A.26	Naltrexone – alcohol use disorder – EML
Draft recommendation	☒ Recommended with square box symbol as representative of pharmacologic class ☐ Not recommended **Justification**: Alcohol use disorder (AUD) is a highly prevalent, chronic, relapsing condition characterized by an impaired ability to stop or control alcohol use despite clinically significant impairment, distress, or other adverse consequences. It is a preventable and treatable chronic condition. Naltrexone was first approved in 1994 and has been shown to decrease relapse to heavy drinking and total alcohol consumption. It is a first-line therapy for many patients. In 2010, it received the additional indication for treatment of opioid use disorder. Based on all available data in the public domain, in treatment for AUD, naltrexone has been found to be slightly more efficacious in promoting abstinence. Although combining psychosocial and pharmacological treatments for AUD could be more efficacious than either treatment alone.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable **Comments**: Alcohol is a psychoactive substance that poses health risks, and the extent and effects of these risks vary widely among consumers. Repeated drinking can lead to alcohol dependence, which is manifested by poorly controlled drinking. The concept of "harmful" use of alcohol, introduced in 2010, represents the consumption of alcohol that leads to harmful health and social consequences for the drinker and those around him. Alcohol use represents a significant social and public health burden worldwide. Five percent of the world's adult population suffers from alcohol use disorders, and alcohol dependence affects 2.6 percent of adults worldwide, or 144 million people. Mortality attributable to alcohol use is higher than that attributable to diseases such as tuberculosis, HIV/AIDS and diabetes. In 2016, alcohol use led to approximately 3 million deaths worldwide (5.3% of all deaths), of which 2.7 million were among men. Young people are disproportionately affected by alcohol use; among 20-39 year olds, 13.5% of all deaths were attributed to alcohol. Alcohol is estimated to reduce life expectancy by 0.9 years over the next 30 years. Alcohol dependence is among the main leading health risk factors in most developed and developing countries. There is a WHO global alcohol action plan 2022-2030 to reduce the harmful use of alcohol. Therapeutic success of psychosocial programs for relapse prevention is moderate, but could potentially be increased by adjuvant treatment. Pharmacologically controlled drinking in the treatment of patients suffering from alcohol dependence or AUD is an emerging concept.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable **Comments**: Endogenous opioids are released following alcohol consumption, contributing to positive reinforcement effects that may promote continued drinking in the alcohol-dependent individual. Naltrexone works as a nonselective antagonist. It reduces the rewarding effects of alcohol and results in reduction in alcohol consumption. A Cochrane review, which used 50 randomized controlled trials showed the number needed to treat (NNT) to reduce heavy drinking to be 12 and decreased the daily drinking NNT of 25. Another systematic review showed abstinence with an NNT of 20 and a decreased the heavy drinking NNT of 12. Additional recent trials demonstrate that naltrexone reduces the rewarding effects of alcohol, alcohol craving, drinks per drinking day, and relapse rates, strengthening the initial findings. Naltrexone is initiated after resolution of any alcohol withdrawal symptoms (usually 3–7 days after the last drink) and maintenance dose of oral naltrexone is one daily intake of 50 mg during 6 to 12 months. Extended-release injectable naltrexone, administered once monthly, may be beneficial for individuals who have difficulty adhering to oral medication. A six-month multisite trial of injectable naltrexone in found significant reductions in heavy-drinking days versus placebo. Several national guidelines include naltrexone (alongside acamprosate) as a recommended first-line medicine in the treatment for alcohol use disorder.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments:
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable **Comments**: Adverse effects of naltrexone can be sedation, dizziness, nausea, vomiting, abdominal pain, insomnia, anxiety, reduced energy, joint and muscle pain. Due to its hepatotoxicity, liver function tests should be performed prior to initiation. Although no standard monitoring frequency is defined, baseline, 1 and 3-month and annual LFTs should be checked Naltrexone is contraindicated in patients with acute hepatitis or liver failure.

Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable **Comments**: Naltrexone, by blocking the analgesic effect of opioids, can precipitate withdrawal from opioids in those who are opioid dependent. Providers could consider challenging patients with a small dose of naloxone before initiating naltrexone in anyone suspected of using opioid analgesics to avoid precipitated withdrawal. Although this may not be necessary in the setting of adequate patient education.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☐ No ☐ Not applicable **Comments**: Among patients with compensated cirrhosis, pharmacological treatments and counseling are extremely cost-effective, and in some cases cost saving, interventions to prevent decompensation and improve health. Naltrexone were found to be cost-saving from both healthcare and societal perspectives in many analysis.
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☐ No ☐ Not applicable Comments:
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☐ No ☐ Not applicable **Comments:** The 2016 WHO mhGAP Intervention Guide for Mental, Neurological and Substance Use Disorders in Non-Specialized Health Settings recommends considering pharmacologic intervention to prevent relapse in alcohol dependence, including acamprosate, naltrexone and disulfiram.