I.13	N-acetylcysteine – acute liver failure
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Acute liver failure is noted to be a relatively rare, but associated with a poor prognosis, particularly where transplantation is unavailable. It is caused by a range of aetiologies and a reasonable estimate of the burden of disease from each is presented in the application.
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 seeks to expand the indication for NAC treatment beyond paracetamol overdose to a range of other causes of acute liver failure. In particular, the drug is proposed to have a role where acute liver failure is mediated by glutathione deficiency including dengue infection , mushroom toxicity, alcoholic hepatitis, heat stroke and viral hepatitis.
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: An additional study of relevance in DILI (Moosa et al CID 2020) was identified
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 report notes that the inclusion of NAC in EML listing is not founded on strong RCT data. The evidence for each proposed aetiology group is provided Indirect evidence based on the disease association with the R418Q SNP in GSS gene are presented to support association with glutathione pathway. Not clear how the phenotypes studied map to the indications for treatment. A detailed review of evidence for efficacy across a range of indications is provided, the evidence for which varies between indications.

Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Reference is made to a substantive body of observational data based on the experience of using NAC over 40 years highlighting adverse events of oral and IV therapies. Particular emphasis is given to nausea and anaphylactoid reactions
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: In general NAC needs to be given under close medical supervision, but its indication is for acute liver failure which will generally require management in a tertiary hospital setting
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	It seems likely that there is little harm from treatment from NAC, but also that the evidence of efficacy across the range of indications proposed is limited. Overall the overall risk/benefit is uncertain
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The evidence is mixed. Most evidence presented is from case reports and case series. Meta-analyses are reported, including two RCTs. Ref 45 describes a "randomised case control trial" but the methods are not reported clearly and a high proportion of patients did not have a defined aetiology. Ref 71-3 describes a double blind RCT where there was no significant difference on primary outcome, but there was a positive effect in a subgroup of mild liver failure.
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:
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: The application states that the treatment is not approved by any regulatory authority for indications other than paracetamol overdose.

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: There a not relevant WHO guidelines for liver failure where it can be included. AASLD guidelines recommend NAC for paracetamol induced (or suspected) liver failure and suggest is may be used (based on lower quality evidence for drug induced liver injury and mushroom poisoning.
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Limited data is provided on this issue, but in general where the drug is accessible, it is off patent and within affordable limits
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.	Based on the information provided there is insufficiently strong evidence to add new indications to NAC within the EML which would go beyond existing regulatory approvals and practice guidelines. The substantial review of literature is appreciated, but higher quality studies would be beneficial in the high burden conditions to support recommendations.
References (if required)	Introduction to the Revised American Association for the Study of Liver Diseases Position Paper on Acute Liver Failure 2011. AASLD Lee et al EASL Clinical Practice Guidelines on the management of acute liver failure 2017 A randomised controlled trial of IV NAC in the management of anti-tuberculous DILI Moosa et al CID 2020