REPORT EPCLUSA® sofosbuvir/velpatasvir

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: sofosbuvir/velpatasvir **Brand Name:** Epclusa **Originator/licensee:** Gilead Sciences Ireland UC **Classification:** NI **ATC code:** J05AP55 **OrphanStatus:** **Eu:** No **Us:** No **Mechanism of action:** The combination sofosbuvir/ velpatasviris a first all oral, pan genotypic treatment for Hepatitis C.The sofosbuvir component of the drug is an inhibitor of the HCV NS5B RNA dependent RNA polymerase, which undergoes intracellular metabolism to form uridine analogue triphosphate and inhibits the viral replication by incorporating into HCV RNA and acts as a chain terminator.Velpatasvir is an inhibitor of HCV NS5A protein, which blocks the action of the protein and inhibits the viral replication[1].	**Authorized Indication:** **EMA:** sofosbuvir/velpatasvir are indicated for the treatment of HCV infection in pts aged ≥3 years of age[2]. **FDA:**sofosbuvir/velpatasvir are indicated for the treatment of adults and pediatric patients 3 years of age and older with chronic HCV GT 1, 2, 3, 4, 5, or 6 infection: • without cirrhosis or with compensated cirrhosis • with decompensated cirrhosis for use in combination with ribavirin [3] **Route of administration:**OS **Licensing status** **EU CHMP P.O. date:** 11/11/2021 **FDA M.A. date:** 10/06/2021 **EU Speed Approval Pathway:** Yes **FDA Speed Approval Pathway:** No --- **ABBREVIATIONS:** **AE:** Adverse Events **CHC:** chronic hepatitis C **CHMP:** Committee for Medicinal Products for Human Use **DAA**: Direct-acting Antiviral **FDC:** fixed dose combination **GLE**: Glecaprevir **GT**: Genotype **HCV**: Hepatitis C virus **LLOQ:**lower limit of quantitation **M.A.:** Marketing Authorization **NS5A:** non-structural protein 5A **NS5B:** non-structural protein 5B **PIB:** Pibrentasvir **P.O.:** Positive Opinion **pts:** patients **RNA:** Ribonucleic acid **SAE:** Serious Adverse Events **SVR12:** Sustained Virologic Response at 12 Weeks	**Summary of clinical EFFICACY:** **NCT03022981**is a phase II, open-label, multi-cohort study (Cohort 1: n=102, pts aged 12 to <18 years of age; Cohort 2: n=73, pts aged 6 to <12 years of age; and Cohort 3: n=41, pts aged 3 to <6 years of age) investigating the pharmacokinetics, safety and efficacy of sofosbuvir/velpatasvirFDC in pediatric pts with chronic HCV. Cohort 1 received sofosbuvir/velpatasvir 400mg/100mg FDC tablets once daily for 12 weeks. Cohort 2 received sofosbuvir/velpatasvir 200mg/50mg pediatric tabletsonce daily for 12 weeks. Cohort 3 received sofosbuvir/velpatasvir 150mg/37.5mg oral granules once daily for 12 weeks. The efficacy endpoint was the percentage of pts with SVR12 after discontinuation of therapy. SVR was defined as HCV-RNA <LLOQ 12 weeks after completing study therapy. In Cohort 1: 95.1% of pts achieved SVR12 (95% CI:88.9 to 98.4). In Cohort 2: 93.2% of pts achieved SVR12 (95% CI: 84.7 to 97.7). In Cohort 3: 82.9 of pts achieved SVR12 (95% CI: 67.9 to 92.8) [3,4]. **Summary of clinical SAFETY:** NCT03022981: SAEswere reported in 2/102 (1.96%) pts in Cohort 1 (both for suicidal ideation), 2/73 (2.74%) in Cohort 2 (constipation and hallucination) and no SAEs occurred in Cohort 3. Non-serious AE occurred in 65/102 (63.73%) pts in Cohort 1, 53/73 (72.60%) subjects in Cohort 2 and 26/41 (63.41%) pts in Cohort 3. The most common AEs were (in Cohort 1, in Cohort 2, in Cohort 3, respectively): headache (29.41% vs.15.07% vs. 4.88 %), fatigue (21.57% vs. 12.33% vs. 12.20%), vomiting (8.82% vs. 16.44% vs. 26.83 %), nausea (16.67%vs.6.85% vs. 0%), pyrexia (9.80% vs. 10.96% vs. 14.63%),diarrhoea (6.86% vs. 8.22% vs. 12.20%),abdominal upper pain (9.80% vs.4.11% vs.4.88 %),upper respiratory tract infection (2.94% vs. 9.59% vs. 4.88%)[3,4]. **Ongoing studies:** ● ***For the same indication:***Yes ● ***For other indications:***No **Discontinued studies (for the same indication):**No --- **References:** 1. https://www.ema.europa.eu/en/documents/product-information/epclusa-epar-product-information_en.pdf 2. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/epclusa-0 3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214187s000lbl.pdf 4. https://clinicaltrials.gov/ct2/show/results/NCT03022981 5. https://gallery.farmadati.it/Home.aspx 6. https://www.drugs.com/price-guide/epclusa 7. https://www.epicentro.iss.it/epatite/dati-seieva#c 8. https://aasldpubs.onlinelibrary.wiley.com/doi/pdf/10.1002/hep.31060 9. https://www.hcvguidelines.org/unique-populations/children 10. 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=	**Cost of therapy:** In Italy, the combinationsofosbuvir/velpatasvir is available at two different dosages: - the price of 28 tablets/pack of sofosbuvir/velpatasvir 400mg/100mg is 24,824.77€ (retail price). - the price of 28 tablets/pack of sofosbuvir/velpatasvir200mg/50mg is 36,666.67€ (retail price,reimbursement is pending for this dosage) [5]. In the U.S.A. the cost of the combination of sofosbuvir/velpatasvir 28 oral pellet 150mg/37.5mg is $26,026. [6] The recommended dosage of sofosbuvir/velpatasvir in pediatric pts ≥3 years of ageis based on weight: - <17kg: 150mg/37.5 mg per day(12 week-treatment costs $78,078) - 17kg to <30 kg: 200 mg/50 mg per day (12 week-treatment costs 110,.000.01€) - at least 30kg: 400 mg/100 mg per day (12 week-treatment costs 74,474.31€) [3] **Epidemiology:** In Italy, the incidence of CHC at December 2020 was: - 0/100,000 among children aged 0-14 years old; - 0.04/100,000 among people aged 15-24 years old [7] --- **POSSIBLE PLACE IN THERAPY** **- Treatment-naive or interferon-experienced children and adolescents (without cirrhosis or with compensated cirrhosis):** •an 8-week course of the daily FDC 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 FDC 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 [8-9]. **OTHER INDICATIONS IN DEVELOPMENT:** - **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:**- **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION :** Dasabuvir, Boceprevir, Narlaprevir[10] *Service reorganization: No *Possible off label use:No

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