MEDICATION COVERAGE POLICY

PHARMACY AND THERAPEUTICS ADVISORY COMMITTEE

Health Plan of San Joaquin

POLICY	Acute and Chronic Bowel Disease	**P&T DATE**	9/14/2021
THERAPEUTIC CLASS	Gastrointestinal Disorders	**REVIEW HISTORY** (MONTH/YEAR)	Previous Chronic Bowel Disease: 5/20, 5/19, 2/18, 2/17, 2/16, 2/15, 2/13 Previous Bowel Movements: 5/20, 9/19, 9/18, 12/16, 9/15, 9/12, 5/08
LOB AFFECTED	Medi-Cal		

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.

❖ PART 1: INFLAMMATORY BOWEL DISEASE OVERVIEW

Inflammatory bowel disease (IBD) is the chronic inflammation of a part (Ulcerative Colitis) or of an entire (Crohn's Disease) digestive tract. Although the exact etiology of IBD is unknown, effective management of IBD and its symptoms help in improving a patient's quality of life. Health Plan of San Joaquin has adopted the treatment goals and recommendations of the most recent practice guidelines from the American College of Gastroenterology (ACG) and National Institute for Health and Care Excellence (NICE) in the management of Ulcerative Colitis and Crohn's Disease.[1,2] The below criteria, limits, and requirements for certain agents are in place to ensure appropriate use of those agents and to help members towards induction and maintenance of remission of symptoms.

IBD Non-Biologic Agents Formulary Positioning: *(Current as of 6/2021)*

Therapeutic Class	Generic Name (Brand Name)	Available Strengths	Formulary Limits	Average Cost/Rx*	Notes
Oral Amino-salicylates	**Sulfasalazine (Azulfidine)** *Tablets*	IR: 500 mg	--	$19.03	
		DR: 500 mg		$28.84	
	Balsalazide (Colazol) *Capsules*	750 mg	--	$104.05	
	Mesalamine:				
	Apriso *Capsules*	ER: 0.375 mg	**PA; QL; FL**	--	Treatment failure or intolerance to Balsalazide, Sulfasalazine, or Mesalamine enema for 3 months for induction or maintenance. Max 120 capsules per 30 days, 6 fills per 180 days.
	Delzicol *Capsules*	DR: 400 mg	**PA**	--	Treatment failure or intolerance to Balsalazide, Sulfasalazine, or Mesalamine enema for 3 months for induction or maintenance.
	Pentasa *Capsules*	CR: 250 mg	**PA**	$523.57	Reserve for treatment failure or intolerance to Delzicol,or Apriso, for 3 months.
		CR: 500 mg		$856.26	
	Mesalamine (Lialda) *Tablets*	DR: 1.2 mg	**PA, QL**	$336.33	Reserve for treatment failure or intolerance to Delzicol,or Apriso, for 3 months. Max 120 tabs per 30 Days
	Mesalamine (Asacol HD) *Tablets*	DR: 800 mg	**PA; QL**	--	Reserve for treatment failure or intolerance to Delzicol,or Apriso, for 3 months. Max 120 tabs per 30 Days
	Olsalazine (Dipentum) *Capsules*	250 mg	**NF**	--	Alternatives: sulfasalazine, balsalazide
Topical Amino-salicylates	**Mesalamine** *Enema Solution*	4 GM/60 ml	--	--	

(Rowasa, Canasa)	**Mesalamine** *Suppository*	1000 mg	**PA**	$472.43	Reserved for patients unable to administer mesalamine enema.
Cortico-steroids	**Prednisone (Deltasone)** *Tablets, Solution*	1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 50 mg, 5mg/5ml	--	$169.72	
		5mg/ml	**NF**		Alternatives: Prednisone 5mg/5mL solution
	Budesonide:				
	Budesonide (Entocort)	Delayed release 3 mg capsules	**PA, QL, FL**	$89.30	Reserved for induction of remission in those intolerant to conventional glucocorticoids. Maximum of 3 months of induction therapy plus additional 1 month to taper off. 3 capsules of 3 mg per day dosing therefore update criteria for quantity to 90 capsules per month, 360 capsules per 365 days.
	Budesonide (Uceris)	Extended release 24-hour 9 mg tablets	**NF**	$1001.81	
	Budesonide (Uceris)	2 mg Rectal Foam	**NF**	$678.49	
Immuno-modulators	**6-Mercaptopurine**	50 mg	--	$44.70	
	Azathioprine (Azasan, Imuran)	50 mg	--	$14.60	
		75 mg	NF	--	Alternatives: Azathioprine 50 mg tablet
		100 mg	NF	--	

PA = Prior Authorization; ST = Step Therapy; NF = Non-Formulary; SP = Specialty Pharmacy; IR = Immediate Release; DR = Delayed Release; CR = Controlled Release; SR = Sustained Release * Based on pharmacy claims from 3/2018-2/2019 ^No claims, based on AWP price

Anti-inflammatory Biologic Agents Formulary Positioning: *(Current as of 6/2021)*

