A.17	Glecaprevir + pibrentasvir – hepatitis C virus infection
Does the application adequately address the issue of the public health need for the medicine?	X Yes ☐ No ☐ Not applicable Comments: The case for treatment of HCV in children is clear and this is reflected in the development of paediatric formulations. The public health case outline in the application makes a strong case for the burden of end stage disease. Reference is made to an estimated 3.26 million children living with chronic HCV infection, and 20 countries account for 80% of all cases in patients 0-18 years of age. The countries with the highest number of children with chronic HCV include Pakistan, China, India, Nigeria, and Egypt.
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 describes well the therapeutic benefits of G/P for children - It is pangenotypic (and thus genotyping is not essential for its use) - It is usually given for 8 weeks, in comparison to most other therapies approved for 12 weeks - It has a good safety and drug interaction profile
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: The application summarises key studies. Summary data of a large meta-analysis of data from children and adolescents is presented. Among 39 included studies (1796 subjects), the pooled proportion among those receiving all doses of treatment and reaching sustained virologic response at post-treatment week 12 was 100% (95% confidence interval:100-100). Considering subjects receiving at least one dose of treatment, lowest estimates were reported among children with cirrhosis (83%).
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). Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? The data is presented on a modest number of patients included as part of the industry sponsored DORA study (pp6-7). High efficacy was seen in the age groups studied and bridging PK data is presented (now published, see references) for approval.

Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Comment is made in relation to the meta-analysis. Headache and fatigue were the most common adverse events. Serious adverse events were uncommon.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	The evidence provided from children and adolescents supports a favourable profile for gle/pib in this group
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Evidence is limited in children to relatively small cohort studies, the evidence in children is therefore low-moderate. Effectiveness data is extrapolated from outcomes in adults with bridging PK data and small treatment studies.
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: In general, it is possible to use the medication without viral genotyping, which would add cost and complexity to management. However, there may be individual circumstances where genotyping remains an important part of decision on duration of therapy
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: In May 2021 EMA issued an extended indication for the treatment of chronic hepatitis C virus (HCV) infection in adults and children aged 3 and older

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: Medicine is recommended treatment option for WHO adult guidelines. It is under discussion for proposed revision to adolescent and paediatric guidelines, so not yet included. Will be important to explore whether this will happen with technical department, though seems likely particularly in light of EMA recommendation.
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Of the available pangenotypic medications, GP is one of the last to be given access to voluntary licensing systems (via MPP) . Therefore its use globally has to date been limited in comparison to other pan genotypic options but where available generically, its price is similar to alternative pan genotypic options.
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.	Glecaprevir/pibrentasvir should be listed as a fixed dose combination (FDC) formulation, on the core list of the Model List of Essential Medicines for Children (EMLc) aged 3 and over. Dosing should be in line with the weight based considerations outlined If further real-world data on the use of GP in children is available, it would be helpful to include in the review.
References (if required)	Jonas et al Hepatology 2021 Apr 2. doi: 10.1002/hep.31841