

A.17	Glecaprevir/Pibrentasvir – hepatitis C (children)
<p>Does the application adequately address the issue of the public health need for the medicine?</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>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.</p>
<p>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.</p>	<p>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, <b>Glecaprevir/Pibrentasvir (GLE/PIB)</b> has the major advantages of DAAs in adults and pediatric patients, including:</p> <p>So far, no antiviral agents (DAAs) are listed in WHO EMLc for the treatment of HCV hepatitis.</p> <ol style="list-style-type: none"> <li>1. GLE/PIB is the only pangenotypic DAA formulation approved for use over an 8-week treatment duration and currently included in the WHO EML core list for treatment of chronic hepatitis C virus (HCV) in adults and adolescents aged 12-17 years or weighing at least 35 kg.</li> <li>2. GLE/PIB was already included as one of the three recommended pan-genotypic regimens for adults in the 2018 WHO Guidelines for the Care and Treatment of Persons Diagnosed with Chronic HCV Infection.</li> <li>3. High rates of sustained virologic response (SVR) are measured at 12 weeks after the completion of GLE/PIB therapy in children of 3 years of age or older, for whom an appropriate paediatric granules formulation is available and expected to be approved in 2021.</li> <li>4. The combination of GLE/PIB has a relatively low or manageable risk of drug-drug interactions and can be used in children receiving antiretroviral therapy for HIV infection.</li> <li>5. Dose adjustment is not needed for patients with renal impairment or for patients with moderate to severe liver impairment.</li> </ol>
<p>Have all important studies and all relevant evidence been included in the application?</p>	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>If no, please provide brief comments on any relevant studies or evidence that have not been included:</p>

<p>Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>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).</p> <ol style="list-style-type: none"> <li>1. High rate (95%) of sustained viral response (SVR) was achieved in almost all reported studies of GLE/PIB across all ages and genotypes studied.</li> <li>2. GLE/PIB has shown high SVR at 12 weeks seen in children <math>\geq 3</math> to <math>&lt;12</math> years of age with chronic HCV-infection. No virologic failures were seen on the dose ratio of 50 mg/20 mg GLE/PIB.</li> <li>3. GLE/PIB can be offered to patients having failed NS5B inhibitor containing regimens.</li> <li>4. A recently published systematic review included 39 studies (1796 subjects) showed that the pooled proportion was 100% among children and adolescents receiving all doses of treatment with DAAs and reaching sustained virologic response at post-treatment week 12.</li> <li>5. Effectiveness of GLE/PIB in children can be extrapolated from larger adult efficacy trials using pharmacokinetic bridging and small confirmatory trials, as accumulated data from interferon-based treatment trials and other DAA treatment trials suggest that children respond to treatment as well or better than adults.</li> </ol> <p>Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?</p> <p>Yes.</p> <ol style="list-style-type: none"> <li>1. To date, Abbvie's registrational study has enrolled children with chronic HCV infection at sites in Belgium, Canada, Germany, Japan, Puerto Rico, Russian Federation, Spain, United Kingdom, United States across four age groups: 12-17 years (n=47), 9-11 years (n=29), 6-8 years (n=27) and 3-5 years (n=24).</li> <li>2. The DORA part 2 was a phase 2/3, non-randomized, open-label, multinational study that evaluated the efficacy, safety and pharmacokinetics of GLE/PIB paediatric formulation in children aged <math>\geq 3</math> to <math>&lt;12</math> years with chronic hepatitis C infection (genotype 1-6) who were divided into 3 age cohorts.</li> </ol>
<p>Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>In the youngest DORA cohort, AEs were mild with no serious AEs and 1 AE leading to discontinuation. The most common adverse events observed among the 80 patients included headache (14%), vomiting (14%) and diarrhea (10%). GLE/PIB was generally well-tolerated in the paediatric registrational trial. GLE/PIB was generally well-tolerated in the paediatric registrational trial.</p>