Therapeutic Class	Generic Name (Brand Name)	Available Strengths	Form. Limits	Estimated Cost per Month*	Notes
Tumor Necrosis Factor-α Blockers	**Infliximab-dyyb (Inflectra), Infliximab-abda (Renflexis)**	100 mg	**PA, SP**	--	Reserved for treatment failure to adequate trial or oral immunosuppressive agents, or for Cimzia: for women that are currently pregnant or breastfeeding. Must be initiated by a gastroenterologist. Restricted to specialty pharmacy.
	Adalimumab (Humira) *SQ injection*	40 mg/0.8 ml pen	**PA, SP**	$6,951.74	
		40 mg/0.8 ml syringe		--	
		40 mg/0.4 ml (CF)pen		$5,451.50	
	Certolizumab (Cimzia) *SQ injection* **(For Crohn's Disease only)**	400 mg	**PA, SP**	--	
	Golimumab (Simponi) *SQ injection* **(For Ulcerative Colitis only)**	100mg	**PA, SP**	$5,701.05	
	Infliximab (Remicade) *IV infusion*	100 mg	**NF**	--	Alternatives: Inflectra and Renflexis
	Tolfacitinib (Xeljanz)	5 mg	**PA, SP**	--	**(For Ulcerative Colitis only)**

Janus Associated Kinase Inhibitor	*Tablets*	10 mg	**PA, SP**	$4,897.83	Reserved for treatment failure or intolerance to TNF inhibitors Must be initiated by a gastroenterologist. Restricted to specialty pharmacy
		XR 11 mg	**NA**	--	
IL-12, IL-23 Inhibitor	**Ustekinumab (Stelara)** *SQ Syringe*	45 mg/0.5 ml	**PA, SP**	--	Must be initiated by a gastroenterologist. Restricted to specialty pharmacy **(For Crohn's Disease)** Reserved for treatment failure to Corticosteroids, Thiopurines, Methotrexate, and TNF inhibitors **(For Ulcerative Colitis)** Reserved for 18 years and older with moderate to severe ulcerative colitis with treatment failure to Mesalamine, Thiopurine, Cyclosporine, and TNF inhibitor
		90 mg/ml	**PA, SP**	$22,933.42	
Selective Adhesion Molecule Inhibitor	**Natalizumab (Tysabri)** *IV infusion*	300 mg	**PA, SP**	--	**(For Crohn's Disease only)** Reserved for patients with contraindication to **ALL** other agents. Restricted to specialty pharmacy. Must be initiated by a gastroenterologist.
	Vedolizumab (Entyvio) *IV infusion*	300 mg	**PA, SP**	--	Reserved for treatment failure or intolerance to TNF inhibitors. Restricted to specialty pharmacy. Must be initiated by a gastroenterologist.

**Based on pharmacy claims from 3/2020-2/2021*

❖ 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).

Oral Aminosalicylates

Sulfasalazine (Azulfidine); Balsalazide (Colazol)

Sulfasalazine (Azulfidine); Balsalazide (Colazol):

- ❒ **Coverage Criteria:** NONE
- ❒ **Limits:** NONE
- ❒ **Required Information for Approval:** NONE

Mesalamine (Pentasa, Delzicol, Apriso, Asacol HD, Lialda), Olsalazine (Dipentum)

Mesalamine (Apriso, Delzicol):

- ❒ **Coverage Criteria:**
  - Reserved Treatment failure or intolerance to Balsalazide, Sulfasalazine, or Mesalamine enema for 3 months for induction or maintenance.
- ❒ **Limits:**
  - **Apriso:**

- Quantity Limit: 120 capsules per 30 days
- Fill Limit: 6 fills per 180 days

❒ **Required Information for Approval:**
- History of fills for Balsalazide, Sulfasalazine, or Mesalamine enema for 3 months.

Mesalamine (Pentasa, Asacol HD, Lialda):

❒ **Coverage Criteria:**
- Reserve for treatment failure or intolerance to Delzicol, or Apriso, for 3 months.

❒ **Limits:**
- 120 capsules/tablets per 30 days

❒ **Required Information for Approval:**
- History of fills for Delzicol, or Apriso, for 3 months..

❒ **Not on Formulary:** Dipentum (Olsalazine)

Topical Aminosalicylates
Mesalamine Enema (Rowasa)

Mesalamine Enema (Rowasa):

❒ **Coverage Criteria:** NONE
❒ **Limits:** NONE
❒ **Required Information for Approval:** NONE

Mesalamine (Canasa)

Mesalamine (Canasa):

❒ **Coverage Criteria:** Canasa is reserved for patients unable to administer mesalamine enema.
❒ **Limits:** NONE
❒ **Required Information for Approval:** Documented inability to administer Mesalamine enema

Corticosteroids
Prednisone (Deltasone)

Prednisone (Deltasone):

❒ **Coverage Criteria:** NONE
❒ **Limits:** NONE
❒ **Required Information for Approval:** NONE
❒ **Not on Formulary:** Prednisone 5 mg/mL solution

Budesonide (Entocort EC, Uceris)

Budesonide (Entocort EC):

❒ **Coverage Criteria:**
- **Entocort EC** is reserved for induction of remission in those intolerant to conventional glucocorticoids.

