BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

PANCREATIC ENZYME REPLACEMENT THERAPIES:
CREON® (pancrelipase)
PANCREAZE® (pancrelipase)
PERTZYE® (pancrelipase)
VIOKACE® (pancrelipase)
ZENPEP® (pancrelipase)
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

CREON® (pancrelipase lipase-protease-amylase) DR
PANCREAZE® (pancrelipase lipase-protease-amylase) DR
PERTZYE® (pancrelipase lipase-protease-amylase) DR
ZENPEP® (pancrelipase lipase-protease-amylase) DR

ORIGINAL EFFECTIVE DATE: 02/15/2024 | ARCHIVE DATE: | LAST REVIEW DATE: 02/20/2025 | LAST CRITERIA REVISION DATE:

PHARMACY COVERAGE GUIDELINE

PANCREATIC ENZYME REPLACEMENT THERAPIES:

- **Criteria for initial therapy:** Creon (pancrelipase), Pancreaze (pancrelipase), Pertzye (pancrelipase), Zenpep (pancrelipase), and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist or Pulmonologist

2. Age of individual is consistent with the FDA approved product labeling

3. Individual has a diagnosis of exocrine pancreatic insufficiency (EPI) confirmed by **ONE** of the following:
    a. Cystic fibrosis with suspected or known EPI
    b. Chronic pancreatitis, pancreatectomy or other known condition associated with EPI (see Definitions section) with at least **FOUR** of the following signs and symptoms:
        i. Post-prandial abdominal pain or cramping
        ii. Bloating
        iii. Excessive flatulence
        iv. Greasy stools or steatorrhea
        v. Frequent loose stools
        vi. Unexplained weight loss
        vii. Deficiency in fat soluble vitamins (i.e., A, D, E, and K)
    c. No established condition associated with EPI with **BOTH** of the following:
        i. Results of pancreatic function test is consistent with EPI (e.g., Fecal elastase-1, Fecal chymotrypsin, serum trypsinogen, secretin stimulation test, etc.)
        ii. At least **FOUR** of the following signs and symptoms:
            1. Post-prandial abdominal pain or cramping
            2. Bloating
            3. Excessive flatulence
            4. Greasy stools or steatorrhea
            5. Frequent loose stools
            6. Unexplained weight loss
            7. Deficiency in fat soluble vitamins (i.e., A, D, E, and K)

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. **For PANCREAZE, PERTZYE**: Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **BOTH** the following:
    a. Creon
    b. Zenpep

6. Other causes of chronic diarrhea, bloating, excessive flatulence and steatorrhea have been ruled out (e.g., small intestinal bacterial overgrowth, celiac disease, giardiasis, etc.)

7. Individual is not currently taking any other pancreatic enzyme replacement therapy (e.g., Creon, Pancreaze, Pertzye, Viokace, Zenpep)

Initial approval duration: 6 months

PHARMACY COVERAGE GUIDELINE

PANCREATIC ENZYME REPLACEMENT THERAPIES:

- **Criteria for continuation of coverage (renewal request):** Creon (pancrelipase), Pancreaze (pancrelipase) Pertzye (pancrelipase), Zenpep (pancrelipase), and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist or Pulmonologist

  2. Individual's condition has responded while on therapy with response defined as **TWO** of the following:
     a. Decrease in abdominal pain or cramping
     b. Decrease in diarrhea (i.e., improved stool consistency)
     c. Resolution in fatty stools or steatorrhea
     d. Weight gain
     e. Improvement in fat soluble vitamin deficiencies

  3. Individual has been adherent with the medication

  4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

  5. Individual has not developed any significant adverse drug effects that may exclude continued use such as: fibrosing colonopathy

  6. Individual is not currently taking any other pancreatic enzyme replacement therapy (e.g., Creon, Pancreaze, Pertzye, Viokace, Zenpep)

  Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-Cancer Medications**

  2. **Off-Label Use of Cancer Medications**

VIOKACE® (pancrelipase lipase-protease-amylase)

- **Criteria for initial therapy:** Viokace (pancrelipase) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist

  2. Individual is 18 years of age or older

3. Individual has a diagnosis of exocrine pancreatic insufficiency (EPI) with chronic pancreatitis or pancreatectomy with **FOUR** of the following:
    a. Post-prandial abdominal pain or cramping
    b. Bloating
    c. Excessive flatulence
    d. Greasy stools or steatorrhea
    e. Frequent loose stools
    f. Unexplained weight loss
    g. Deficiency in fat soluble vitamins (i.e., A, D, E, and K)

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **BOTH** the following:
    a. Creon
    b. Zenpep

6. Will be used in combination with a proton pump inhibitor (e.g., omeprazole, pantoprazole, lansoprazole, esomeprazole, etc.)

