There are currently two treatments on the Barnsley formulary for the treatment of opioid-induced constipation. Both are peripherally acting opioid receptor antagonists, which decrease the constipating effects of opioids without altering their central analgesic effects. Naloxegol was the existing treatment and naldemedine has been added since NICE TA651 in September 2020.

Naldemedine (Rizmoic®)

Background Information	Naldemedine is recommended by NICE as an option for treating opioid induced constipation in adults who have previously had laxative treatment. The clinical evidence shows that naldemedine increases the frequency of bowel movements compared with no treatment and other peripherally acting mu-opioid receptor antagonists (PAMORA). There is limited experience of use in patients being treated with opioid medicinal product(s) at daily doses of more than the equivalent of 400mg of morphine. There is no experience in patients treated for constipation induced by partial opioid mu-agonists (buprenorphine). Target population: Adult and older adult, no data for <18yrs)
BNF therapeutic class	2.2 – Constipation
Indication	Naldemedine is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative.
Dosage and administration	The recommended dose of naldemedine is 200micrograms (ONE TABLET) daily. It may be used with or without laxative(s). It may be taken at any time of the day but it is recommended to be taken at the same time every day. It may be taken with or without food. Alteration of the analgesic dosing prior to initiating naldemedine is not required. Discontinue treatment of naldemedine if the treatment of the opioid medication is discontinued. No dosage adjustments are required in patients older than 65. No adjustments are required in patients with renal impairment. No adjustments are required in patients with mild or moderate hepatic impairment. **Pregnancy:** Naldemedine should not be used during pregnancy unless the clinical condition of the woman requires treatment with naldemedine. It may precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier. **Breast feeding:** Naldemedine should not be used during breast-feeding. A risk to the suckling child cannot be excluded.

Cautions and Contraindications	**Contraindications** Severe hepatic impairment Hypersensitivity to the active substance or to any of the excipients of naldemedine Patients with known or suspected gastrointestinal obstruction or perforation or patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation. Concomitant use with strong CYP3A inhibitors **Cautions:** Age 75 years and older – limited therapeutic experience Severe renal impairments – monitor due to limited therapeutic experience Opioid withdrawal syndrome – see SPC for product Patients who have had an MI, stroke or TIA within 3 months of screening should be monitored. Concomitant use with moderate CYP3A inducers (efavirenz). Cardiovascular disorders – safety and efficacy has not been established. Patients who have clinically important disruptions to the blood brain barrier (advanced Alzheimer's disease, active multiple sclerosis and primary brain malignancies).
Adverse Drug Reactions	Abdominal pain, vomiting and diarrhea have been reported. Patients should be advised to report severe, persistent or worsening symptoms to their physician. In cases of severe diarrhea or abdominal pain, the patient should be monitored and treated for dehydration using rehydration and appropriate treatment as needed. Potential opioid withdrawal (uncommon). Monitor for symptoms such as hyperhidrosis, chills, lacrimation increase, hot flush, pyrexia, sneezing, feeling cold, abdominal pain, diarrhea, nausea, vomiting, arthralgia, myalgia and tachycardia.
Monitoring	No on-going monitoring required
Interactions	Concomitant use of naldemedine with strong CYP3A inhibitors (grapefruit juice, itraconazole, ketoconazole, ritonavir, indinavir, saquinavir, telithromycin and clarithromycin) leads to an increase in naldemedine exposure and may increase the risk of adverse reaction therefore should be avoided. Concomitant use of naldemedine with strong CYP3A inducers (St John's Wort), rifampicin, carbamazepine, phenobarbital and phenytoin) leads to a decrease in naldemedine exposure and may reduce the efficacy of naldemedine.

Naloxegol (Moventig®)

Background Information	Naloxegol is recommended by NICE as a possible treatment for people with opioid induced constipation that has had an inadequate response to laxatives. An inadequate response is defined as opioid induced constipation symptoms of at least moderate severity in at least 1 of the 4 stool symptom domains (that is, incomplete bowel movement, hard stools, straining or false alarms) while taking at least 1 laxative class for at least 4 days during the prior 2 weeks. When naloxegol therapy is initiated, it is recommended that all currently used maintenance laxative therapy should be halted, until clinical effect of naloxegol is determined. NB: some patients with advanced progressive disease on opioids often have multiple causes for constipation and will usually continue to require conventional laxatives in addition. Target population: Adult and older adult, no data for <18yrs)
BNF therapeutic class	2.2 - Constipation
Indication	Naloxegol is a possible treatment for people with opioid induced constipation that has had an inadequate response to laxatives.
Dosage and administration	The recommended dose of naloxegol is 25 mg once daily naloxegol should be taken on an empty stomach at least 30 minutes prior to the first meal of the day or 2 hours after the first meal of the day. The manufacturer advises reduce initial dose to 12.5mg daily with concurrent use of moderate inhibitors of CYP3A4, increasing to 25mg daily if well tolerated.
Cautions and Contraindications	**Contraindications** Patients with known or suspected gastrointestinal (GI) obstruction or in patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation. Patients with underlying cancer who are at heightened risk of GI perforation, such as those with: • Underlying malignancies of gastrointestinal tract or peritoneum • Recurrent or advanced ovarian cancer • Vascular endothelial growth factor (VEGF) inhibitor treatment Concomitant use with strong CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, itraconazole or telithromycin; protease inhibitors such as ritonavir, indinavir or saquinavir; grapefruit juice when consumed in large quantities). **Cautions:** Conditions with increased potential for gastrointestinal perforation Clinically important disruptions of the blood-brain barrier (potential to reverse analgesic effect of opioid) – caution in primary brain tumours, CNS metastases, Alzheimer's, active MS etc. Congestive heart failure or recent history of MI (within 6 months)

Adverse Drug Reactions	The most commonly reported adverse reactions with naloxegol (≥ 5%) are: abdominal pain, diarrhea, nausea, headache and flatulence. The majority of gastrointestinal adverse reactions were graded as mild to moderate, occurred early in treatment and resolved with continued treatment. They were often reported as having a component of cramping discomfort. Naloxegol at therapeutic doses has minimal uptake across the blood brain barrier. In some patients, however, a constellation of symptoms has been reported, which resembles the syndrome of central opioid withdrawal. Most such reports were observed shortly after initial administration with the medicinal product and were mild or moderate in intensity.
Monitoring	No on-going monitoring required
Interactions	• ketoconazole or itraconazole increases plasma concentrations of Naloxegol • clarithromycin telithromycin • ritonavir, indinavir or saquinavir – • any laxatives • methadone increased risk of GI adverse reactions • diltiazem or verapamil increases plasma concentration of naloxegol • rifampin carbamazepine reduce plasma concentrations of naloxegol • Grapefruit juice may increase exposure to naloxegol

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Development Process

This guideline was developed following an AMBER-G (Amber with guidance) classification status of naloxegol and naldemedine for the treatment of opioid induced constipation, by the Barnsley Area Prescribing Committee. This information has been subject to consultation and endorsement by the Area Prescribing Committee on 10th March 2021.