Report MAVIRET® Glecaprevir/Pibrentasvir

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: glecaprevir/pibrentasvir **Brand Name:** MAVIRET® **Originator/licensee:** AbbVie Deutschland GmbH & Co. KG **Classification:** NI **ATC code:** J05AP57 **Orphan Status:** **Eu:** No **Us: -** **Mechanism of action:** GLE/PIB is a fixed-dose combinationof two pan-genotypic targeting multiple steps in the HCV viral lifecycle: glecaprevir is a pan-genotypic inhibitor of the HCV NS3/4A protease necessary for viral replication; pibrentasvir is a pan-genotypic inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly [1].	**Authorized Indication:** **EMA:** GLE/PIB is indicated for the treatment of chronic HCV infection in adults and children aged 3 years and older [2]. **FDA: -** **Route of administration:** OS **Licensing status** **EU CHMP P.O. date:**22/04/2021 **FDA M.A. date: -** **EU Speed Approval Pathway:** Yes **FDA Speed Approval Pathway: -** ----- **ABBREVIATIONS:** **AE:** adverse event **AUC:** area under the plasma concentration-time curve **CHMP:** Committee for Medicinal Products for Human Use **CI**: Confidence Interval **DAA**: Direct-acting Antiviral **GLE**: Glecaprevir **GT**: Genotype **HCV:** hepatitis C virus **PIB:** Pibrentasvir **PK**: pharmacokinetics **pts**: patients **SAE**: serious adverse event **SVR12**: Sustained Virologic Response at Post-treatment Week 12 **WHO**: World Health Organization	**Summary of clinical EFFICACY:** **STUDY M16-123DORA (NCT03067129):** is a phase II/III, non-randomized, open-label, multinational study. Part 2 of the study evaluated children 3- <12 years of age, who were given a pediatric formulation of GLE/PIB. Eligible pts (n=80) were children with chronic HCV infection, GT 1-6, with or without compensated cirrhosis, who were divided into 3 cohorts by age: cohort 2 (9-<12 years), cohort 3 (6-<9 years), cohort 4 (3-<6 years) and given weight-based doses of GLE/PIB for 8, 12, or 16 weeks. The primary efficacy endpoint was SVR12 **(**HCV RNA less than 15 IU/mL at post-treatment week 12). The overall SVR12 rate was 96% (77/80 pts, 95% CI, 90 to 99%). The single SVR12 rates were 93% (27/29 pts, 95% CI, 78 to 98%) for cohort 2, 100% (27/27 pts, 95% CI, 88 to 100%) for cohort 3 and 96% (23/24 pts, 95% CI, 80 to 99%) for cohort 4. The primary PK endpoint was the steady-state AUC values at 0 and 24 hours for GLE and PIB. Final pediatric dosages determined to be efficacious were 250 mg GLE + 100 mg PIB (children weighing ≥30 kg to <45 kg), 200 mg GLE + 80 mg PIB (≥20 kg to <30 kg), and 150 mg GLE + 60 mg PIB (12 kg to < 20 kg) [3]. **Summary of clinical SAFETY:** AEs occurred in 71% of pts. The most common AEs were headache (14%), vomiting (14%) and diarrhoea (10%). No treatment-emergent SAEs were reported. Two children discontinued treatment prematurely: one child refused to swallow the granule formulation and one child discontinued treatment due to a drug-related rash [3]. **Ongoing studies:** • ***For the same indication:*** Yes • ***For other indications:*** No **Discontinued studies (for the same indication):** No ----- **References:** 1. https://ec.europa.eu/health/documents/community-register/2019/20190311144028/anx_144028_en.pdf 2. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/maviret 3. https://aasldpubs.onlinelibrary.wiley.com/doi/epdf/10.1002/hep.31841 4. https://gallery.farmadati.it/Home.aspx 5. https://www.who.int/publications/i/item/global-hepatitis-report-2017 6. https://journals.lww.com/jpgn/Fulltext/2018/03000/Treatment_of_Chronic_Hepatitis_C_Virus_Infection.32.aspx 7. https://aasldpubs.onlinelibrary.wiley.com/doi/pdf/10.1002/hep.31060 8. https://www.hcvguidelines.org/unique-populations/children 9. https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=Glecaprevir%2Fpibrentasvir&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= 10. https://adisinsight.springer.com/drugs/800044162 11. https://clinicaltrials.gov/ct2/results?cond=Hepatitis+C&term=&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= 12. https://adisinsight.springer.com/search	**Cost of Therapy:** 84 coated tablets of GLE100 mg/PIB 40 mg cost € 12.635 (ex-factory price) [4].The price of the paediatric formulation (granules) is not available. The paediatric dosage depends on weight. **Epidemiology:** The global estimate for viraemic prevalence in the paediatric population aged 0–18 years was 0·13% (95% uncertainty interval 0·08–0·16), corresponding to 3·26 million (2·07–3·90) children with HCV in 2018. HCV prevalence increased with age in all countries and territories. HCV prevalence in women of childbearing age was the strongest predictor of HCV prevalence in children aged 0–4 years (p<0·0001). Prevalence of HCV in adults was significantly associated with HCV prevalence in children aged 5–19 years (p<0·0001), and the proportion of HCV infections in people who inject drugs was significantly associated with HCV prevalence in children aged 15–19 years (p=0·036)[5][6]. ----- **POSSIBLE PLACE IN THERAPY** - **Treatment-naive or interferon-experienced children and adolescents** (without cirrhosis or with compensated cirrhosis) [7] [8]: ● an 8-week course of the daily fixed-dose combination of GLE 300 mg/PIB 120 mg is recommended as first-line option in treatment-naive adolescents aged ≥12 years or weighing ≥ 45 kg with any GT. ● a 12-week course of the combination of ledipasvir/sofosbuvir is recommended for use in children aged 3-17 years with GT 1, 4, 5, or 6 infection. - **DAA-experienced children and adolescents** with HCV GT 1, 2, 4, 5, 6: a daily fixed-dose combination of GLE 300 mg/PIB 120 mg is recommended for pts aged ≥12 years or weighing ≥45 kg with prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors [7] [8]. **OTHER INDICATIONS IN DEVELOPMENT:**No [9][10]. **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT**: - **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION**: narlaprevir, yimitasvir, grazoprevir, radalbuvir, furapravir [11][12]. *Service reorganization: No *Possible off label use: No

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