❒ **Limits:** 90 capsules per month, 360 capsules per 365 days, maximum of 4 months.
❒ **Required Information for Approval:**
- Documented intolerance to conventional glucocorticoids

❒ **Not on Formulary:** Uceris Tablets and rectal foam

Immunomodulators
6-Mercaptopurine, Azathioprine (Azasan, Imuran)

6-Mercaptopurine, Azathioprine (Imuran):

❒ **Coverage Criteria:** NONE
❒ **Limits:** NONE
❒ **Required Information for Approval:** NONE
❒ **Not on Formulary:** Azasan 75mg and 100mg tablets

Tumor Necrosis Factor α Blockers
Infliximab-abda (Renflexis),Infliximab-dyyb (Inflectra), Adalimumab (Humira), Adalimumab (Cyltezo), Certolizumab Pegol (Cimzia), Golimumab (Simponi)

Infliximab-abda (Renflexis),Infliximab-dyyb (Inflectra), Adalimumab (Humira), Certolizumab Pegol (Cimzia), Golimumab (Simponi):

- ❒ **Coverage Criteria:**
  - **Inflectra/Renflexis/Humira:**
    - Reserved for treatment failure to adequate trial of oral immunosuppressive agents (Azathioprine, Mercaptopurine, Mesalamine, and Sulfasalazine) OR intolerance to corticosteroids.
  - **Cimzia:** Reserved for treatment of Crohn's disease and must meet one of the following:
    - [1] Reserved for treatment failure to adequate trial of oral immunosuppressive agents (Azathioprine, Mercaptopurine, Mesalamine, and Sulfasalazine) OR intolerance to corticosteroids OR
    - [2] women that are currently pregnant or breastfeeding.
  - **Simponi:** Reserved for the treatment of Ulcerative colitis.
    - Reserved for treatment failure to adequate trial of oral immunosuppressive agents (Azathioprine, Mercaptopurine, Mesalamine, and Sulfasalazine) OR intolerance to corticosteroids.
- ❒ **Limits:** Must be prescribed by a gastroenterologist. Restrict to Specialty Pharmacy.
- ❒ **Other Notes:** Medication is to be dispensed by HPSJ's designated specialty pharmacy. Biologics exceeding labeled standard maintenance doses may be approved 1 month at a time. Subsequent fills of the increased maintenance dose will require documentation of symptom improvement.
- ❒ **Not on Formulary:** Remicade, Adalimumab (Cyltezo)

Selective Adhesion Molecule Inhibitor
Natalizumab (Tysabri), Vedolizumab (Entyvio)

Natalizumab (Tysabri):

- ❒ **Coverage Criteria:** *(for the treatment of Crohn's disease)* Reserved for patients with contraindication to ALL other agents.
- ❒ **Limits:** NONE
- ❒ **Required Information for Approval:** Documentation showing contraindication to ALL other agents and a negative anti-JCV antibody detection test result.
  - Must be initiated by a gastroenterologist.
- ❒ **Notes:** Not restricted to Specialty Pharmacy because Natalizumab is a limited distribution drug. Biologics exceeding labeled standard maintenance doses may be approved 1 month at a time. Subsequent fills of the increased maintenance dose will require documentation of symptom improvement.

Vedolizumab (Entyvio):

- ❒ **Coverage Criteria:** Reserved for treatment of Ulcerative Colitis or Crohn's disease with treatment failure or intolerance to one TNF inhibitor for 2 months.
- ❒ **Limits:** NONE
- ❒ **Required Information for Approval:** Documentation showing fill history or documentation of treatment failure or intolerance to TNF inhibitors.
  Must be initiated by a gastroenterologist.

Janus Associated Kinase Inhibitor
Tofacitinib (Xeljanz)

Tofacitinib (Xeljanz):

- ❒ **Coverage Criteria:***(for the treatment of Ulcerative Colitis)* Reserved for treatment failure or intolerance to TNF inhibitors.
- ❒ **Limits:** NONE
- ❒ **Required Information for Approval:** Fill history or documentation of treatment failure or intolerance to TNF inhibitors.
- ❒ **Notes:** Restricted to specialty pharmacy

IL-12, IL-23 Inhibitor
Ustekinumab (Stelara)

Ustekinumab (Stelara):

For the treatment of Crohn's Disease

- ❒ **Coverage Criteria***:* Reserved for treatment failure to Corticosteroids, Thiopurines, Methotrexate, and TNF inhibitors.
- ❒ **Limits:** NONE

- ❒ **Required Information for Approval:** Fill history or documentation of treatment failure to Corticosteroids, Thiopurines, Methotrexate, and TNF inhibitors.
- ❒ **Notes:** Must be prescribed by gastroenterologist. Restricted to specialty pharmacy**.** Biologics exceeding labeled standard maintenance doses may be approved 1 month at a time. Subsequent fills of the increased maintenance dose will require documentation of symptom improvement

For the treatment of Ulcerative Colitis:

- ❒ **Coverage Criteria:** Reserved for treatment failure to Mesalamine, Thiopurine, Cyclosporine, and TNF inhibitor
- ❒ **Limits:** NONE
- ❒ **Required Information for Approval:** Documented diagnosis of moderate to severe ulcerative colitis and fill history or documentation of treatment failure to Mesalamine, Thiopurine, Cyclosporine, and TNF inhibitor
- ❒ **Notes:** Must be prescribed by gastroenterologist. Restricted to specialty pharmacy**.** Biologics exceeding labeled standard maintenance doses may be approved 1 month at a time. Subsequent fills of the increased maintenance dose will require documentation of symptom improvement

❖ CLINICAL JUSTIFICATION

American College of Gastroenterology (ACG) and NICE guidelines states 5-ASA effectiveness in irritable bowel disease. Both oral and rectal 5-ASA have are used in mild to moderately active disease states, with combination of oral and rectal therapy resulting in better outcome than with monotherapy. Oral corticosteroids should be used in short term induction therapy due to systemic effects associated with long term use. Although Budesonide is formulated to target ileal area of the colon, given its low bioavailability and efficacy, budesonide is reserved for patients with disease involving ilea area who are intolerant to conventional oral corticosteroid therapy. Immunomodulators and biologics are reserved for moderate to severe disease states due to systemic effects on immune system.

