Brand Name: Epclusa

Generic Name: sofosbuvir and velpatasvir

Manufacturer[5]: Gilead Sciences, Inc.

Drug Class[1,2]: Antivirals, Anti-hepatitis agents[1,2]

Uses:[1,2,3,4,5]

Labeled Uses: The combination of sofosbuvir and velpatasvir is approved for the treatment of chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection. Sofosbuvir-velpatasvir is approved for the use of chronic HCV in those with compensated and decompensated cirrhosis.

Unlabeled Uses: N/A

Mechanism of Action[1,2,3,4,5]: Sofosbuvir is a prodrug converted to its active form (GS-461203) which is a nucleotide analogue inhibitor of the HCV NS5B polymerase. Velpatasvir is a HCV NS5A inhibitor, a protein necessary for viral replication.

Pharmacokinetics[1,2,3,4,5]:

Absorption:

T_{max}	Sofosbuvir: 0.5 – 1 hour Velpatasvir: 3 hours
V_d	Not reported
t ½	Sofosbuvir: 0.5 hour Active metabolite sofosbuvir: 25 hours Velpatasvir: 15 hours
Clearance	Not reported
Protein Binding	Sofosbuvir: 61 – 65% Velpatasvir: >99.5%
Bioavailability	Not reported

Metabolism:

Sofosbuvir is a pro-drug that is metabolized to its active metabolite (GS-461203) by hydrolysis. Cathepsin A, CES1, and HINT1 are involved in sofosbuvir metabolism. The major inactive, circulating metabolite of sofosbuvir is GS-331007

Velpatasvir is a substrate of and metabolized by CYP2B6, CYP2C8, and CYP3A4. Velpatasvir is not an inducer or inhibitor of any of these aforementioned CYP enzymes.

Elimination:

Kidney:

80% of the sofosbuvir dose is excreted in the urine.
0.4% of the velpatasvir is excreted in the urine.

Feces:

14% of the sofosbuvir dose is excreted in the feces.
94% of the velpatasvir dose is excreted in the feces.

Bile:

The major route of elimination for velpatasvir, 77% excreted in the bile.

Efficacy:

Feld, J, Jacobson, I, Hezode, C, Asselah, T, Ruane, P, Gruener, N, & Abergel, A. (2015, December). Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *The New England Journal of Medicine, 373*(27), 2599-2606.

Study Design: Phase 3, multicenter, multinational, double-blind, placebo-controlled, parallel-group design study

Description of study: *Methods:* 706 patients infected with chronic hepatitis C virus (HCV) genotypes 1, 2, 4, and 6 were randomized 5:1 to receive a fixed-dose combination tablet containing 400 mg of sofosbuvir and 100 mg of velpatasvir or placebo, respectively. Patients with compensated cirrhosis and patients who failed a previous treatment, excluding those with prior treatment with a HCV NS5B or NS5A, were also included in the study. Those with HCV genotype 5 were not randomized and all 35 patients received sofosbuvir-velpatasvir. The combination product or placebo was given once daily for 12 weeks. The primary efficacy endpoint was the rate of sustained virologic response. Secondary endpoints were the rate of adverse events and discontinuations because of adverse events. Adverse events were recorded and graded according to a standardized scale. *Outcome Results:* Sustained virologic response among patients who received 12 weeks of sofosbuvir-velpatasvir was 99% (95% confidence interval [CI] 98 to > 99). None of those in the placebo group had a sustained virologic response. Less than 1% of those receiving at least one dose of sofosbuvir-velpatasvir had virologic failure. No significant difference was observed in the rates of any

adverse events in the sofosbuvir-velpatasvir group and the placebo group, 78% and 77% respectively. Most common adverse events reported were headache, fatigue, nasopharyngitis, and nausea.

Limitations: Those with HCV genotype 5 were not randomized and all received the active drugs sofosbuvir-velpatasvir, therefore this group was not compared to placebo. Patients with HCV genotype 3 were not enrolled in the study. Those receiving a HCV NS5B or NS5A inhibitor for prior treatment were excluded from the study, therefore limiting the ability to extrapolate these results to that specific patient population. Adherence for both groups was not documented. A writer employed by Gilead Sciences, the manufacturer of sofosbuvir-velpatasvir, wrote the initial draft of the manuscript. Gilead Sciences also funded the study and supplied the drug.

