orally once daily**	**£542**

Costs from BNF online on 16 December 2019. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The company estimated that there would be 10,403 patients eligible for treatment with naldemedine in year one and 10,367 in year five. Assuming a 15% uptake rate in year 1 rising to 25% by year 5 and an annual treatment discontinuation rate of 64%, 566 patients were assumed to be treated in year one rising to 940 by year 5.

The gross impact on the medicines budget was estimated to be £284k in year one, rising to £471k in year five. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £280k in year one and £454k in year five.

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This assessment is based on data submitted by the applicant company up to and including 15 February 2020.

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.