The 2019 ACG Clinical Guideline for Ulcerative Colitis in Adults recommends vedolizumab for induction of remission with moderate to severely active UC in patients who have previously failed anti-TNF therapy. The 2018 ACG Clinical Guideline for Management of Crohn's Disease in Adults indicates that for patients with moderately to severely active CD and objective evidence of active disease, anti-integrin therapy (with vedolizumab) with or without an immunomodulator is more effective than placebo and should be considered to be used for induction of symptomatic remission in patients with Crohn's disease.

The American Gastroenterological Association released a report for Inflammatory Bowel Disease in Pregnancy in 2019 that indicates aminosalicylates, biologics, or immunomodulator therapies may be continued during pregnancy and through delivery.[38] The guidelines indicate while most biologics, aside from certolizumab, actively cross the placenta, safety data from prospective trials and large nationwide cohorts of women who continued taking biologics in pregnancy have not shown an increase in adverse fetal outcomes.[38] Per the package insert, certolizumab pegol concentrations were minimal/undetectable in multiple samples of infant plasma and in breast milk. Providers who place greater importance for known safety profiles for pregnant and breastfeeding patients may preference biologic therapy. Hence, patients that are pregnant or currently breastfeeding and have a clinical indication for Cimzia treatment can bypass usual step therapy requirements for Cimzia treatment.[28-37]

PART 2: IRRITABLE BOWEL SYNDROME, CONSTIPATION & DIARRHEA OVERVIEW

Inflammatory bowel syndrome (IBS) is a common disorder of bowel function that causes change in bowel habits resulting in either constipation (IBS-C) or diarrhea (IBS-D), along with symptoms such as abdominal pain, bloating, and other non-intestinal symptoms. Although the exact etiology of IBS is unknown, effective management of IBS

and its symptoms help in improving a patient's quality of life. Health Plan of San Joaquin has adopted the treatment goals and recommendations of the most recent practice guidelines from the American Gastroenterological Association (AGA) and The National Institute for Health Care and Excellence Guidelines (NICE) in the management of IBS-C and IBS-D.[1,2,12] The below criteria, limits, and requirements for certain agents are in place to ensure appropriate use of those agents.

Constipation affects approximately about -12 million Americans.[25] Many of the people with chronic constipation are on pain medication worsening constipation. Basic effects of opioid induced constipation is mechanically different from other forms of constipation.
Acute diarrhea can be defined as the passage of a greater number of stools of decreased form from the normal lasting less than 14 days, while persistent diarrhea is defined as diarrhea lasting between 14 and 30 days and chronic diarrhea lasts for greater than 30 days. Diarrhea can be caused by a number of factors, including infection. Acute diarrheal infection (also called gastroenteritis) is a leading cause of outpatient visits, hospitalizations, and lost quality of life occurring in both domestic settings and among travelers. According to the American College of Gastroenterology, use of antibiotics for community-acquired diarrhea should be discouraged as most cases are viral in origin & not shortened with antibiotics.[15]
Prescription & OTC constipation and diarrhea medications are used to relieve symptoms and/or regulate bowel movements. While there are many available agents to relieve constipation and diarrhea, non-pharmacologic recommendations should be incorporated into every patient care plan. The purpose of this coverage policy is to review HPSJ's coverage criteria of constipation and diarrhea agents.

IRRITABLE BOWEL SYNDROME, CONSTIPATION & DIARRHEA Agents Formulary Positioning:

Drug	Available Strengths	Formulary Limit	Average Cost/Rx*	Notes
Bulk Forming				
Psyllium Husk with Sugar (Metamucil, Natural Fiber, Konsyl)	3.4 gram/7 gram powder	--	$7.48	
	3.4 gram oral powder packet	NF	--	
Psyllium Husk with Aspartame (Metamucil Fiber)	3.4 gram/5.8 gram powder	--	$12.94	
	3.4 gram oral powder packet	NF	--	
Psyllium Seed (Reguloid, Hydrocil Instant)	Reguloid Laxative Powder	--	$3.05	
	Hydrocil Instant Packet	NF-	--	
Psyllium Seed with Dextrose (Natural Fiber Lax, Fiber Smooth, Konsyl-D, Natural Vegetable Laxative Powder)	Fiber oral powder	--	$6.34	
	Metamucil Fiber Wafer 2.5 gram oral Wafer	--	--	
Osmotic				
Polyethylene Glycol 3350 (Miralax, Clearlax, Purelak, Gavilax, Smoothlax)	17gram/dose oral powder jar	QL	$10.24	Limited to 1054 grams per 30 days.
	17g/dose oral powder packet	NF	$27.74	
Peg 3350/Na Sulf/ Bicarb/Cl/KCl (Gavilyte, Golytely, Colyte)	Gavilyte-C 240 gram-22.72 gram-6.72 gram-5.84 gram oral solution	--	$10.67	
	Gavilyte-G 236 gram-22.74 gram-6.74 gram-5.86 gram oral solution	--	$11.50	
	PEG 3350 and ELS	--	--	
	Golytely 236 gram-22.74 gram-6.74 gram-5.86 gram oral solution	NF	--	
	Golytely 227.1 gram-21.5 gram-6.36 gram oral packet	NF	--	
Sodium chloride/ NaHCO3/KCl/Peg (Trilyte, Gavilyte-N, Nulytely)	Trilyte With Flavor Packets 420 gram oral solution	--	$14.40	
	PEG 3350 and ELS	--	--	