Conclusions: Once daily sofosbuvir-velpatasvir appears to be efficacious and safe for those with HCV genotypes 1, 2, 4, 5, and 6. Those with compensated cirrhosis or those that have failed a previous treatment for HCV, excluding those previously treated with a HCV NS5B or HS5A inhibitor, may also benefit from sofosbuvir-velpatasvir. Further studies are needed to assess the role of sofosbuvir-velpatasvir for HCV genotype 3 and those with decompensated cirrhosis.

Foster, G., Afdhal, N., Roberts, S., Brau, N., Gane, E., Pianko, S., & Lawitz, E. (2015, December 31). Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *New England Journal of Medicine, 373*(27), 2608-2616.

Study Design: Two randomized, controlled, phase 3, open-label design studies

Description of the study: *Methods:* 266 patients with HCV genotype 2 infection were randomized 1:1 to receive sofosbuvir-velpatasvir once daily or sofosbuvir plus weight-based ribavirin for 12 weeks in one study. In another study, 552 patients with HCV genotype 3 infection were randomized 1:1 to receive sofosbuvir-velpatasvir once daily or sofosbuvir plus weight based ribavirin for 12 weeks. Both studies specified 20% of the patients enrolled would be those that did not achieve sustained virologic response after previous treated with an interferon-containing regimen, as long as the patient did not discontinue the interferon treatment due to side effects. Both studies also specified that another 20% of the subjects enrolled would be those with compensated cirrhosis. The primary efficacy endpoint for the two trials was a sustained virologic response 12 weeks post treatment. *Outcomes*: Sustained virologic response was observed in 99% (95% CI, 96 -100) of the subjects with HCV genotype 2 in the sofosbuvir-velpatasvir group compared to 94% (95% CI, 88 – 97) in the sosfosbuvir and ribavirin group. Sustained virologic response was observed in 95% (95% CI, 92 – 98) of the subjects with HCV genotype 3 receiving sofosbuvir-velpatasvir compared to 80% (95% CI 75-85) of those received sofosbuvir and ribavirin. In both trials, only one patient receiving sofosbuvir-velpatasvir discontinued all treatment due to adverse events. Nine patients with HCV genotype 3 in the

sofosbuvir and ribavirin group discontinued due to adverse events. Four patients with HCV genotype 2, reported serious adverse events, two patients of the four receiving sofosbuvir-velpatasvir. Six patients with HCV genotype 3 receiving sofosbuvir-velpatasvir reported serious adverse events. Fifteen patients with HCV genotype 3 receiving sofosbuvir and ribavirin reported serious adverse events. The most common reported adverse events between the two trials were fatigue, nausea, and headache.

Limitations: Both trials used an open label study design. A writer employed by Gilead Sciences, the manufacturer of sofosbuvir-velpatasvir, wrote the initial draft of the manuscript. Those receiving ribavirin were not instructed to take the medication with food. Adherence was not documented in either study. Gilead Sciences funded the study and provided the active drug.

Conclusions: Sofosbuvir-velpatasvir appears to a more safe and efficacious regimen for those with HCV genotypes 2 and 3 than sofosbuvir and ribavirin. Those with HCV genotype 3 may experience more side effects with sofosbuvir-velpatasvir than other genotypes. Sofosbuvir-velpatasvir may not be as efficacious for HCV genotype 3 but still receive more benefit than sofosbuvir and ribavirin.

Curry, M., O'Leary, J., Bzowej, N., Muir, A., Korenblat, K., Frenkel, J., & Reddy, K. (2015, December 31). Sofosbuvir andvelpatasvir for HCV in patients with decompensated cirrhosis. *New England Journal of Medicine, 373*(27), 2618-2627.

