A.30	Sofosbuvir/Daclatasvir – 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, SOF/VEL has the major advantages of DAAs in adults and pediatric patients, including: 1. Multiple small observational studies in patients younger than 18 years of age evaluating SOF plus DAC have been reported. SVR was achieved in 97.7% of the non-cirrhotic group and 100% in the cirrhotic group. 2. SVR ranged from 96.7% to 100% in the 11 abstracts and publications reporting SOF plus DAC that were included in the systematic review of DAA use in children. However, interferon-based therapy was long and difficult to tolerate, had a low success rate, and required extensive clinical and laboratory monitoring during treatment. 3. The use of currently available low-cost DCV formulations together with approved doses of pediatric SOF formulations would expand considerably access to HCV treatment in children. 4. SOF/DAC is currently the preferred regimen for treatment of adults with chronic HCV infection in LMIC because of its effectiveness against all common genotypes with near 100% success in achieving SVR and the increasing availability of low-cost generic products with WHO-prequalified products available from multiple suppliers at the lowest prices of any DAA regimens.
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. SOF/DAC has become the preferred regimen for treatment of adults with chronic HCV infection in LMIC because of its effectiveness against all common genotypes with near 100% success in achieving SVR. 2. The systematic review of DAA showed 96.7% to 100% of SVR in the small studies reporting SOF plus DAC treatment in children (206 receiving SOF plus DAC, plus ribavirin in a small number). 3. The effectiveness of SOF/DAC in children can be extrapolated from larger adult efficacy trials using pharmacokinetic bridging, small confirmatory trials, and modeling and simulation exercises. Small pediatric trials have included patients down to 17kg and modeling and simulation supports use down to 14kg. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? 1. There are sufficient evidences show the excellent efficacy of SOF/DAC for treatment of chronic HCV infection in adults with near 100% success in achieving SVR to all common genotypes. 2. Many of the small studies have been conducted in LMIC with high burden of HCV infection showed excellent results of DAA treatment regimens including SOF/DAC in children and adolescents.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: 1. SOF/DAC is well-tolerated and serious adverse events are uncommon. 2. Discontinuation of treatment prior to completion of the 12-week course was not described in the pediatric cohorts reviewed. 3. According to the systematic review, the most commonly reported adverse events occurring in more than 5% of pediatric patients receiving any DAA included headache (19.9%), fatigue (13.9%), nausea (8.1%), and abdominal pain (7.0%). 4. No negative effects of SOF plus DAC treatment on weight and linear growth was observed in their expanded cohort of adolescents.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: SOF/DAC has favourable safety/tolerability profile in adult and pediatric patients. No serious adverse events were observed among paediatric patients. Thus, no adverse effects are of concern, which may require special monitoring.

Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	1. SOF/DAC provides effective treatment for all common genotypes of HCV, with 96.7% to 100% of SVR in paediatric patients ≥17kg. 2. Treatment with SOF/DAC is well-tolerated and safe in children and adolescents. No specific safety issues are of concern and no special laboratory monitoring is required prior to initiating or while receiving SOF/DAC therapy. 3. SOF/DAC 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/DAC 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. 5. SOF/DAC is the preferred regimen of choice in LIMCs with the increasing availability of low-cost generic products. Overall, the overall benefit to risk ratio of GLE/PIB is 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/DAC 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 (260) in reported studied. Thus, accumulating data are needed in real-world study to further assess its efficacy and other potential serious adverse effects in various settings and young children.
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/DAC and effectiveness because no specific safety issues associated with SOF/DAC treatment in pediatric patients are of concern and SVR was achieved almost in 96.7% to 100% of pediatric patients receiving SOF/DAC treatment.
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 results of local clinical trial may be needed to get the approval of license and use.

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/DAC is the preferred regimen 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 2018 WHO Guidelines in 2021 and the regimen will be recommended as a first line therapy for pediatric patients for whom 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. Multiple generic suppliers have WHO-prequalified or ERP-reviewed SOF, DAC, and SOF/DAC products will be available in the international setting. Thus, SOF/DAC will be available from multiple suppliers at the lowest prices of any DAA regimens. 2. Alignment of the adult and pediatric regimens for LMIC markets provides significant opportunity to advance the treatment and cure of chronic HCV among children.
Any additional comments	SOF/DAC 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.
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/DAC has become the preferred regimen in LMIC for adults with chronic HCV because of its favorable safety/tolerability profile, high success in achieving SVR, and availability of low-cost generic products. Accumulated data suggest that children responded to treatment as well or better than adults. 2. SOF/DAC is expected to be added as a treatment for children with chronic HCV infection in the updated 2018 WHO Guidelines in 2021. The SOF/DAC regimen will be recommended as a first line therapy for pediatric patients for whom dosing recommendations and an appropriate formulation are available. 3. Small pediatric trials have included patients down to 17kg and modeling and simulation supports use down to 14kg. 4. SOF/DAC 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. Alignment of the adult and pediatric regimens for LMIC markets provides significant opportunity to advance the treatment and cure of chronic HCV among children. **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/DAC has become the preferred regimen in LMIC for treatment of chronic HCV because of its favorable safety/tolerability profile, high success in achieving SVR, and availability of low-cost generic products. I recommend the inclusion of sofosbuvir/daclatasvir, as a fixed dose combination (FDC) product for treatment of chronic hepatitis C infection among pediatric patients (≥14kg) on the core list of the Model List of Essential Medicines for Children (EMLc).**
References (if required)	