Description of Antivirals for Hepatitis C

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Objectives

- Compare the different classes of direct-acting antiviral agents
- List monitoring parameters for hepatitis C (HCV) medications
- Identify important counseling points for HCV medications

Treatment Options

HCV Therapies - DAAs

Medication	NS5B	NS5A Inh	NS3 PI	Other
Harvoni®	sofos**buvir**	ledip**asvir**		
Epclusa®	sofos**buvir**	velpat**asvir**		
Vosevi®	sofos**buvir**	velpat**asvir**	voxilapr**evir**	
Mavyret®		pibrent**asvir**	glecapr**evir**	
Zepatier®		elb**asvir**	grazopr**evir**	

HCV Treatment by Genotype

Medication	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Genotype 6
Harvoni®	X			X	X	X
Epclusa®	X	X	X	X	X	X
Vosevi®	X	X	X	X	X	X
Mavyret®	X	X	X	X	X	X
Zepatier®	X			X		

Drug Interactions

- Always perform a drug interaction check before beginning treatment with any of the hepatitis C medications

- Lexicomp

- University of Liverpool HEP C Drug Interactions – This is generally the most up to date information available on interactions
  - https://hep-druginteractions.org/checker

NS5B/NS5A Inhibitors

- ledipasvir/sofosbuvir (Harvoni®)
- velpatasvir/sofosbuvir (Epclusa®)

ledipasvir/sofosbuvir (Harvoni®)

- **Ledipasvir/Sofosbuvir**
  - Minimal DDIs, **no food effect**
    - **Interaction with acid reducing medications**
  - **Do not use in patients with GFR < 30 (due to sofosbuvir component)**

- Genotypes **1,** 4, 5, 6

- Approved for Pediatrics
  - Children ≥ 12 years or weight ≥ 35kg
  - Without cirrhosis or with compensated cirrhosis

LDV NS5A inhibitor → **SOF - NS5B nucleotide polymerase inhibitor**

Harvoni® [package insert]. Gilead Sciences, Foster City, CA

Approved: Oct 10, 2014

Ledipasvir/sofosbuvir

- Approved for 8 weeks of treatment in treatment naïve, non-cirrhotic, non-African American, genotype 1 patients with a viral load < 6 million IU per mL

- Genotype 1 pediatric patients (≥ 12 yoa or weight ≥ 35kg) with/without cirrhosis

Harvoni® [package insert]. Gilead Sciences, Foster City, CA

velpatasvir/sofosbuvir (Epclusa®)

- **velpatasvir/sofosbuvir**
  - Minimal DDIs, **no food effect**
    - **Interaction with acid reducing medications**
  - **Do not use in patients with GFR < 30 (due to sofosbuvir component)**

VEL NS5A inhibitor → **SOF** - NS5B nucleotide polymerase inhibitor

- **Pan-genotypic**
  - Genotypes 1,2,3,4,5,6

Epclusa® [package insert]. Gilead Sciences, Foster City, CA

Approved: June 28, 2016

NS5B / NS5A Inhibitor / NS3/4A Protease Inhibitor

- Sofosbuvir/velpatasvir/voxilaprevir (Vosevi®)

Sofosbuvir/velpatasvir/voxilaprevir (Vosevi®)

- One tablet daily **with food** (food increases the AUC of voxilaprevir)

- **Pan-genotypic**
  - genotypes 1,2,3,4,5,6

- **Approved for treatment failures – not 1st line therapy**
- FDA approved on July 20, 2017

Vosevi® [package insert]. Gilead Sciences, Foster City, CA

Sofosbuvir/velpatasvir/voxilaprevir - Treatment Failures

Genotype	Previous Regimen Included	Duration of Treatment
1, 2, 3, 4, 5, 6	NS5SA inhibitor[1]	12 weeks

[1]—NS5A medications included in clinical trials: daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir

Vosevi® [package insert]. Gilead Sciences, Foster City, CA

Sofosbuvir/velpatasvir/voxilaprevir - Precautions

- **Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C)**
  - Due to higher exposure to protease inhibitor
  - Bilirubin increased ≤ 1.5 x ULN in ~10% of patients in clinical studies
    - No jaundice
    - Levels decreased after completing treatment