Study Design: Phase 3, multicenter, randomized, open-label, controlled

Description of the study: *Methods:* 267 patients with HCV genotypes 1 – 6 infection and Child-Pugh-Turcotte (CPT) class B decompensated cirrhosis were randomized 1:1:1 to receive sofosbuvir-velpatasvir once daily for 12 weeks, sofosbuvir-velpatasvir plus ribavirin for 12 weeks, or sofosbuvir-velpatasvir for 24 weeks. Sustained virologic response at 12 weeks after the end of therapy was the primary endpoint. Change in baseline in CPT and Model for End-Stage Liver Disease (MELD) scores 12 weeks post treatment were secondary efficacy end point. *Outcomes:* Sustained virologic response was 83% (95% CI 74 -90) in patients who received sofosbuvir-velpatasvir for 12 weeks, 94% (95% CI, 87-98) for those receiving sofosbuvir-velpatasvir plus ribavirin, and 86% (95% CI, 77-92) in those receiving sofosbuvir-velpatasvir for 24 weeks. No significant difference in rates among the three groups was detected in a post hoc analysis of the findings. 47% of patients had an improvement in CPT over baseline, 42% had no change, and 11% had worsening in CPT score. 51% of patients had an improvement in their MELD score, 22% had no change, and 27% had a worsening in the score. Nine patients discontinued study treatment because of an adverse effect (1 in the sofosbuvir-velpatasvir 12-week group, 4 in the sofosbuvir-velpatasvir plus ribavirin group, and 4 in the sofosbuvir-velpatasvir 24-week treatment group). Serious adverse events occurred in 19% of patients who

received sofosbuvir-velpatasvir for 12 weeks, 16% of those who received sofosbuvir-velpatasvir plus ribavirin, and 18% of those who received sofosbuvir-velpatasvir for 24 weeks. Hepatic encephalopathy and sepsis were the most common serious adverse events. Fatigue, nausea, and headache were the most common adverse events in all groups). Nine deaths occurred in the study, most deaths resulted from complications of end-stage liver disease. No deaths were deemed due to therapy.

Limitations: This study used an open label design. All genotypes were not represented equally (0% HCV genotype 5, less than 1% HCV genotype 6, 3% genotype 4, 4% HCV genotype 2, 15% genotype 3, and 78% genotype 1). Those with renal dysfunction (creatinine clearance less than 50 milliliters/minute) and thrombocytopenic (platelet cell count less than 30,000) were excluded from enrollment. Only 6% of the patients were African American. Power was not sufficient to detect significant differences among the three treatment groups. Only those with moderate liver dysfunction were enrolled. Gilead Sciences funded the study and provided the active drugs.

Conclusions: Sofosbuvir-velpatasvir, with or without ribavirin, for 12 weeks and sofosbuvir-velpatasvir for 24 weeks appears to be safe and effective treatment regimens for those with HCV and decompensated cirrhosis. Due to the study being unable to detect significant differences between the treatment regimens, it is uncertain on which treatment regimen is best for this patient population. Further research is warranted on sustained virologic response and mortality benefits beyond 12 weeks post treatment in this patient population. Also, further research is needed to equally represent all the HCV genotypes in those with cirrhosis.

Contraindications[1,2,3,4,5]:

Specific contraindications for sofosbuvir-velpatasvir have not yet been determined.

If sofosbuvir-velpatasvir is administered with ribavirin, the contraindications for ribavirin apply.

The use of sofosbuvir-velpatasvir in combination with ribavirin is contraindicated in pregnant women and in the male partners of women who are pregnant.

Precautions[1,2,3,4,5]:

Concomitant use with amiodarone is not recommended due to reports of symptomatic bradycardia and fatal cardiac arrest with use of sofosbuvir-containing HCV regimens.

Concomitant use with P-glycoprotein inducers or moderate to potent CYP2B6, CYP2C8, or CYP3A4 inducers is not recommended due to the therapeutic level of sofosbuvir-velpatasvir being reduced.

The use of sofosbuvir-velpatasvir in pregnancy or breast-feeding has not been studied. Therefore it is not known if this combination can be used in this population.

If HCV and HIV coinfection exists, consider treating both viral infections concurrently due to the benefits of concurrent therapy outweighing the risks.

The safety and efficacy of sofosbuvir-velpatasvir has not been established in those with renal impairment (eGFR < 30 mL/minute/1.73m^2) or renal failure.