7. Other causes of chronic diarrhea, bloating, excessive flatulence and steatorrhea have been ruled out (e.g., small intestinal bacterial overgrowth, celiac disease, giardiasis, etc.)

8. Individual is not currently taking any other pancreatic enzyme replacement therapy (e.g., Creon, Pancreaze, Pertzye, or Zenpep)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Viokace (pancrelipase) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist

2. Individual's condition has responded while on therapy with response defined as **TWO** of the following:
    a. Decrease in abdominal pain or cramping
    b. Decrease in diarrhea (i.e., improved stool consistency)
    c. Resolution in fatty stools or steatorrhea
    d. Weight gain
    e. Improvement in fat soluble vitamin deficiencies

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Will be used in combination with a proton pump inhibitor (e.g., omeprazole, pantoprazole, lansoprazole, esomeprazole, etc.)

6. Individual has not developed any significant adverse drug effects that may exclude continued use such as fibrosing colonopathy

7. Individual is not currently taking any other pancreatic enzyme replacement therapy (e.g., Creon, Pancreaze, Pertzye, Zenpep)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Exocrine pancreatic insufficiency (EPI) is defined as inadequate activity or deficiency of the pancreatic enzymes within the intestinal lumen, resulting in maldigestion and malabsorption. EPI is the consequence of several different diseases which result in inadequate enzyme digestion. Mechanisms of EPI include inadequate synthesis and secretion of pancreatic enzymes, decreased stimulation, pancreatic ductal obstruction and decreased pancreatic enzyme activity in the small bowel. The most common causes of EPI are cystic fibrosis, chronic pancreatitis, and pancreatectomy, but other pancreatic conditions may lead to EPI as well.

Mild EPI may be asymptomatic or cause mild abdominal pain and bloating. Bowel movements are usually normal appearing. Moderate to severe EPI causes bloating, cramping, flatulence, and steatorrhea. Overt steatorrhea occurs when approximately 90 percent of the glandular function of the pancreas is lost. Symptoms of steatorrhea include loose, greasy, foul-smelling stools that are difficult to flush. This results in maldigestion of fat and protein and weight loss.

In individuals with well-established chronic pancreatitis, cystic fibrosis, pancreatectomy, or another underlying pancreatic disease such as pancreatic adenocarcinoma, a clinical diagnosis of EPI can be made based on symptoms. If the diagnosis is unclear or the individual does not have an established underlying disease, pancreatic function tests are used to confirm the diagnosis. Once EPI is confirmed, the individual should still be evaluated for the cause of the pancreatic dysfunction. Pancreatic enzymes should not be used as a test or trial to determine if someone has pancreatic insufficiency.

The mainstay of treatment for EPI is pancreatic enzyme replacement therapy (PERT). PERT serve as exogenous versions of hormones and enzymes required for normal digestion. The FDA approved PERTs have been given the generic name pancrelipase. They are porcine enzymes and contain mixtures of pancreatic lipase, amylase,

and protease. Lipase is a digestive enzyme involved in the hydrolysis and degradation of fats. Impairments in lipase metabolism lead to the malabsorption of fats. Amylase is a digestive enzyme involved in the hydrolysis and digestion of starches. Impairments in amylase metabolism lead to complex carbohydrates malabsorption. Proteases are enzymes involved in the breakdown of proteins and amino acids. Imbalances or insufficiency of proteases can lead to poor absorption of amino acids and breakdown of essential proteins.

