



## Clinical Guideline

Oscar Clinical Guideline: Pancreatic Digestive Enzymes - pancrelipase (Brand Names: Creon; Pancreaze; Pertzye; Viokace; Zenpep) (PG027, Ver. 8)

### Pancreatic Digestive Enzymes - pancrelipase

- Brand Names: Creon; Pancreaze; Pertzye; Viokace; Zenpep

#### Disclaimer

*Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.*

*Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.*

|                                                           |   |
|-----------------------------------------------------------|---|
| Pancreatic Digestive Enzymes - pancrelipase               | 1 |
| Summary                                                   | 2 |
| Definitions                                               | 4 |
| Clinical Indications                                      | 4 |
| Medical Necessity Criteria for Clinical Review            | 4 |
| General Medical Necessity Criteria                        | 4 |
| Medical Necessity Criteria for Initial Clinical Review    | 5 |
| Initial Indication-Specific Criteria                      | 5 |
| Exocrine Pancreatic Insufficiency                         | 5 |
| Medical Necessity Criteria for Subsequent Clinical Review | 6 |
| Subsequent Indication-Specific Criteria                   | 6 |
| Exocrine Pancreatic Insufficiency                         | 6 |
| Experimental / Investigational, or unproven               | 6 |
| References                                                | 6 |
| Clinical Guideline Revision / History Information         | 8 |

## Summary

The pancreas is an organ located in the abdomen. It has two main functions: it releases hormones (insulin and glucagon) to help regulate blood sugar; and it produces enzymes that help digest and convert the food we eat into energy for the body's functions.

Digestive enzymes produced by the pancreas enter the small intestine and break down fats, starch, and protein from food. Exocrine pancreatic insufficiency (EPI) occurs when pancreatic enzymes are not produced, resulting in maldigestion or an inability to digest food properly. Those with EPI experience broad symptoms such as abdominal discomfort, bloating, cramping, increased flatulence, nutritional and vitamin deficiency, weight loss, and diarrhea or steatorrhea. Edema (swelling), anemia (low red blood cell count), osteopenia (loss of bone mass) or osteomalacia (softening of bones), and certain neurologic disorders may result from severe nutritional deficiencies.

EPI can be caused by chronic pancreatitis, cystic fibrosis, previous pancreatic surgery, blockage of pancreatic duct, Shwachman-Diamond syndrome (a rare genetic condition), relapsing acute pancreatitis, and other disorders of the digestive tract. EPI is treated with dietary adjustments, vitamin supplementation (primarily the fat-soluble vitamins A, D, E, and K), and pancreatic enzyme replacement therapy (PERT) which is the mainstay of treatment for EPI. If abdominal symptoms do not improve with PERT, alternate causes of symptoms should be evaluated and treated.

PERT products all contain porcine-derived amylases, lipases, and proteases. Individuals with known hypersensitivity to pork proteins should not use these products. The formulations available in the US are categorized as enteric-coated (Creon, Pancreaze, Pertzeye, and Zenpep) and non-enteric coated (Viokace). Enteric coating prevents the enzymes from being denatured by gastric acid as the coating dissolves in the duodenum. The PERT products are not interchangeable due to their different enzyme contents and release mechanisms. New prescriptions will be needed when switching between products.

The choice of PERT products will depend on indications. The prescribed dose should be individualized and adjusted based on the individual's weight, fat content of the diet, severity of steatorrhea, and clinical symptoms. The total daily PERT dose should reflect food consumption of approximately three meals plus two or three snacks per day. Half of the prescribed dose is usually for snacks. The initial dose is generally 500 lipase units/kg/meal orally and 250 lipase units/kg/snack orally. However, dosing can differ by population:

- Adults: The initial dose is at least 40,000–50,000 USP units of lipase per meal, with half that dose for snacks. Typical effective doses range from 70,000–100,000 units of lipase per meal.
- Pediatrics: The initial dose is generally 500 lipase units/kg/meal orally and 250 lipase units/kg/snack orally.
- Infants ( $\leq 12$  months): 2,000–4,000 lipase units per 120 mL of formula or per breastfeeding session.

Dosing is increased to a maximum of 2,500 lipase units/kg/meal, 4,000 lipase units/g fat ingested/day, or 10,000 lipase units/kg/day. Higher doses should be used with caution and only if they are

documented to be effective by 3-day fecal fat measurements that indicate a significantly improved fat absorption.