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<p>Are there any adverse effects of concern, or that may require special monitoring?</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>No serious adverse events were observed among pediatric patients in DORA study and GLE/PIB was generally well-tolerated in the paediatric registrational trial. Even in the adult registrational trials including 2,300 subjects, serious adverse reactions were unusual (less than 0.1%) and transient (transient ischemic attack). Thus, no adverse effects are of concern, which may require special monitoring.</p>
<p>Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)</p>	<ol style="list-style-type: none"> <li>1. GLE/PIB is the only pangenotypic DAA formulation approved for use over an 8 week treatment duration and high rates of SVR are measured at 12 weeks after the completion of GLE/PIB therapy in children of 3 years of age or older.</li> <li>2. Paediatric granules formulation is available and is expected to be approved in 2021.</li> <li>3. The combination of GLE/PIB has a relatively low or manageable risk of drug-drug interactions and can be used in children receiving antiretroviral therapy for HIV infection.</li> <li>4. Dose adjustment is not needed for patients with renal impairment or for patients with moderate to severe liver impairment.</li> <li>5. There are no specific safety issues associated with GLE/PIB and no special laboratory monitoring is required prior to initiating or while receiving GLE/PIB therapy.</li> </ol> <p>Overall, the overall benefit to risk ratio of GLE/PIB is greatly favourable.</p>
<p>Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)</p>	<p>The overall quality of the evidence for GLE/PIB as a pangenotypic treatment option in children <math>\geq 3</math> years of age with chronic HCV infection is moderate-high. To date, the number of pediatric patients with chronic HCV infection receiving GLE/PIB treatment is very limited (80 subjects) in registration trails. Thus, accumulating data are needed in real-world study to further assess its efficacy and other potential serious adverse effects in different settings and pediatric patients.</p>
<p>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)</p>	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>No special laboratory tests are required to monitor the potential adverse effects of GLE/PIB and effectiveness because no specific safety issues associated with GLE/PIB treatment in pediatric patients are of concern and SVR was achieved almost in 100% of pediatric patients treated with GLE/PIB.</p>

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<p>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)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>AbbVie and the Medicines Patent Pool (MPP) have entered a new, royalty-free licensing agreement to accelerate access to GLE/PIB in 99 low- and middle-income countries and territories at affordable prices, enabling access to and treatment scale-up with GLE/PIB</p>
<p>Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: <a href="https://www.who.int/publications/who-guidelines">https://www.who.int/publications/who-guidelines</a>)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>GLE/PIB was already included as one of the three recommended pan-genotypic regimens for adults with chronic HCV infection. GLE/PIB is expected to be added as a treatment for adolescents and children with chronic HCV infection in the planned update to the chapter on treatment in adolescents and children in the 2018 WHO Guidelines at the end of 2021 when an appropriate pediatric formulation is available.</p>
<p>Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.</p>	<ol style="list-style-type: none"> <li>AbbVie and the Medicines Patent Pool (MPP) have entered a new, royalty-free licensing agreement to accelerate access to GLE/PIB in 99 low- and middle-income countries and territories at affordable prices, enabling access to and treatment scale-up with GLE/PIB. Through this agreement, AbbVie will grant WHO prequalified generic manufacturers to license, manufacture and supply generic versions of GLE/PIB, while maintaining the highest quality and production standards.</li> <li>GLE/PIB will become widely accessible and affordable worldwide with the expected availability of a generic product by multiple quality assured generic suppliers.</li> </ol>
<p>Any additional comments</p>	<p>GLE/PIB 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.</p>
<p>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.</p>	<ol style="list-style-type: none"> <li>Effective treatment of chronic HCV infection in children is key to succeed in achieve the targets for a global HCV elimination by 2030.</li> <li>GLE/PIB provides effective treatment for all common genotypes of HCV. High rates of sustained virologic response (SVR) are measured at 12 weeks after the completion of therapy in children of 3 years of age or older.</li> <li>Treatment with GLE/PIB is well-tolerated in children and the great majority of patients can complete a treatment course in 8 to 16 weeks.</li> <li>GLE/PIB has a relatively low or manageable risk of drug-drug interactions and can be used in children receiving antiretroviral therapy for HIV infection.</li> <li>No special laboratory tests are required to monitor the potential adverse effects of GLE/PIB and effectiveness.</li> <li>The the overall benefit to risk ratio of GLE/PIB is greatly favourable.</li> <li>GLE/PIB is expected to be added as a treatment for adolescents and children with chronic HCV infection in the planned update to the chapter on treatment in adolescents and children in the 2018 WHO Guidelines at the end of 2021 when the pediatric granule formulation is approved.</li> </ol>

	<p>8. GLE/PIB will become widely accessible and affordable worldwide with the expected availability of a generic product by multiple quality assured generic suppliers.</p> <p><b>Conclusion: I recommend the inclusion of GLE/PIB on the core list of the Model List of Essential Medicines for Children (EMLc) for treatment of chronic hepatitis C infection among paediatric patient of 3 years of age or older.</b></p>
References (if required)	