Pancreatic enzyme products have been available in the United States since before the 1938 passage of the Food, Drug and Cosmetic Act. In 2004, the Food and Drug Administration (FDA), declared pancreatic enzyme products require new FDA approval by 2010 or they would be removed from the market. This and helping standardize the manufacturing process and require the labeling of the amount of lipase in each capsule.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Underlying causes of pancreatic exocrine insufficiency:

- Chronic pancreatitis
- Cystic Fibrosis
- Main Pancreatic duct obstruction (adenocarcinoma, intraductal papillary mucinous neoplasm, pancreas divisum, etc.).
- Pancreatectomy
- Gastric resection
- Short bowel syndrome
- Hereditary hemochromatosis
- Alpha 1 antitrypsin deficiency
- Shwachman-Diamond-Oski syndrome

Delayed-release capsule containing enteric-coated microtablets, porcine origin.
Pancreatic Enzyme Products:

Pancrelipase preparations	Description	Lipase (USP units)	Amylase (USP units)	Protease (USP units)
Pancreaze 2600	Delayed-release capsule containing enteric-coated microtablets, porcine origin.	2600	15,200	8800
Pancreaze 4200		4200	24,600	14,200
Pancreaze 10,500		10,500	61,500	35,500
Pancreaze 16,800		16,800	98,400	56,800
Pancreaze 21,000		21,000	83,900	54,700
Pancreaze 37,000		37,000	149,000	97,300
Creon 3	Delayed-release capsule containing enteric-coated minimicrospheres, porcine origin	3000	15,000	9500
Creon 6		6000	30,000	19,000
Creon 12		12,000	60,000	38,000
Creon 24		24,000	120,000	76,000
Creon 36		36,000	180,000	114,00
Zenpep 3	Delayed-release capsule containing enteric-coated beads, porcine origin.	3000	14,000	10,000
Zenpep 5		5000	24,000	17,000
Zenpep 10		10,000	42,000	32,000
Zenpep 15		15,000	63,000	47,000
Zenpep 20		20,000	84,000	63,000

Zenpep 25		25,000	105,000	79,000
Zenpep 40		40,000	168,000	126,000
Viokace 10,440	Regular-release (non-enteric-coated) tablet, porcine origin.	10,440	39,150	39,150
Viokace 20,880		20,880	78,300	78,300
Pertzye 4	Delayed-release capsule containing bicarbonate-buffered, enteric-coated microspheres, porcine origin.	4000	15,125	14,375
Pertzye 8		8000	30,250	28,750
Pertzye 16		16,000	60,500	57,500
Pertzye 24		24,000	90,750	86,250

Resources:

Creon (pancrelipase) product information, revised by manufacturer AbbVie Inc. 02-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 27, 2024.

Pancreaze (pancrelipase) product information, revised by manufacturer Vivus LLC. 02-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 27, 2024.

Pertzye (pancrelipase) product information, revised by manufacturer Digestive Care, Inc. 02-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 27, 2024.

Viokace (pancrelipase) product information, revised by manufacturer Aimmune Therapeutics, Inc. 02-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 27, 2024.

Zenpep (pancrelipase) product information, revised by manufacturer Aimmune Therapeutics, Inc. 02-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 27, 2024.

Gardner TB, Adler DG, Forsmark CE, et al. ACG Clinical Guideline: Chronic Pancreatitis. Am J Gastroenterol 2020; 115:322-339. Re-evaluated January 10, 2025.

Arvanitakis M, Ockenga J, Bezmarevic M, et al. ESPEN guideline on clinical nutrition in acute and chronic pancreatitis. Clinical Nutrition. 2020; 39:612-631. Re-evaluated January 10, 2025.

Freedman SD, Forsmark CE. Chronic pancreatitis: Management. In: UpToDate, Adler DG, Robson KM (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2024. Topic last updated March 04, 2024. Accessed January 10, 2025.

Stevens T, Conwell DL. Exocrine pancreatic insufficiency. In: UpToDate, Adler DG, Robson KM (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2024. Topic last updated November 08, 2023. Accessed January 10, 2025.

Sabharwal S, Schwarzenberg SJ. Cystic fibrosis: Overview of gastrointestinal disease. In: UpToDate, Heyman MB, Hoppin AG. (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2024. Topic last updated December 18, 2024. Accessed January 10, 2025.

Katkin, JP, Baker RD, Baker SS. Cystic fibrosis: Assessment and management of pancreatic insufficiency. In: UpToDate, Chmiel, JF, Heyman MB, Hoppin AG. (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2024. Topic last updated October 01, 2024. Accessed January 10, 2025.