A.31	Sofosbuvir/Velpatasvir – hepatitis C (children)
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: A modelling exercise estimated 3.26 million children are living with chronic HCV infection, and 20 countries account for 80% of all cases in patients 0-18 years of age. The highest number of children with chronic HCV infection is reported in LMICs including Pakistan, China, India, Nigeria, and Egypt. including children and adolescents in national HCV treatment program can help achieve the global goal of HCV elimination.
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.	Relative to previous interferon-based therapy (inclusion in the complementary list of the WHO EML) which was long and difficult to tolerate, had a low success rate, and required extensive clinical and laboratory monitoring during treatment, **Sofosbuvir/Velpatasvir (SOF/VEL)** has the major advantages of DAAs in adults and pediatric patients, including: (1) a pan-genotypic fixed dose combination; (2) a high SVR rate >90% with treatment courses of 12 weeks observed in in children 3 years of age or older; (3) greatly improved safety profile; (4) no requirement of special laboratory monitoring prior to and during treatment; (5) a relatively low or manageable risk of drug-drug interactions; (6) inclusion as one of the three DAA regimens for adults in the 2018 WHO Guidelines for chronic HCV infection and in the core list of 2017 WHO EML, and expected to be added as a treatment for adolescents and children in the 2021 update WHO Guidelines. In the clinical studies to date, SOF/VEL has not been compared to other DAA regimens regardless of the population being studied. There are no comparative pediatric trials available.
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). 1. A pediatric trial of Epclusa® (sofosbuvir and velpatasvir) in patients < 18 years of age with chronic HCV infection at sites in the U.S., U.K., Italy, and Belgium launched by Gilead Sciences showed an overall 93.7% of SVR in children 3-17 years (12-17 years: n=102, 6-11 years: n-=3, 3-5 years: n=41). Only 2 experienced virologic failure; other failure was due to participants being lost to follow-up (n=8) or spitting up or being unable to swallow the study drug tablets (n=2). In the third cohort 3-5 years of age (n=41) in the trial who received SOF/VEL 150mg/37.5mg if at least 17kg or SOF/VEL granule formulation if < 17kg, no virologic failures were documented, and the 7 treatment failures were associated with either early treatment discontinuation or lost to follow-up. Regulatory review has approved SOF/VEL use in children 6 years of age and older or weighing at least 17kg. Regulatory submission of young children 3-5 years of age is described as pending. 2. In an additional observational study evaluating SOF/VEL in five complex pediatric patients undergoing allogeneic hematopoietic cell transplant was recently published, no major drug interactions were observed with either cyclosporine or sirolimus, and five patients achieved virologic response and normalization of liver enzymes without significant adverse events during treatment. Four of the five patients remained disease free and with SVR after a median of 15 months of follow-up. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? 1. Gilead Sciences conducted pediatric trial of Epclusa® (sofosbuvir and velpatasvir) in patients 3-17 years of age with chronic HCV infection at sites in the U.S., U.K., Italy, and Belgium launched by Gilead Sciences. 2. No clinical trials and studies have conducted in LMICs. **3.** So far, evidence of effectiveness of SOF/VEL is just based on information from HICs.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: 1. SOF/VEL is well-tolerated and serious adverse events are uncommon. 2. Among the 175 pediatric patients 6-17 years of age receiving a 12-week course of SOF/VEL treatment, the most common adverse events included headache (23%), fatigue (18%), nausea (13%), vomiting (12%), and cough (11%). Four patients had serious adverse events reported during the trial: auditory hallucinations, constipation (both in the younger cohort) and two adolescents with suicidal ideation and suicide attempts. However, additional assessment of the psychiatric events revealed that 27% of the study participants had some relevant psychiatric medical history. 3. The most common adverse events observed among the 41 patients 3-5 years of age included vomiting (27%), cough (15%), pyrexia (15%), rhinorrhea (15%), fatigue (12%), nasal congestion (12%), and diarrhea (12%). One patient in this age

