

## Clinical and Cross-Discipline Team Leader Review Addendum

<b>Addendum Date</b>	April 26, 2019
<b>From</b>	Nicholas Rister, MD
<b>Through</b>	Prabha Viswanathan, MD
<b>Subject</b>	Combined Clinical and Cross-Discipline Team Leader Review Addendum
<b>NDA #</b>	209394
<b>Supplement#</b>	S-006
<b>Applicant</b>	AbbVie Inc.
<b>Date of Submission</b>	October 12, 2018
<b>Priority or Standard</b>	Priority
<b>PDUFA Goal Date</b>	April 30, 2019
<b>Proprietary Name</b>	Mavyret®
<b>Non-Proprietary Name</b>	Glecaprevir (GLE)/Pibrentasvir (PIB)
<b>Dosage form(s) / Strength(s)</b>	GLE 100 mg/PIB 40 mg fixed dose combination tablets <span style="float: right;">(b) (4)</span>
<b>Applicant Proposed Indication(s)/Population(s)</b>	
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Treatment of adult and pediatric patients 12 years of age and older or weighing at least 45 kg with HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis.

### Subpopulation Efficacy/Safety Analysis for Post-liver and Post-kidney Transplant Pediatric Populations

The adult GLE/PIB development program included dedicated clinical trials in several subpopulations of patients including those with receipt of a liver or kidney transplant; however, this subpopulation was not enrolled in the pediatric efficacy supplement (NDA 209394 Supplement 6, Trial M16-123). Supplement 2 of NDA 209394 included adult patients in this subgroup and was previously reviewed Dr. Lara Stabinski. It was found to support the use of GLE/PIB in post-liver or post-kidney transplant adults infected with HCV GT 1-6. Please refer to her full clinical review included as part of the Clinical, Biostatistical, Clinical Pharmacology, Clinical Virology and CDTL Summary Review dated July 24, 2018.

In brief, an adult efficacy study (MAGELLAN-2) assessed the safety and efficacy of GLE/PIB in HCV GT1-6-infected, HCV treatment-naïve or treatment-experienced post-liver or post-kidney adult transplant recipients without cirrhosis. MAGELLAN-2 enrolled and treated 100 subjects, 80 who were post-liver transplant and 20 who were post-kidney transplant, with GLE/PIB daily for 12 weeks. The overall SVR12 (95% CI) rate was 98% (93.0%, 99.4%) with one treatment-naïve, GT3-infected subject experiencing post-treatment relapse and one subject with missing

SVR12 data. One additional subject experienced post-treatment relapse after achieving SVR12. PK data did not indicate a need for dose-adjustment in relationship to transplant or common doses of anti-rejection medications such as cyclosporin.

The post-liver and kidney transplant natural history for adults and children is similar regarding immunosuppressive regimens and complications (i.e. rejection, infection). Additionally, given the sufficient similarity in the natural history of chronic HCV disease between children and adults, and the similarities in the treatment and PK/pharmacodynamic (PD) relationship between adults and adolescents, extrapolation of efficacy between populations is possible provided that drug exposure is matched. GLE and PIB exposures have found to be comparable and data from the three Trial M16-123 participants completing 16 weeks of GLE/PIB, along with the safety data demonstrated over 8 weeks in the remainder of the cohort, support the safety of GLE/PIB in adolescents. Therefore, the clinical team recommends extending the pediatric approval to children who are post-liver or post-kidney transplant aged 12 to 17 years.

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