	Gavilyte-N 420 gram solution	NF	--	
	Nulytely With Flavor Packets	NF	--	
Sodium/Potassium/Mag Sulfates (Suprep Bowel Prep)	Suprep Bowel Prep Kit 17.5-3.13 gram oral solution	NF	$107.03	
Magnesium Hydroxide (Milk of Magnesia)	400mg/5mL suspension	--	$3.24	
Magnesium Citrate (Citroma)	1.745g/30mL solution (296mL Bottle)	--	$1.71	
Glycerin (Fleet Pedia-Lax, Sani-Supp)	Adult rectal suppository	--	$1.25	
	Child rectal suppository	--	$3.04	
	Fleet Glycerin 5.4 gram/5.4 mL liquid rectal suppository	NF	--	
	Pedia-Lax 2.8 gram/2.7 mL rectal solution	NF	--	
Stool Softener				
Sennosides/Docusate Sodium (Senna S, Senna Plus)	8.6mg/50mg tablet	--	$1.16	
Cathartic				
Sodium Phosphates (Fleet Enema Extra, OsmoPrep Tablet)	7.2 gram-2.7 gram/15 mL oral liquid	NF	--	
	19 gram-7 gram/197 mL enema	NF	--	
	OsmoPrep tablet	NF	--	
Antidiarrheals				
Bismuth subsalicylate (Pepto-Bismol, Bismatrol, Kao-Tin)	262 mg chewable tablet	--	$6.23	
	262 mg tablet	--	$6.58	
	262 mg/15 ml oral suspension	--	$4.81	
	525 mg/15 ml oral suspension	--	$4.43	
Diphenoxylate HCl/Atropine (Lomotil)	2.5 mg-0.025 mg liquid	NF	$71.40	
	2.5 mg-0.025 mg tablet	--	$14.63	
Loperamide (Imodium)	2 mg capsule	--	$4.66	
	2 mg tablet		$3.71	
	1 mg/5 ml oral solution		--	
	1 mg/7.5 ml oral solution		$3.60	
Opium Tincture	10 mg/ml tincture	NF	$667.99	
Antispasmodics				
Dicyclomine (Bentyl)	10 mg capsule	--	$7.00	
	10 mg /5 mL solution		$20.88	
	20 mg tablet		$11.50	
Hyoscyamine (Anaspaz, Cystospaz, Levsin)	0.125 mg ODT	--	$30.99	
	0.125 mg tablet SL		$5.40	
	0.375 mg ER tablet		$44.55	
	0.125 mg tablet		$11.03	
	125 mcg/5 mL elixir		--	
	0.125 mg/mL drop	AL	--	Restrict use to children and infants < 2 years old only.
Tricyclic Antidepressants				
Amitriptyline (Elavil)	10 mg tablet	--	$2.41	Avoid use in members over 65 years old.
	25 mg tablet		$3.46	
	50 mg tablet		$7.75	
	75 mg tablet		$12.18	
	100 mg tablet		$14.97	
	150 mg tablet		$25.97	
Clomipramine (Anafranil)	25 mg capsule	NF	$153.57	

	50 mg capsule		$109.37	
	75 mg capsule		$195.65	
Desipramine (Norpramin)	10 mg tablet	--	$12.77	
	25 mg tablet		$19.17	
	50 mg tablet		$33.31	
	75 mg tablet		--	
	100 mg tablet		$16.50	
	150 mg tablet		--	
Doxepin (Sinquan)	Silenor 3 mg tablet	NF	--	
	Silenor 6 mg tablet		--	
	10 mg/5 ml solution	--	$3.68	
	10 mg capsule		$13.33	
	25 mg capsule		$14.28	
	50 mg capsule		$17.44	
	75 mg capsule		$34.39	
	100 mg capsule		$29.76	
	150 mg capsule		$19.32	
Imipramine (Tofranil)	10 mg tablet	--	$2.09	
	25 mg tablet		$4.29	
	50 mg tablet		$4.86	
Nortriptyline (Pamelor)	10 mg/5 ml oral concentrate	--	$94.40	
	10 mg capsule		$4.09	
	25 mg capsule		$4.45	
	50 mg capsule		$5.18	
	75 mg capsule		$7.77	
Trimipramine	25 mg capsule	NF	--	
	50 mg capsule			
	100 mg capsule			
Chloride Channel Activator				
Lubiprostone (Amitiza)	8 mcg capsule	PA; QL	$378.52	Reserved for women 18 year and older who have failed treatment with linaclotide (Linzess) or naloxegol (Movantik). Patient must have also failed regularly scheduled, dose optimized polyethylene glycol (Miralax), AND two of the following: bisacodyl, Senna, psyllium, magnesium citrate or hydroxide. Restricted to 60 capsules per 30 days.
	24 mcg capsule	PA; QL	$344.96	
Guanylate Cyclase-C Agonist				
Linaclotide (Linzess)	72 mcg capsule	PA; QL	$399.97	Linzess is reserved for patients with treatment failure of properly titrated and regularly scheduled dosing of polyethylene glycol for 2 months (as evidenced by prescription history fills) AND two of the following: bisacodyl, Senna, psyllium, magnesium citrate or hydroxide. Restricted to 30 capsules per 30 days.
	145mcg capsule	PA; QL	$398.29	
	290 mcg capsule	PA;QL	$423.95	
Plecanatide (Trulance)	3 mg tablets	NF	$446.56	
5-HT3 Antagonist				
Alosetron (Lotronex)	0.5 mg tablet	NF	--	
	1 mg tablet			
5-HT4 Receptor Agonist				
Prucalopride (Motegrity)	1 mg tablet	PA	--	Reserved for patients with Idiopathic Chronic Constipation, with treatment failure of properly titrated and regularly scheduled dosing of polyethylene glycol for 2
	2 mg tablet			