	group discontinued treatment due to an adverse event but there were no serious adverse events. 4. No negative effects on weight gain, height, BMI, radiographic bone age, or sexual maturation from treatment initiation to 24 weeks post-treatment completion.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: Overall, SOF/VEL has favorable safety/tolerability profile in paediatric patients. Serious adverse events were uncommon among paediatric patients 3-17 years of age in clinical trial. Regarding uncommon adverse effects such as auditory hallucinations and constipation in two children 6-11 years of age and suicidal ideation and suicide attempts in two adolescents, further monitoring and assessment are required.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	1. SOF/VEL provides effective treatment for all common genotypes of HCV, with 93.7% of SVR in paediatric patients 3-17 years. 2. Treatment with SOF/DAC is well-tolerated and serious adverse effects are uncommon. No special laboratory monitoring is required prior to or during SOF/VEL treatment. 3. SOF/VEL has a relatively low or manageable risk of drug-drug interactions and can be used in patients receiving antiretroviral therapy for HIV infection with some dose modification. 4. SOF/VEL is expected to be added as a treatment for children and adolescents in the updated 2018 WHO Guidelines and the regimen will be recommended as a first line therapy for pediatric patients for whom dosing recommendations and an appropriate formulation are available. Overall, the overall benefit to risk ratio of GLE/PIB is greatly favourable.
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 for SOF/VEL as a pangenotypic treatment option in children with chronic HCV infection is moderate-high. To date, the number of pediatric patients with chronic HCV infection receiving SOF/DAC treatment is relatively small (175) in pediatric clinical trial conducted in HICs. The evidence is lacking in LIMCs with a high burden of HCV infection. Thus, accumulating data are needed in real-world study to further assess its efficacy and potential uncommon serious adverse effects in various settings and large number of paediatric patients.
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: No special laboratory tests are required to monitor the potential adverse effects of SOF/VEL. Given that uncommon adverse effects such as auditory hallucinations and constipation were observed in two children 6-11 years of age and suicidal ideation and suicide attempts were observed in two adolescents, which were most likely associated with the underlying psychiatric medical conditions, health providers should be informed about these uncommon adverse effects and are trained on how to assess and explain these effects.

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 some countries, the registration of the new medicine requires the report of local clinical trial.
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: SOF/VEL is one of the three recommended pan-genotypic DAA regimens for adults with chronic HCV infection. SOF/DAC is expected to be added as a treatment for children and adolescents in the updated 2021 WHO Guidelines if pediatric dosing recommendations and an appropriate formulation are available.
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	1. At present, there is a single generic formulation of SOF/VEL 400mg/100mg which is now widely available. 2. Gilead offers "access pricing" for their branded Epclusa® to government programs in 101 selected LMIC at a flat price of $300/28-tablet bottle, or $900 for a full treatment course, which will be affordable in LMIC settings with a high burden of HCV infection.
Any additional comments	SOF/VEL should be listed in the international pharmacopoeia standards as soon as possible because it has been already included as one of the three recommended pan-genotypic regimens for chronic HCV infection in the WHO guideline to accelerate national registration and approval for local use.
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.	1. SOF/VEL is one of the three recommended pan-genotypic DAA regimens for adults with chronic HCV infection. 2. SOF/VEL is expected to be added as a treatment for children and adolescents in the updated 2018 WHO Guidelines if pediatric dosing recommendations and an appropriate formulation are available in 2021. 3. Pediatric registrational trial of SOF/VEL conducted in patients 3-17 years of age has shown a high rate of SVR and good tolerablilty/safety profiles. 4. SOF/VEL has a relatively low or manageable risk of drug-drug interactions and can be used in patients receiving antiretroviral therapy for HIV infection with some dose modification. 5. Accessibility and affordability of SOF/VEL will be guaranteed in LMIC settings because a single generic formulation of SOF/VEL 400mg/100mg is now widely available and Gilead offers "access pricing" for their branded Epclusa® to government programs in 101 selected LMICs with a high burden of HCV infection. Conclusion: Effective treatment of chronic HCV infection in pediatric patients and including children and adolescents in national HCV treatment program will help achieve the global goal of HCV elimination by 2030. SOF/VEL has become one regimen of three DAA regimens in the WHO guideline for treatment of chronic HCV and listed

	in the core list of WHO EML because of its favorable safety/tolerability profile and high success in achieving SVR. Additionally, wide availability of a generic product will improve its accessibility and affordability in LMICs with a high burden of HCV infection. Thus, I recommend to include SOF/VEL, as a fixed dose combination (FDC) product for treatment of chronic hepatitis C infection in pediatric patients 3-17 years of age in the core list of the Model List of Essential Medicines for Children (EMLc).
References (if required)	