Vosevi® [package insert]. Gilead Sciences, Foster City, CA

Acid Suppression Agents and NS5A Inhibitors ledipasvir & velpatasvir

- Proton Pump Inhibitors
  - Only doses ≤ omeprazole 20 mg
    - Pantoprazole mg ≠ omeprazole mg
  - **SOF/LED** – Administer simultaneously on an empty stomach
  - **SOF/VEL (/VOX)** - Take with food 4 hours before omeprazole
- Consider discontinuation of acid suppression therapy if patient is able to tolerate
  - Reduce PPI by 50% per week to lowest dose, then discontinue to minimize rebound acid hypersecretion

Acid Suppression Agents and NS5A Inhibitors ledipasvir and velpatasvir

Antacids

- aluminum hydroxide
- magnesium hydroxide

- Separate administration by four hours

H_2RAs

- famotidine
- ranitidine

- Administer concurrently or 12 hours apart
- Not to exceed doses >40 mg famotidine twice daily

NS5A Inhibitors / NS3/4A Protease Inhibitors

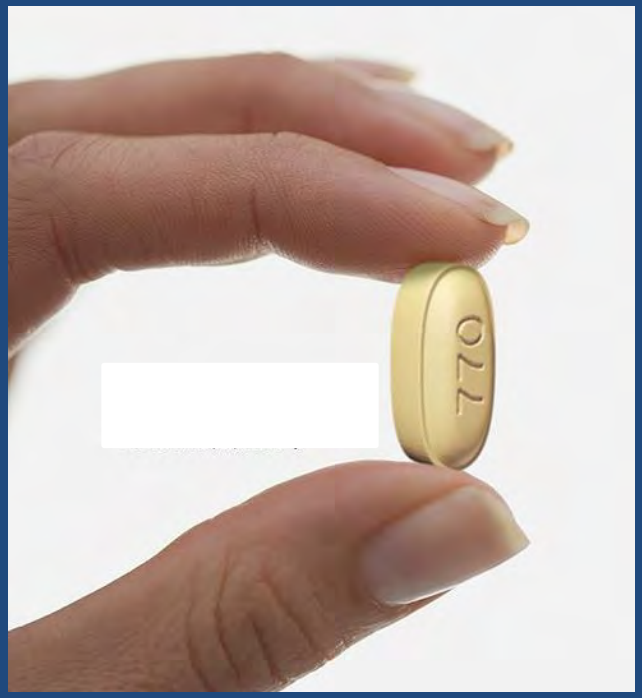
- elbasvir/grazoprevir (ZEPATIER ®)
- glecaprevir/pibrentasvir (Mavyret ®)

elbasvir/grazoprevir (ZEPATIER®)

- Genotypes 1 and 4
- Elbasvir 50 mg
  - NS5A inhibitor
- Grazoprevir 100 mg
  - NS3/4A protease inhibitor

- One tablet once daily with or without food

- FDA-approved Jan 28, 2016



ZEPATIER® [package insert]. Kenilworth, NJ: MERCK

Special Considerations

- Must perform resistance testing in genotype 1a
  - NS5A resistance-associated polymorphisms
    - addition of ribavirin and extension of therapy from 12 to 16 weeks
- No interactions with acid-reducing medications
- No dosage adjustment is recommended in patients with renal insufficiency
  - including patients with end-stage renal disease and patients on hemodialysis

glecaprevir/pibrentasvir (Mavyret®)

- 100mg/40mg tablet
  - **Take 3 tablets once daily with food**

- **Pan-genotypic**
  - Genotypes 1,2,3,4,5,6
- Approved for some treatment failures
- No dosage adjustment in patients with mild, moderate, or severe renal impairment, including dialysis
- FDA Approval August 3, 2017

Mavyret® [package insert]. North Chicago, IL: AbbVie Inc.

glecaprevir/pibrentasvir - Treatment Naïve

- All genotypes (no cirrhosis)
  - 8 weeks
- All genotypes (with cirrhosis - Child-Pugh A)
  - 12 weeks

glecaprevir/pibrentasvir - GT 1 Treatment Experienced

Genotype	Previous Treatment	Treatment Duration (No Cirrhosis)	Treatment Duration Compensated Cirrhosis (Child-Pugh A)
1	NS5A inhibitor[1] without prior treatment with NS3/4A protease inhibitor	16 weeks	16 weeks
	NS3/4A protease inhibitor[2] without prior treatment with NS5A inhibitor	12 weeks	12 weeks

[1] – In clinical trials, subjects were treated with ledipasvir/sofosbuvir or daclatasvir with interferon and ribavirin

[2] – In clinical trials, subjects were treated with simeprevir+sofosbuvir, or simeprevir, boceprevir, or telaprevir with interferon+ribavirin

Mavyret® [package insert]. North Chicago, IL: AbbVie Inc.

glecaprevir/pibrentasvir - Drug Interactions

- **Ethinyl estradiol-containing products**
  - **Coadministration of GLE/PIB may increase the risk of ALT elevations and is not recommended**
  - **Change patients to progesterone birth control**

- Omeprazole
  - Package insert states no dose adjustments required
  - 40mg daily is highest dose studied
    - 20mg: Coadminister with GLE/PIB
    - 40mg: Give one hour before GLE/PIB

- No interaction with antacids or H2 blockers

Mavyret® [package insert]. North Chicago, IL: AbbVie Inc.

