

MEDICATION COVERAGE POLICY

PHARMACY AND THERAPEUTICS ADVISORY COMMITTEE

POLICY:	Liver Disease	P&T DATE:	9/11/2018
CLASS:	Gastrointestinal Disorders	REVIEW HISTORY:	2/17, 9/15
LOB:	MCL	(month/year)	

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the HPSJ Pharmacy and Therapeutic Advisory Committee.

OVERVIEW

Liver disease can be caused by various factors – infectious disease (hepatitis B, C), chronic alcoholism, nonalcoholic fatty liver disease, medications, etc. Chronic liver disease can progress to ascites and cirrhosis, which can lead to complications and eventually may require liver transplant. Hepatitis B and C medications can help reduce the risk of long-term complications from chronic hepatitis and transmission of disease to others. Certain antibiotics and blood pressure medications can treat or prevent liver disease complications, such as hepatic encephalopathy, variceal bleeding, ascites, and spontaneous bacterial peritonitis.

Table 1: Formulary Liver Disease Treatment Agents

Indication	Drug	Available Strengths	FML Limit	Notes	Cost Per Rx
Hepatic Encephalopathy Prophylaxis	Lactulose (Generlac/ Kristalose)	20g/30mL Oral Solution; 10g, 20g Powder Packet	--		\$13.68
	Rifaximin (Xifaxan)	550mg Tablet	PA	For HE: Xifaxan is reserved for treatment failure of compliant use of lactulose evidenced by consistent lactulose fills. For IBS-D: Restricted to 42 tablets per 14 days. Restricted to 3 fills per 365 days. Xifaxan is reserved for patients who have failed treatment with at least one antispasmodic, one TCA, and loperamide; or failed treatment with at least one antispasmodic and one TCA for use in abdominal pain relief.	\$1,276.29
	Metronidazole (Flagyl)	250mg, 500mg Tab	--		\$7.82
	Neomycin (Neo-Fradin)	500mg Tab	--		\$7.84
	Bromocriptine (Parlodel)	2.5mg Tab, 5mg Capsule	--		\$135.14
Variceal Bleeding Prophylaxis*	Propranolol (Inderal)	20mg/5mL, 40mg/5mL Oral Solution; 60mg, 80mg, 120mg, 160mg ER Cap.; 10mg, 20mg, 40mg, 60mg, 80mg Tab	--		\$14.72
	Nadolol (Corgard)	20mg, 40mg, 80mg Tab	--		\$46.84
Treatment of Ascites	Spirolactone (Aldactone)	25mg, 50mg, 100mg Tab	--		\$8.55
	Furosemide (Lasix)	10mg/mL, 40mg/5mL Oral Solution; 20mg, 40mg, 80mg Tab	--		\$0.79

Spontaneous Bacterial Peritonitis Prophylaxis	Sulfamethoxazole -Trimethoprim (Septra/Bactrim)	200mg-40mg/5mL Suspension; 400mg-80mg, 800mg-160mg Tab	--		\$10.25
	Ciprofloxacin HCL (Cipro)	100mg, 250mg Tab 500mg, 750mg Tab	QL --	Limit 28 tablets per 30 days	\$2.20
Treatment of Hepatitis B	Entecavir (Baraclude)	0.5mg, 1mg Tab	PA; SP	Documentation of appropriate diagnosis is required.	\$680.26
	Adefovir Dipivoxil (Hepsera)	10mg Tab	PA; SP	Documentation of appropriate diagnosis is required.	--

FML = Formulary; PA = Prior Authorization Required; QL = Quantity Limit; SP = Restricted to Specialty Pharmacy

*Additional formulary non-selective beta-blockers are included in the Hypertension Coverage Policy

⊕ EVALUATION CRITERIA FOR APPROVAL/EXCEPTION CONSIDERATION

Below are the coverage criteria and required information for each agent. These coverage criteria have been reviewed approved by the HPSJ Pharmacy & Therapeutics (P&T) Advisory Committee. For conditions not covered under this Coverage Policy, HPSJ will make the determination based on Medical Necessity as described in HPSJ Medical Review Guidelines (UM06).

Hepatic Encephalopathy Prophylaxis

Lactulose (Generlac), Metronidazole (Flagyl), Neomycin (Neo-Fradin), Bromocriptine (Parlodel), Rifaximin (Xifaxan)

Lactulose (Generlac), Metronidazole (Flagyl), Neomycin (Neo-Fradin), Bromocriptine (Parlodel)

- Coverage Criteria:** None
- Limits:** None
- Required Information for Approval:** N/A

Rifaximin (Xifaxan) 550 mg tablets

- Coverage Criteria:**
 - For use in Hepatic encephalopathy, Xifaxan is reserved for treatment failure of compliant use of lactulose evidenced by consistent lactulose fills.
 - For use in IBS-D, Xifaxan is reserved for patients who have failed treatment with at least one antispasmodic, one TCA, and loperamide; or failed treatment with at least one antispasmodic and one TCA for use in abdominal pain relief.
- Limits:**
 - Quantity limit: Restricted to 42 tablets per 14 days.
 - Fill limit: Restricted to 3 fills per 365 days.
- Required Information for Approval:** Proper chart note documentation and pharmacy fill history of at least one antispasmodic and one TCA for use in antispasmodic relief and at least one antispasmodic, one TCA, and loperamide for use in IBS-D.

