



Naloxegol

Updated: March 24, 2020.

OVERVIEW

Introduction

Naloxegol is a peripherally acting opioid antagonist which is used to treat constipation caused by chronic opioid use for noncancer pain. Naloxegol has not been linked to serum enzyme elevations during therapy or to clinically apparent liver injury.

Background

Naloxegol (nal ox' ee gol) is a pegylated, semisynthetic opiate receptor antagonist which is similar structurally to naltrexone, but is peripherally restricted and thus has few if any effects on the central nervous system. Naloxegol is a polyethylene glycol (PEG) derivative of alpha-naloxol, an opiate antagonist. The addition of the large PEG molecule to naloxol does not block its engagement with opioid receptors, but does prevent the drug from crossing the blood brain barrier. As a consequence, the opioid antagonist reverses the peripheral but not the central nervous system effects of opiates, such as pain relief and euphoria. In large, preregistration trials, naloxegol was found to increase spontaneous bowel movement frequency and reduce constipation related side effects of opiates used for analgesia in patients with chronic pain. Naloxegol was approved for use in the United States in 2014 and is available as tablets of 12.5 and 25 mg under the brand name Movantik. The recommended dosage is 25 mg once daily, reducing the dose to 12.5 mg daily for intolerance. Side effects include abdominal pain, diarrhea, nausea, flatulence, anxiety, restlessness and sweating. Withdrawal symptoms can occur, but are rare. In persons not taking opioids, naloxegol has minimal effects on constipation. Rare but potentially severe adverse events include withdrawal symptoms, hypersensitivity reactions and gastrointestinal perforation.

Hepatotoxicity

Therapy with naloxegol has not been linked to serum enzyme elevations or to clinically apparent liver injury. In preregistration studies, liver test abnormalities arose in less than 1% of treated patients but were transient, mild and not associated with symptoms. There were no reported cases of liver injury with jaundice or symptoms. Since its approval and more widescale use, there have been no published reports of hepatotoxicity attributed to naloxegol.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which naloxegol might cause liver injury is not known. Naloxegol is extensively metabolized in the liver, largely by CYP 3A4 and it is susceptible to drug-drug interactions with agents that induce or inhibition CYP 3A activity. Most opioid-antagonists appear to have little intrinsic hepatotoxicity.

Drug Class: [Gastrointestinal Agents, Cathartics and Laxatives](#); [Opioid Antagonists](#); [Substance Abuse Treatment Agents](#)

Other Drugs in the Class: [Nalmefene](#), [Naloxone](#), [Naltrexone](#)

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Naloxegol – Movantik®

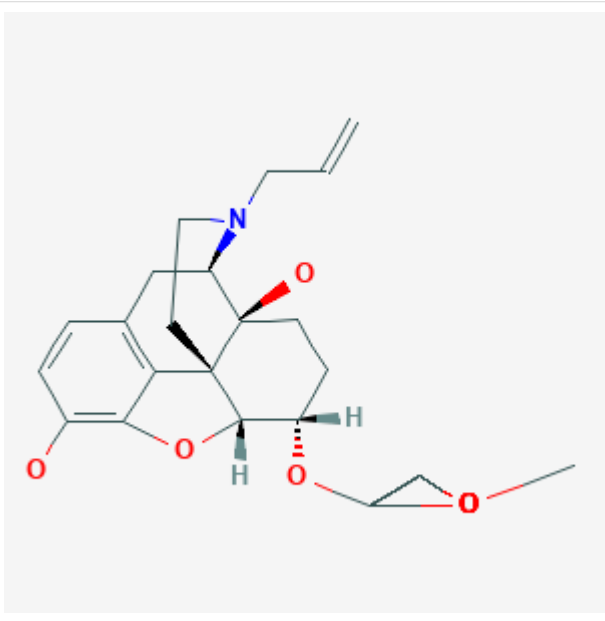
DRUG CLASS

Opioid Antagonists

COMPLETE LABELING

Product labeling at [DailyMed](#), National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Naloxegol	854601-70-0	C ₃₄ -H ₅₃ -N-O ₁₁	

ANNOTATED BIBLIOGRAPHY

References updated: 20 March 2020

Zimmerman HJ. Narcotic analgesics. In, Zimmerman HJ. *Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver*. 2nd ed. Philadelphia: Lippincott, 1999, pp. 710-11.