Most Common Adverse Effects to All DAAs

- Most commonly reported side effects (~10%)
  - Headache
  - Fatigue
- Less common side affects (<10%)
  - Nausea
  - Diarrhea
  - Insomnia

Special Points of Interest

- Statins – All reviewed DAAs have interactions with many of the statins
  - Reference the package insert and Liverpool interaction checker for necessary adjustments

- All reviewed DAAs can ↑ levels of digoxin
  - Frequent level monitoring recommended when co-administered

- Inducers of P-gp/CYP3A decrease plasma concentrations of all DAAs (Do not use with DAAs)
  - Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, and phenytoin (**no interaction with levetiracetam**)
  - Antimycobacterials: rifabutin, rifampin, rifapentine

Special Points of Interest

- Ensure patients taking GLE/PIB are not also taking ethinyl estradiol containing birth control (Change to progesterone if possible)

- Do not use GLE/PIB or SOF/VEL/VOX in decompensated cirrhotic patients (Child-Pugh B or C) due to increased protease inhibitor exposure which can lead to liver failure

- Most of the reviewed DAAs have interactions with acid reducing medications
  - Best choice for patients taking acid reducing medications is GLE/PIB (up to 40mg omeprazole)
  - Patients taking >40mg omeprazole, least amount of concern is with elbasvir/grazoprevir

Special Points of Interest

- Sofosbuvir containing regimens (SOF/LED, SOF/VEL, SOF/VEL/VOX):
  - Contraindicated when GFR<30
  - Concerns for serious symptomatic bradycardia when combined with amiodarone

- DAAs are likely to interact with HIV medications (check package insert for specific medications)
  - Avoid Harvoni, Eplcusa, or Vosevi with **Truvada** due to risk of increased Tenofovir Disoproxil Fumarate levels which can damage the kidneys (Can use Mavyret)

Risk of Hepatitis B Reactivation

- Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated

- Ensure that patients have their Hepatitis B serology prior to initiating Hepatitis C Therapy

Common 1st Line Therapies

Drug	FDA-Approved Indication
Harvoni (SOF/LED)	Adults with chronic HCV--Genotypes 1,4,5,6 • With/without cirrhosis (compensated or decompensated) • GFR>30 • 8-12 weeks -depends on GT, race and viral load Pediatrics patients-GT 1,4,5,6 • Without cirrhosis or with compensated cirrhosis
Epclusa (SOF/VEL)	Adults with chronic HCV--Genotype 1-6 • With/without cirrhosis (compensated or decompensated) • GFR>30 • 12 weeks for treatment naïve
Mavyret (GLE/PIB)	Adults Genotypes 1-6 • Without cirrhosis or with compensated cirrhosis • 8 weeks for treatment naïve non-cirrhotic • 12 weeks for treatment naïve compensated cirrhosis

DAAs and Statins

Statin	Mavyret®	Epclusa®	Harvoni®	Vosevi®
Rosuva statin	D[1] Max: 10 mg/day	D Max: 10 mg daily	X Contraindicated	X Contraindicated
Atorva statin	X contraindicated	C[2] Statin levels may be increased-use lowest necessary dose and monitor for AE of statin	C Statin levels may be increased-use lowest necessary dose and monitor for AE of statin	D Lowest Approved Dose
Simva statin	X contraindicated	Statin levels may be increased-use lowest necessary dose and monitor for AE of statin	Statin levels may be increased-use lowest necessary dose and monitor for AE of statin	D Lowest Approved Dose
Lova statin	X contraindicated	C monitor for AE of statin	C monitor for AE of statin	D Lowest Approved Dose
Prava statin	D Reduce dose by 50%	No Interaction	Statin levels may be increased-use lowest necessary dose and monitor for AE of statin	D Max: 40mg daily

1 – based on study with 12 people
2 – based on rosuvastatin study
AE – myalgia/myopathy; increased AST/ALT

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