				months (as evidenced by prescription history fills) AND two of the following: bisacodyl, Senna, psyllium, magnesium citrate or hydroxide.
Tegaserod (Zelnorm)	2 mg tablet 6 mg tablet	NF	--	
Mixed Mu-Opioid Receptor Agonist, Delta Opioid Receptor Antagonist, And Kappa Opioid Receptor Agonist				
Eluxadoline (Viberzi)	75 mg tablets 100 mg tablets	ST	-- $1,410.92	Step therapy to tricyclic antidepressants.
Peripherally acting Opioid Antagonist				
Methylnaltrexone (Relistor)	8 mg/0.4 mL subcutaneous solution	NF	--	
	12 mg/0.6 mL subcutaneous solution	NF	--	
	150 mg tablet	NF	$1,967.69	
Naldemedine (Symproic)	0.2 mg tablet	PA	$394.27	Reserved for patients with opioid-induced constipation with chronic non-cancer pain and treatment failure of dose-optimized, regularly scheduled polyethylene glycol for 2 months (as evidenced by prescription history fills) AND two of the following: bisacodyl, Senna, magnesium citrate or hydroxide.
Naloxegol (Movantik)	12.5 mg tablet	PA	$373.32	Reserved for patients with opioid-induced constipation with chronic non-cancer pain and treatment failure of dose-optimized, regularly scheduled polyethylene glycol for 2 months (as evidenced by prescription history fills) AND two of the following: bisacodyl, Senna, lactulose, magnesium citrate or hydroxide.
	25 mg tablet	PA	$390.09	
Prokinetic				
Metoclopramide (Reglan)	5 mg/5 mL solution	--	$8.77	
	5 mg tablet	--	$1.98	
	10 mg tablet	--	$1.90	
Antibiotics				
Rifaximin (Xifaxan)	550 mg tablet	PA; QL; FL	$2,408.25	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 one TCA for use in abdominal pain relief. For HE: Xifaxan is reserved for treatment failure of compliant use of lactulose evidenced by consistent lactulose fills.

**Cost per Rx based on HPSJ utilization historical data from March 2019 through February 2020*

❖ 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).

Bulk Forming Laxative

Psyllium Husk with Sugar (powder), Psyllium Husk with Aspartame (powder), Psyllium Seed (powder), Psyllium Seed with Dextrose (powder, wafer)

- ❒ **Coverage Criteria:** None
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** N/A
- ❒ **Other Notes:** None
- ❒ **Non-Formulary:** Psyllium Husk with Aspartame (packet), Psyllium Husk with Sugar (packet), Psyllium Seed (packet)

Osmotic Laxative

Polyethylene Glycol 3350 (powder jar), Peg 3350/Na Sulf/ Bicarb/Cl/KCl (Gavilyte-C, Gavilyte-G, Sodium chloride/ NaHCO3/KCl/Peg (Trilyte), Lactulose, Magnesium oxide (400 mg tablet), Magnesium hydroxide, Magnesium citrate, Glycerin (Adult and Child suppository)

Polyethylene Glycol 3350 (powder jar)

- ❒ **Coverage Criteria:** None
- ❒ **Limits:** 1054g per 30 days
- ❒ **Required Information for Approval:** N/A
- ❒ **Other Notes:** None
- ❒ **Non-Formulary:** Polyethylene Glycol 3350 (powder packet)

Peg 3350/Na Sulf/ Bicarb/Cl/KCl (Gavilyte-C, Gavilyte-G, Sodium chloride/ NaHCO3/KCl/Peg (Trilyte), Lactulose (solution), Magnesium oxide (400 mg tablet), Magnesium hydroxide, Magnesium citrate, Glycerin (Adult and Child suppository)

- ❒ **Coverage Criteria:** None
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** N/A
- ❒ **Other Notes:** None
- ❒ **Non-Formulary:** Polyethylene Glycol 3350 (oral solution), Golytely (solution, powder packet), Gavilyte-N, Nulytely, Suprep Bowel Prep Kit, Prepopik Powder Packet, Moviprep, OsmoPrep, Suprep