- (Expert review of hepatotoxicity published in 1999; mentions that trials of naltrexone have reported serum aminotransferase elevations in up to 30% of recipients, an effect that appeared to be partially dose dependent; naloxegol not discussed).
- Larrey D, Ripault MP. Illegal and recreational compounds. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. *Drug-induced liver disease*. 3rd ed. Amsterdam: Elsevier, 2013, pp. 456-7.
- (Review of hepatotoxicity discusses buprenorphine, an orally available morphine analogue, which has been linked to cases of severe acute liver injury, usually as a result of intravenous administration; naloxegol not discussed).
- Yaksh TL, Wallace MS. Opioids, analgesia, and pain management. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. *Goodman & Gilman's the pharmacological basis of therapeutics*. 13th ed. New York: McGraw-Hill, 2018, pp. 355-86.
- (Textbook of pharmacology and therapeutics).
- Webster L, Dhar S, Eldon M, Masuoka L, Lappalainen J, Sostek M. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation. *Pain*. 2013;154:1542–50. PubMed PMID: 23726675.
- (Among 207 patients with opioid-use related constipation treated with naloxegol [5, 25 or 50 mg once daily] or placebo for 4 weeks, spontaneous bowel movements increased with higher doses of naloxegol, while side effects included abdominal pain, diarrhea and nausea, but there were “no clinically relevant changes in serum chemistry”).
- Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology*. 2013;144:1419–25. PubMed PMID: 23419359.
- (In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, none of which were attributed to naloxegol or other opioid antagonist).
- Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med*. 2014;370:2387–96. PubMed PMID: 24896818.
- (Among 1362 patients with opioid induced constipation treated in two controlled trials with naloxegol [12.5 or 25 mg daily] or placebo, spontaneous bowel movements were more frequent with naloxegol, particularly with a 25 mg dose, and adverse events were largely mild gastrointestinal intolerance without change in pain scores or opioid dose; no mention of ALT elevations or hepatotoxicity, but there were no liver related serious adverse events).
- Webster L, Chey WD, Tack J, Lappalainen J, Diva U, Sostek M. Randomised clinical trial: the long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation. *Aliment Pharmacol Ther*. 2014;40:771–9. PubMed PMID: 25112584.
- (Among 804 patients with opioid induced constipation treated with naloxegol [25 mg daily] or placebo for 52 weeks, adverse events that were more frequent with naloxegol included abdominal pain [18% vs 3%], diarrhea [13% vs 6%], nausea [9% vs 4%], headache [9% vs 5%], and flatulence [7% vs 1%]; no mention of ALT elevations or hepatotoxicity).
- Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A, Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. *Ann Hepatol*. 2014;13:231–9. PubMed PMID: 24552865.

- (Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, none were attributed to naloxegol or other opioid antagonist).
- Chalasan N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. *Gastroenterology*. 2015;148:1340–52.e7. PubMed PMID: 25754159.
- (Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to naloxegol or other opioid antagonist).
- Leonard J, Baker DE. Naloxegol: treatment for opioid-induced constipation in chronic non-cancer pain. *Ann Pharmacother*. 2015;49:360–5. PubMed PMID: 25471070.
- (Review of the pharmacology, clinically efficacy and safety of naloxegol; discusses common mild gastrointestinal side events and lack of evidence for increase in cardiovascular complications or withdrawal symptoms with naloxegol; no mention of ALT elevations or hepatotoxicity).
- Naloxegol (Movantik) for opioid-induced constipation. *Med Lett Drugs Ther*. 2015;57(1478):135–7. PubMed PMID: 26393826.
- (Concise review of the mechanism of action, efficacy and safety of naloxegol shortly after its approval for use in the US; mentions dose related gastrointestinal side effects, but not ALT elevations or hepatotoxicity).
- Eldon MA, Kugler AR, Medve RA, Bui K, Butler K, Sostek M. Safety, tolerability, and pharmacokinetics of multiple ascending doses of naloxegol. *Clin Pharmacol Drug Dev*. 2015;4:442–8. PubMed PMID: 27137716.
- (Among 32 healthy volunteers given increasing doses of naloxegol or placebo for 7 days, minor gastrointestinal side effects occurred with the highest doses, but there were no serious adverse events or discontinuations because of side effects; no mention of ALT levels or hepatotoxicity).
- Leppert W, Woron J. The role of naloxegol in the management of opioid-induced bowel dysfunction. *Therap Adv Gastroenterol*. 2016;9:736–46. PubMed PMID: 27582887.
- (Review of the mechanism of action, clinical efficacy and safety of naloxegol as therapy of opioid induced constipation does not mention or discuss ALT elevations or hepatotoxicity).
- Webster L, Tummala R, Diva U, Lappalainen J. A 12-week extension study to assess the safety and tolerability of naloxegol in patients with noncancer pain and opioid-induced constipation. *J Opioid Manag*. 2016;12:405–19. PubMed PMID: 28059433.
- (Among 302 patients participating in an extension study of naloxegol for opioid induced constipation, adverse events were more common with the higher dose (25 mg daily: 41%) vs lower dose (12.5 mg daily: 34%) vs placebo (31%), but serious adverse events were similar (5% vs 6%) and there was no mention of ALT elevations or hepatotoxicity).
- Nalamachu S, Gudin J, Datto C, Coyne K, Poon JL, Hu Y. Efficacy and safety of naloxegol for opioid-induced constipation assessed by specific opioid medication, opioid dose, and duration of opioid use. *J Opioid Manag*. 2018;14:211–21. PubMed PMID: 30044486.
- (Among 1337 adults with opioid induced constipation treated with naloxegol (12.5 or 25 mg) or placebo once daily for 12 weeks, adverse event rates were similar (52% and 64% vs 51%); no mention of ALT elevations or hepatotoxicity).
- Opioids for pain. *Med Lett Drugs Ther*. 2018;60(1544):57–64. PubMed PMID: 29664446.
- (Concise review of the efficacy, safety and costs of opioids used for pain mentions that the 3 opioid antagonists that are used to treat opioid induced constipation-methylnaltrexone, naloxegol and nalmedine-have similar degrees of efficacy and toxicities).