I.13 (item number)	N-acetylcysteine - non-acetaminophen-induced acute liver failure (application title)
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Acute Liver Failure (ALF) has high morbidity and mortality, occurs globally, affects all age groups and has various causes (aside from acetaminophen toxicity) including virus which affects numerous countries especially those with limited resources. In some cases, liver transplant is needed.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	The application is for repurposing NAC which already included in the EML for additional indication. In the EML, NAC is indicated for "Exposure to or harmful effects of undetermined intent of analgesics, antipyretics or non-steriodal anti-inflammatory drugs"
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included:
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☐ Yes ☒ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). The review of evidence included 3 systematic reviews, the latest being 2015. Most of the evidence are from lesser quality of evidence (observational studies, case report/series) and only a few clinical trials. Although majority of studies show benefits (improved survival, lower transplant rate, shorter hospital stay, reduce ICU admission, improved liver function) yet the level of certainty is also low due to weak study design.

	Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? An RCT conducted among pediatric subjects failed to show benefit of NAC. There is no specific mention on studies involving elderly subjects Many studies conducted in LMIC especially for ALF caused by dengue, although all show benefit, yet the designs are weak.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The safety is similar as what is observed in current use of NAC
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: The adverse events are similar as what is reported in current use of NAC
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	The overall benefit to risk is still uncertain. Although the risk is similar with current use of NAC yet the benefit seems likely, yet it is not supported by high quality of evidence.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The overall quality of the evidence are low.

Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments: It has been used widely for its present indication.
Are you aware of 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: It is already included in the EML and has been used widely for its present indication.
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: No WHO guideline on the management of ALF. In a 2016 guideline by the European Association for the Study of the Liver (EASL) which recommend the use of NAC for Drug-induced liver injury, it is stated that “In non-paracetamol ALF NAC did not improve survival overall, but did improve outcome in adults with mild grades of Hepatic Encephalopathy”. In a 2017 guideline by the American Gastroenterological Association Institute, it is stated that “In patients presenting with non–acetaminophen-associated ALF, the AGA recommends that NAC only be used in the context of clinical trials”.
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	NAC is widely used globally and very affordable.

Any additional comments	
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	The evidence on the benefit is still not supported by high quality evidence, although the safety has been ascertained for the existing indication. Furthermore, the most current guidelines are still not recommending the use of NAC for the proposed indication. Therefore, additional indication for the current use of NAC in the EML is not recommended.
References (if required)	European Association for the Study of the Liver. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. Journal of Hepatology 2017 vol. 66:1047–1081. The AGA Institute. American Gastroenterological Association Institute Guidelines for the Diagnosis and Management of Acute Liver Failure. Gastroenterology 2017;152:644–647