Stool Softners, Stimulants

Docusate Sodium, Sennosides/Docusate Sodium (Senna S, Senna Plus), Bisacodyl, Sennosides

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

Chloride Channel Activators

Linaclotide, Lubiprostone

Linaclotide (Linzess)

- ❒ **Coverage Criteria:** Linzess is reserved for patients with treatment failure of properly titrated and regularly scheduled dosing of polyethylene glycol for 2 months (as evidenced by prescription history fills) AND two of the following: bisacodyl, Senna, psyllium, magnesium citrate or hydroxide.
- ❒ **Limits:** Limited to 30 capsules per 30 days.
- ❒ **Required Information for Approval:** Proper chart note documentation and pharmacy fill history of at least 2 months of regularly scheduled Miralax, and of two other formulary alternatives.

Lubiprostone (Amitiza)

- ❒ **Coverage Criteria:** Lubiprostone (Amitiza) is reserved for women 18 year and older who have failed treatment with linaclotide (Linzess) or naloxegol (Movantik). Patient must have also failed regularly scheduled, dose optimized polyethylene glycol (Miralax), AND two of the following: bisacodyl, Senna, psyllium, magnesium citrate or hydroxide
- ❒ **Limits:** Limited to 60 capsules per fill
- ❒ **Required Information for Approval:** Proper chart note documentation and pharmacy fill history of at least 2 months of regularly scheduled Miralax AND Linzess or Movantik, in addition to two other formulary alternatives described in the coverage criteria.

Peripherally Acting Opioid Antagonists

Methylnaltrexone (Relistor), Naldemedine (Symproic), Naloxegol (Movantik)

Naldemedine (Symproic):

- ❒ **Coverage Criteria:** Reserved for patients with opioid-induced constipation with chronic non-cancer pain and treatment failure of dose-optimized, regularly scheduled polyethylene glycol for 2 months (as evidenced by prescription history fills) AND two of the following: bisacodyl, Senna, magnesium citrate or hydroxide.
- ❒ **Limits:** 30 capsules per 30 day.
- ❒ **Required Information for Approval:** Chart note documentation of adequate trials of of properly titrated and regularly scheduled dosing of polyethylene glycol for 2 months (as evidenced by prescription history fills) AND two of the following: bisacodyl, Senna, psyllium, magnesium citrate or hydroxide.
- ❒ **Non-Formulary:** Methylnaltrexone (Relistor)

Naloxegol (Movantik)

- ❒ **Coverage Criteria:** Reserved for patients with opioid-induced constipation with chronic non-cancer pain and treatment failure of dose-optimized, regularly scheduled polyethylene glycol for 2 months (as evidenced by prescription history fills) AND two of the following: bisacodyl, Senna, lactulose, magnesium citrate or hydroxide.
- ❒ **Limits:** 30 day supply.
- ❒ **Required Information for Approval:** Proper chart note documentation and pharmacy fill history of of dose-optimized, regularly scheduled polyethylene glycol for 2 months (as evidenced by prescription history fills) AND two of the following: bisacodyl, Senna, lactulose, magnesium citrate or hydroxide.

5-HT$_4$ Receptor Agonist

Prucalopride (Motegrity)

Prucalopride (Motegrity):

- ❒ **Coverage Criteria:** Reserved for patients with Idiopathic Chronic Constipation, with treatment failure of properly titrated and regularly scheduled dosing of polyethylene glycol for 2 months (as evidenced by prescription history fills) AND two of the following: bisacodyl, Senna, psyllium, magnesium citrate or hydroxide**.**
- ❒ **Limits:** Restricted to 30 capsules per 30 days
- ❒ **Required Information for Approval:** Chart note documentation of adequate trials of of properly titrated and regularly scheduled dosing of polyethylene glycol for 2 months (as evidenced by prescription history fills) AND two of the following: bisacodyl, Senna, psyllium, magnesium citrate or hydroxide.

Antimotility

Loperamide

Loperamide

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

Antidiarheal

Bismuth subsalicylate

Bismuth subsalicylate

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

Antispasmodics

Dicyclomine, Hyoscyamine

Dicyclomine

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

Hyoscyamine

- ❒ **Coverage Criteria:** None

- ❒ **Limits:** Hyoscyamine 0.125 mg/mL drop: Restrict use to children and infants < 2 years old only.
- ❒ **Required Information for Approval:** N/A

Tricyclic Antidepressants

Amitriptyline (Elavil); Nortriptyline (Pamelor); Imipramine (Tofranil); Desipramine (Norpramine); Doxepin (Sinquan) capsules, solution

- ❒ **Coverage Criteria:** None
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** N/A
- ❒ **Other Notes:** None
- ❒ **Non-Formulary:** Clomipramine, Doxepin (Silenor) tablets, Trimipramine

Antibiotic

Rifaximin (Xifaxan)

- ❒ **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 tricyclic antidepressant (e.g. amitriptyline, nortriptyline) for use in abdominal pain relief.
- ❒ **Limits:**
  - For IBS-D
    - Quantity limit: Restricted to 42 tablets per 14 days.
    - Fill limit: Restricted to 3 fills per 365 days.
  - For Hepatic encephalopathy
    - Quantity limit: Restricted to 60 tablets per 30 days.
- ❒ **Required Information for Approval:** Proper chart note documentation and pharmacy fill history of at least one TCA for use in abdominal pain relief for use in IBS-D.