Adverse Effects*[1,2,3,4,5]:

- *Common >10%:*
  - Hematological:
    - Anemia: 26% (moderate)
    - Decreased hemoglobin: 23% (moderate)
  - Gastrointestinal:
    - Diarrhea: 10%
    - Nausea: 9 – 11%
  - Neurological:
    - Headache: 11 – 22%
    - Insomnia: 5 – 11%
  - Other:
    - Fatigue: 15 – 32%

- *Infrequent 1 -10%:*
  - Dermatological:
    - Rash: 2 – 5%
  - Neurological:
    - Irritability: 5%
  - Neuromusclar:
    - Asthenia: 5%

- *Rare < 1%:*
  - Psychiatric:
    - Depression: (moderate)
  - Muscoskeletal:
    - Increase creatine kinase
  - Metabolic:
    - Increased serum lipase

- *Unknown:*
  - Metabolic:
    - Hyperbilirubinemia: (moderate)
  - Cardiovascular:
    - Bradyarrhythmia: (**serious**)

*Unless otherwise indicated, mild adverse effect

Drug Interactions[1,2,3,4,5]:

- Afatinhib:
  - P-glycoprotein inhibitors may increase dose of afatinib.
  - Action: Reduce dose of afatinib by 10 mg.
- Amiodarone:
  - Sofosbuvir may enhance the bradycardic effect of amiodarone.
  - Action: Avoid combination
- Amlodipine:
  - May increase velpatasvir plasma concentrations due to CYP3A4 inhibition
  - Action: avoid taking together if possible.
- Antacids:
  - May decrease the serum concentration of velpatasvir.
  - Action: separate administration of velpatasvir and antacids by 4 hours.
- Asunprevir:
  - OATP1B1/SLCO1B1 Inhibitors may increase the serum concentration of Asunaprevir.
  - Action: Avoid combination
- Carbamazepine:
  - Decreased sofosbuvir exposure
  - Action: Avoid combination
- Cimetadine:
  - Decreased velpatasvir exposure due to increased pH
  - Action: Use caution, consider therapy modification
- Deferasirox:
  - Decrease serum concentration of CYP3A4 substrates
  - Action: Monitor therapy
- Digoxin:
  - Increased digoxin levels
  - Action: Monitor therapy
- Efavirenz:
  - Decreased velpatasvir exposure
  - Action: Avoid combination
- Grazoprevir:
  - OATP1B1/SLCO1B1 Inhibitors may increase the serum concentration of Grazoprevir.
  - Action: Monitor therapy
- Modafinil:
  - May decrease the serum concentration of Sofosbuvir
  - Action: Avoid combination
- Naficillin:
  - Decreased sofosbuvir-velpatasvir exposure
  - Action: Avoid combination
- Nilotinib:

    - May decrease the serum concentration of CYP2B6 Substrates
    - Action: Monitor therapy
- Oxcarbazepine:
    - May decrease the serum concentration of Sofosbuvir.
    - Action: Avoid combination
- Phenobarbital:
    - Decreased sofosbuvir-velpatasvir exposure
    - Action: Avoid combination
- Phenytoin:
    - Decreased Velpatasvir exposure
    - Action: Avoid combination
- Proton pump inhibitors:
    - Decreased serum contraction of Velpatasvir
    - Action: Avoid combination
- Ranolazine:
    - P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration
    - May increase the serum concentration of substrates
    - Action: Monitor therapy
- Rifabutin:
    - Decreased serum concentration of sofosbuvir
    - Action: Avoid combination
- Rifampin:
    - Decreased velpatasvir exposure
    - Action: avoid combination
- Rifapentine:
    - Decreased serum concentration of sofosbuvir
    - Action: Avoid combination
- Rosuvastatin:
    - Velpatasvir may increase concentration
    - Action: Consider therapy modification
- Siltuximab:
    - Decreased serum concentration of CYP3A4 substrates
    - Action: Monitor therapy
- Topotecan:
    - Velpatasvir increase serum concentration
    - Action: Avoid combination
- Venetoclax:
    - P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration
    - Action: Reduce dose by at least 50% in patietns requiring these combinations
        - Consider therapy modification
- **Inducers of CYP2B6, CYP2C8, and CYP3A4:**
    - Decrease the serum concentration of Velpatasvir
    - Action: Avoid combination
- **P-glycoprotein/ABCB1**:
    - Inducers:
        - Decrease serum concentration of sofosbuvir and velpatasvir