Variceal Bleeding Prophylaxis

Propranolol (Inderal), Nadolol (Corgard)

- Coverage Criteria:** None
- Limits:** None
- Required Information for Approval:** N/A

Treatment of Ascites

Spirolactone (Aldactone), Furosemide (Lasix)

- Coverage Criteria:** None
- Limits:** None
- Required Information for Approval:** N/A

Spontaneous Bacterial Peritonitis Prophylaxis

Sulfamethoxazole/Trimethoprim (Septra, Bactrim), Ciprofloxacin (Cipro)

Sulfamethoxazole/Trimethoprim (Septra, Bactrim); Ciprofloxacin (Cipro) 500 mg, 750 mg tablets

- Coverage Criteria:** None
- Limits:** None
- Required Information for Approval:** N/A

Ciprofloxacin (Cipro) 100 mg, 250 mg tablets

- Coverage Criteria:** None
- Limits:** 28 tablets per 30 days
- Required Information for Approval:** N/A

Treatment of Hepatitis B

Entecavir (Baraclude), Adefovir Dipivoxil (Hepsera)

- Coverage Criteria:** Documentation of appropriate diagnosis is required.
- Limits:** None
- Required Information for Approval:** Chart notes and titers indicating that the patient has an active Hepatitis B infection.
- Other Notes:** Medication is to be dispensed by HPSJ's designated specialty pharmacy.

⊕ **CLINICAL JUSTIFICATION**

Cirrhosis is an irreversible disease caused by various toxicants and infectious etiologies. While Cirrhosis is irreversible, symptoms of ascites and progression of disease can be halted with abstinence from the offending toxicant, use of antivirals (if applicable), and use of prophylactic therapies.

According to the American Association for the Study of Liver Disease (AASLD), initial treatment for overt hepatic encephalopathy is lactulose; rifaximin was studied in patients concurrently using lactulose, and thus efficacy is only demonstrated in these patients.¹ AASLD and EASL also recommend secondary prophylaxis after an episode of overt hepatic encephalopathy.¹ For primary prophylaxis of variceal bleeding, AASLD recommends Non-Specific Beta-Blockers (NSBBs) such as propranolol or nadolol, carvedilol, or endoscopic variceal therapy); first-line therapy for secondary prophylaxis is combination of NSBB+EVL, unless the patient received transjugular intrahepatic portosystemic shunt (TIPS).² AASLD guidelines for ascites name sodium restriction (2000 mg per day) and diuretics (oral spironolactone with or without oral furosemide) as first-line treatment in patients with cirrhosis and ascites.³ AASLD guidelines also recommend primary prophylaxis of SBP in patients with cirrhosis and ascites, if the ascetic fluid protein < 1.5 g/dL along with impaired renal function (SCr ≥ 1.2, BUN ≥ 25, or serum Na ≤ 130) or liver failure (Child Pugh Score ≥ 9 and bilirubin ≥ 3). These guidelines also recommend long-term use of antibiotics in patients who have survived an episode of SBP.³ First-line options include sulfamethoxazole/trimethoprim and norfloxacin; however, norfloxacin is no longer available in the United States due to manufacturer discontinuation.⁴ In patients with immune-active chronic hepatitis B (CHB)—defined as elevation of ALT > 2 ULN, or evidence of significant histological disease plus elevated HB DNA > 2,000 IU/mL (HBeAg negative) or above 20,000 IU/mL (HbeAg positive), AASLD recommends Peg-IFN, entecavir, or tenofovir.⁵



REFERENCES

1. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology* 2014;60(2):715-735.
2. Garcia-Tsao G, Abraldez JG, Berzigotti A, Bosch J. Portal Hypertensive Bleeding in Cirrhosis: Risk Stratification, Diagnosis, and Management: 2016 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2017;65(1):310-335.
3. Runyon BA. Management of Adult Patients with Ascites Due to Cirrhosis: Update 2012. http://www.aasld.org/sites/default/files/guideline_documents/adultascitesenhanced.pdf. Updated 2013.
4. Drug Shortages: Norfloxacin Tablets (Noroxin). American Society of Health-System Pharmacists Web Site. <http://www.ashp.org/menu/DrugShortages/DrugsNoLongerAvailable/Bulletin.aspx?id=1099>. Updated April 29, 2014.
5. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD Guidelines for Treatment of Chronic Hepatitis B. *Hepatology* 2005;00(00):1-23.
6. Terrault et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance <https://doi.org/10.1002/hep.29800>. Updated 2018.

REVIEW & EDIT HISTORY

Document Changes	Reference	Date	P&T Chairman
Creation of Policy	HPSJ Formulary Criteria	--	Allen Shek, PharmD, BCPS
Update to Policy	HPSJ Coverage Policy – Gastrointestinal Disorders – Liver Disease 2015-09.docx	9/2015	Jonathan Szkotak, PharmD, BCACP
Update to Policy	HPSJ Coverage Policy – Gastrointestinal Disorders – Liver Disease 2017-02.docx	2/2017	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Gastrointestinal Disorders – Liver Disease 2018-09.docx	9/2018	Johnathan Yeh, PharmD

Note: All changes are approved by the HPSJ P&T Committee before incorporation into the utilization policy

 Please review the **Hepatitis C Coverage Policy** for coverage criteria of hepatitis C treatments.
 **All anti-retroviral and substance use disorder medications not mentioned in this coverage policy are specifically carved out from Medi-Cal Managed Care Plans, and should be billed directly to Medi-Cal Fee-For-Service. The Managed Medi-Cal Prescription Drug Carve-Out list can be found at www.hpsj.com/medication-coverage-policies/ or www.hpsj.com/pharmacy. Please note that Medi-Cal FFS may require submission of a Treatment Authorization Request (TAR) to determine appropriateness of the treatment prior to coverage.**