Prokinetic Agents

Metoclopramide (Reglan)

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

Mixed Mu-Opioid Receptor Agonist, Delta Opioid Receptor Antagonist, Kappa Opioid Receptor Agonist

Eluxadoline (Viberzi)

- ❒ **Coverage Criteria:**
  - For use in IBS-D, Viberzi is step therapy for patients who have failed treatment with at least one tricyclic antidepressant (e.g. amitriptyline, nortriptyline) within their previous treatment history.
- ❒ **Limits:**
  - Quantity limit: Restricted to 60 tablets per 30 days.
- ❒ **Required Information for Approval:** Proper chart note documentation and pharmacy fill history of at least one TCA for use in abdominal pain relief for use in IBS-D.

❖ CLINICAL JUSTIFICATION

HPSJ policy is based on current and updated clinical and practice guidelines. According to ACG 2018 IBS treatment monograph recommends exercise, diet and dietary manipulation to improve overall symptoms of IBS. Updated systemic review and meta-analysis on fiber showed statistically significant improvement in fiber compare to placebo. Polyethylene glycol, Tricyclic antidepressants and loperamide improve diarrhea symptoms as well. SSRIs are now recommended to improve constipation in IBS-D. Tegaserod (Zelnorm) has been reintroduced for emergency treatment of IBS-C and chronic idiopathic constipation (CIC) in women (<55 years of age) in which no alternative therapy exists. Tegaserod (Zelnorm) is only available through emergency- investigational new drug (IND) process.

Bowel regimens can be divided into two categories of drugs: agents with active mechanism, such as bisacodyl, magnesium oxide, and lubiprostone; and those with passive mechanisms, such as psyllium husk and docusate. The HPSJ formulary is structured to favor fiber and laxatives due to recommendations from the American Gastroenterological Association (AGA).[14] Medications from multiple categories can be combined for patients with inadequate relief from one agent. The whole therapeutic picture should be addressed when treating constipation; calcium channel blockers, opiates, and inadequate management of diabetes (due to dehydration) can exacerbate the condition. Patients should maintain adequate hydration, eat fibrous foods, and exercise regularly to ensure the highest level of effectiveness.

Diarrhea can be treated with symptomatic therapy, such as loperamide, diphenoxylate, or bismuth subsalicylate. If the diarrhea has an infectious cause, antibiotics such as azithromycin, fluoroquinolones, and rifaximin can be used depending on presentation of symptoms or location of where the patient traveled. According to the American College of Gastroenterology (ACG)[15] and Infectious Diseases Society of America (IDSA),[16] the most useful antimotility agent is loperamide. Due to extrapyramidal effects, agents such as Metoclopramide should be limited.

The 2021 ACG Clinical Guideline for the Management of Irritable Bowel Syndrome[27] indicate that loperamide is not recommended as first-line therapy for treating IBS-D symptoms because it may improve diarrhea but not improve global IBS symptoms. The guidelines further indicate that eluxadoline (Viberzi) improves global IBS-D symptoms in men and women, and analyses have also shown that eluxadoline improves symptoms in patients with IBS-D who have failed previous trials of loperamide. Finally, the 2021 guidelines recommend against the use of antispasmodics currently available in the United States to treat global IBS symptoms due to limited data supporting their use, with existing data being decades-old, of poor quality, or methodologically limited.

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❖ REVIEW & EDIT HISTORY

Document Changes	Reference	Date	P&T Chairman
Creation of Policy	Amitiza and Laxatives 5-08.doc	5/2008	Allen Shek, PharmD BCPS
Updated Policy	Formulary Realignment 9-18-12.xlsx	9/2012	Allen Shek, PharmD BCPS
Creation of Policy	Biologics Class Review for Crohns 2013-2-19.docx	2/2013	Allen Shek, PharmD
Update to Policy	IBD Class Review 2-17-15.docx	2/2015	Jonathan Szkotak, PharmD
Updated Policy	HPSJ Coverage Policy - Gastrointestinal - Constipation 2015-05.docx	9/2015	Jonathan Szkotak, PharmD BCACP
Update to Policy	Class Review- Biologics, Apremilast, and Tofacitinib in Inflammatory Joint, Skin, and Bowel Diseases.docx	2/2016	Johnathan Yeh, PharmD
Updated Policy	HPSJ Coverage Policy - Gastrointestinal - Constipation 2016-12.docx	12/2016	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Gastrointestinal – Chronic Bowel Disease 2017-02.docx	2/2017	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Gastrointestinal – Chronic Bowel Disease 2018-02.docx	2/2018	Johnathan Yeh, PharmD
Updated Policy	HPSJ Coverage Policy - Gastrointestinal - Constipation 2018-09b.docx	09/2018	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Gastrointestinal – Chronic Bowel Disease 2019-05.docx	5/2019	Matthew Garrett, PharmD
Combined Policy	HPSJ Coverage Policy – Gastrointestinal – Acute and Chronic Bowel Disease 2020-05.docx	5/2020	Matthew Garrett, PharmD
Update to Policy	Acute and Chronic Bowel Disease	9/2021	Matthew Garrett, PharmD

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