        - Action: Avoid combination
    - Inhibitors:
        - Increase the serum concentration of substrates
        - Enhance distribution of substrates
        - Action: Monitor therapy
        - Drugs: Atorvastatin, bosutinib, bentuximab vedotin, colchicine, dabigitran, doxorubicin, edoxaban, everolimus, naloxegol, paxopanib, prucalopride, rifamixin, silodosin, and vincristine.
    - Substrates:
        - P-glycoprotein/ABCB1 inhibitors may increase serum concentration of substrates
        - Enhance distribution of substrates
        - Monitor therapy

Dosing/Administration[1,2,3,4,5]:

Without cirrhosis or with compensated cirrhosis (Child-Pugh A):

Sofosbuvir 400 mg/velpatasvir 100 mg orally once daily for 12 weeks

With decompensated cirrhosis (Child-Pugh B/C):

< 75 kilograms (kg): sofosbuvir 400 mg/velpatasvir 100 mg orally once daily for 12 weeks *plus* ribavirin 1,000 mg/day orally with food twice daily, dose based on creatinine clearance and hemoglobin levels.

> 75 kg: sofosbuvir 400 mg/velpatasvir 100 mg orally once daily for 12 weeks *plus* ribavirin 1,200 mg/day orally with food twice daily, dose based on creatinine clearance and hemoglobin levels.

Renal impairment:

eGFR ≥ 30 mL/minute/1.73 m^2: No dosage adjustments needed
eGFR < 30 mL/minute/1.73 m^2: No dosage adjustments provided. Sofosbuvir and metabolite may accumulate.
End-stage renal disease (ESRD), including hemodialysis: No dosage adjustments provided. Sofosbuvir and metabolite may accumulate.

Use in special circumstances[5]:

Pediatrics: Safety and efficacy of sofosbuvir-velpatasvir have not been established in this population

Geriatrics: Clinical trials included patients > 65-years-old. No overall differences were seen in this population compared to the rest of the subjects enrolled. No dose adjustments are required, but some geriatric patients may be more sensitive to the effects of sofosbuvir-velpatasvir.

Overdosage: No antidote exists for sofosbuvir-velpatasvir. If overdose occurs, monitor vitals and clinical status. Hemodialysis can effectively remove the

predominate metabolite of sofosbuvir but is not as likely to remove velpatasvir due to velpatasvir being highly protein bound.

Conclusion: Sofosbuvir-velpatasvir is a safe and effective therapy for the treatment of chronic HCV genotypes 1, 2, 3, 4, 5 and 6 in those that are treatment naïve and those who have failed a previous treatment for HCV, excluding those previously treated with a HCV NS5B or NS5A inhibitor. Those with HCV genotype 3 seem to experience more side effects and treatment failure than the other genotypes, which warrants further evaluation of this subgroup of patients. Sofosbuvir-velpatasvir, with or without ribavirin, has also shown to be effective for those with compensated and decompensated cirrhosis. Further studies must be conducted to assess which therapy is superior for decompensated cirrhosis. Sofosbuvir-velpatasvir is extensively metabolized by the CYP system therefore requiring extensive drug-drug interaction monitoring. An advantage Epclusa® has over other currently marked HCV medications is a lower price. For example, the Sovaldi® (sofosbuvir) plus ribavirin regimen costs approximately $34,000 a month and the Harvoni® (sofosbuvir-ledipasvir) regimen costs approximately $38,000 per month; whereas Epclusa® costs approximately $30,000 per month. Given that treatment is typically 3 months, a patient could save approximately $14,000 by taking Epclusa® versus Sovaldi® plus ribavirin, and save approximately $24,000 by taking Epclusa® versus Harvoni®. Head-to-head trials are warranted to assess which treatment option is significantly more effective in treating chronic HCV. Overall, with its tolerability, effectiveness for sustained virologic response across all HCV genotypes, lower cost compared to other current treatments, and use in decompensated cirrhosis, sofosbuvir-velpatasvir appears to be clinically useful for the treatment of chronic HCV.

Recommended References:

1. Sofosbuvir, velpatasvir. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2009. Available at: http://www.clinicalpharmacology.com Accessed: September 12, 2016.
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4. Sofosbuvir, celpatasvir. Facts & Comparisons 4. Online [Internet database]. Wolters Kluwer. Available at http://online.factsandcomparisons.com. Accessed September 18, 2016.
5. Epclusa [package insert]. Foster City, CA. Gilead Sciences, Inc.; 2016.

Prepared by: Catessa Howard, PharmD Candidate