A.26	Naltrexone – alcohol use disorder – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: This application refers to the inclusion of naltrexone (a) oral formulation and (b) extended-release injection to the core list of the WHO Model List of Essential Medicines (EML), section 24.5 “Medicines for mental and behavioural disorders >> Medicines for disorders due to psychoactive substance use”, with the indication of maintenance treatment of adults with alcohol use disorder. The treatment of alcohol dependence and harmful use of alcohol is a medical, social and economic priority. There is a need to identify and tackle the variety of factors which increase alcohol consumption and influence its effects, as well as develop and implement appropriate policies to decrease the harmful use of alcohol. The availability of medications for the treatment of alcohol use disorder should be seen as part of this complex scenario of intervention. At the moment, the WHO Model list of Essential Medicines does not include treatment of alcohol use disorder. The 2016 WHO mhGAP Intervention Guide for Mental, Neurological and Substance Use Disorders recommended naltrexone, acamprosate, and disulfiram to prevent relapse in alcohol dependence. However, globally, one in six people with alcohol use disorder receive treatment and rates are even lower in low and lower-middle-income countries. Alcohol dependence is a chronic disease, which can develop when alcohol is heavily used over longer periods of time. Alcohol affects various brain regions, including the opioid receptor system, which mediates euphoric and pleasurable effects of alcohol. By blocking alcohol effects at these receptors, the opioid antagonist naltrexone can reduce alcohol "liking" and "craving" and thus support alcohol dependent patients in cutting down their drinking. A large body of evidence confirmed that naltrexone improves alcohol consumption outcomes in patients with alcohol use disorders. However, the magnitude of treatment effects appears moderate. Naltrexone can be expected to prevent heavy drinking in one out of nine patients, but low levels of medication compliance may reduce the treatment effects. Few data on health outcome, such as accidents, injuries, QoL, function, or mortality are available. Injectable extended-release formulations are more costly than oral naltrexone. However, their monthly administration has the potential to increase treatment adherence. This Reviewer is in favour of including naltrexone on the WHO Model Lists of Essential Medicines for the treatment of alcohol use disorders. This decision should be considered in the light of the Application for the inclusion of acamprosate for the same condition (please refer to Application A1).

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: The most recent global data shows that harmful use of alcohol resulted in 3 million deaths worldwide and this disease burden was higher in low and middle-income countries (LMICs). The spectrum of alcohol misuse ranges from a risky or hazardous use to alcohol use disorder (abuse and dependence), defined according to the DSM-5. Alcohol use disorders are among the top five leading causes of disability-adjusted life years in the 15–44 years age range. Moreover, according to the World Health Organisation, the misuse of alcohol belongs to the globally leading health risk factors, causing 20–30% of oesophageal cancer, liver disease, epilepsy, motor vehicle accidents, homicide, and other intentional injuries. Alcohol consumption is a major potentially avoidable risk factors, thus calling for effective strategies to reduce excessive drinking and maintain abstinence in people who are dependent on alcohol. The coverage for alcohol use disorders is very low or absent in low- or lower middle-income countries (LMICs). Increasing treatment rates is an effective way of reducing this global alcohol-related disease burden. (Mekonen et al., Addiction 2020;116, 2617–2634)

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: Several systematic reviews confirmed that oral naltrexone (and acamprosate) have the best evidence for improving alcohol consumption outcomes for patients with alcohol-use disorders. However, the sizes of treatment effects might appear moderate in their magnitudes. According to a review by the Agency for Healthcare Research and Quality published in 2014, when compared to placebo naltrexone 50 mg oral improved several consumption outcomes, such as return to any drinking (16 studies; 2,347 participants, RD: -0.05, 95% CI -0.10 to -0.00, NNT=20, moderate strength of evidence); return to heavy drinking (19 studies; 2,875 participants, RD: -0.09 (95% CI -0.13 to -0.04, NNT=12, moderate strength of evidence); % drinking day (15 studies; 1,992 participants, Weight Mean Diff: -5.4 (95% CI -7.5 to -3.2, moderate strength of evidence). The review found insufficient direct evidence to conclude on the effects of health outcomes, such as accidents, injuries, QoL, function, or mortality. Only four head-to-head RCTs compared acamprosate with naltrexone and found no statistically significant difference between the two medications for return to any drinking. (Jonas et al., AHRQ Publication No. 14-EHC029-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2014). Similar results were reported by a Cochrane review published in 2010, showing that naltrexone reduced the risk of heavy drinking compared to placebo (RR: 0.83, 95% CI 0.76 to 0.90, 28 studies, 4460 participants) and decreased drinking days by about 4%, MD -3.89 (95% CI -5.75 to -2.04, 26 studies, 3882 participants). Return to any drinking was not statistically significant. Injectable extended-release formulation of naltrexone was assessed in only four out of the 47 RCTs included in the review. It reduced the risk of any drinking (RR = 0.92, 95% CI 0.84 to 1.00) and the % of drinking days (MD - 8.54, 95% CI -15.77 to -1.31) (Rösner et al., Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD001867). The benefit of extended-release injection formulation in terms of treatment adherence has not been fully quantified.
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: Side effects of naltrexone are mainly gastrointestinal, such as nausea, and sedative effects. Extended-release naltrexone appears to cause more frequent episodes of daytime sleepiness, decreased appetite, dizziness, and fatigue. (Rösner et al., Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD001867). Suicide, suicide attempts and ideation were reported in post-marketing surveillance programs.

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Naltrexone should not be used if a patient is currently using opioids to avoid precipitating withdrawal. Naltrexone should be discontinued if there are anticipated opioid requirements within seven days. Oral naltrexone is contraindicated in people with acute hepatitis or liver failure and should be used with precautions in people with hepatic disease.
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: Due to hepatotoxicity and potential increases in levels of liver enzymes, liver function tests should be performed prior to initiation and at intervals of 1, 3, and 6 months, then yearly thereafter (and more frequently if baseline liver function tests are high). Monitoring of liver function may be challenging in low- and middle-income countries. Injectable naltrexone should be administered only by a medical professional and refrigerated during storage.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Robust data on cost effectiveness of alcohol disorders treatments are lacking. Considering the health and social implications of this condition it is likely that small effects on consumption outcomes may be translated in economic benefits, although the clear estimations are not available. Overall, analyses conducted in high income countries suggested that oral naltrexone + counselling may be cost effective compared with counselling alone in people with severe alcohol dependence (Mortimer et al., Alcohol&Alcoholism 2005; 40,549-555) but may be less cost effective than acamprosate (Slattery et al., Health Technology Assessment Board for Scotland 2003). The economic analysis done by the NICE showed that acamprosate is potentially the most cost-effective pharmacological intervention when used with psychological support (National Collaborating Centre for Mental Health (Great Britain). Alcohol Use Disorders: The NICE Guideline on the Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence. RCPsych Publications; 2011). All these models are limited by the short time horizon. Extended-release (XR) injection is more costly than oral formulation. The Application reported that the rate of adoption of injectable naltrexone in US is still limited, and higher prices are likely to be one of the barriers.

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: Naltrexone oral formulation is approved in several countries and is available also as generics. Injectable extended-release naltrexone is still under patent (expiration in 2029 in the United States, 2025 in other countries).
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: Naltrexone is recommended for use as pharmacologic intervention to prevent relapse in alcohol dependence in the mhGAP Intervention Guide Mental Health Gap Action Programme for mental, neurological and substance use disorders in non-specialized health settings (https://www.who.int/publications/i/item/9789241549790).