Adverse effects of PERT which have been reported include fibrosing colonopathy at high doses, hyperuricemia/hyperuricosuria at high doses, abdominal discomfort, flatulence, biliary tract stones, pruritus, and allergic reactions. Viokace contains lactose monohydrate, which may exacerbate symptoms in individuals with lactose intolerance.

The efficacy of PERT is determined by the timing of doses. Pancrelipase should be taken with the first bite of meals and snacks. Improvement in symptoms is reflected by stool consistency, fat-soluble vitamin levels, and gain in muscle strength and weight. The most common reasons for treatment failure include inadequate dosage or inadequate amount of enzymes that reach the duodenum. Changing to another formulation may improve symptoms if the individual is still having inadequate responses after increasing dose, timing PERT with food intake, acid suppression, and lifestyle changes that avoid risk factors for the underlying causes of EPI.

Pertzye is the only product that has G-tube administration information in the package insert; however instructions are available for G-tube administration with other products.

Table 1: Product Label Information

| Product                                           | Formulation                     | FDA-Approved Indications and Usage                                                                                                                                                                                      |
|---------------------------------------------------|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Creon (pancrelipase) delayed-release capsules     | Enteric-coated capsule          | Treatment of exocrine pancreatic insufficiency due to cystic fibrosis (FDA approved in infants, children, adolescents, and adults), chronic pancreatitis, pancreatectomy, or other conditions (FDA approved in adults). |
| Pancreaze (pancrelipase) delayed-release capsules | Enteric-coated capsule          | Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions (FDA approved in infants, children, adolescents, and adults).                          |
| Pertzye (pancrelipase) delayed-release capsules   | Enteric-coated with bicarbonate |                                                                                                                                                                                                                         |
| Zenpep (pancrelipase) delayed release capsules    | Enteric-coated capsule          |                                                                                                                                                                                                                         |
| Viokace (pancrelipase) tablets                    | Non-enteric-coated tablet       | Treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy in combination with a proton pump inhibitor (FDA approved in adults).                                                      |

| Product | Formulation | FDA-Approved Indications and Usage                                                                        |
|---------|-------------|-----------------------------------------------------------------------------------------------------------|
|         |             | Note: Since Viokace is not enteric-coated, it should be taken in combination with a proton pump inhibitor |

NOTE: Pancrelipase products are not interchangeable. All of these products contain a combination of porcine-derived lipases, proteases, and amylases.

### Definitions

“Chronic pancreatitis” is inflammation of the pancreas that does not heal or improve. It may get worse over time and lead to permanent damage. Chronic pancreatitis eventually impairs a patient's ability to digest food and make pancreatic hormones.

“Documentation” refers to written information, including but not limited to:

- Up-to-date chart notes, relevant test results, and/or relevant imaging reports to support diagnoses; or
- Prescription claims records, and/or prescription receipts to support prior trials of formulary alternatives.

“Exocrine pancreatic insufficiency (EPI)” is a condition which occurs when the pancreas does not make enough of a specific enzyme the body uses to digest food in the small intestine.

“Fecal elastase-1 (FE-1)” is a stool test used to diagnose exocrine pancreatic insufficiency. A value <200 µg/g suggests EPI and a value <100 µg/g indicates severe EPI.

“Fibrosing colonopathy” is a disease that arises in people with cystic fibrosis treated with high doses of pancreatic enzyme supplements. Signs and symptoms include thickening of the bowel wall, abdominal pain, abdominal swelling, vomiting, and constipation.

“Hyperuricemia” is an excess of uric acid in the blood.

“Pruritus” is an uncomfortable, irritating, or itchy sensation.

“Steatorrhea” is the result of fat malabsorption and is characterized by pale, bulky, and malodorous stools. These stools often float on top of the toilet water with oily droplets and are difficult to flush.

“[s]” indicates state mandates may apply.

## Clinical Indications

### Medical Necessity Criteria for Clinical Review

#### General Medical Necessity Criteria

The Plan considers pancrelipase (Brand Names: Creon; Pancreaze; Pertzye; Viokace; Zenpep) medically necessary when ALL the following criteria are met:

1. The requested product is prescribed by or in consultation with an appropriate specialist (e.g., pulmonologists, endocrinologists, gastroenterologists, oncologists, among others); *AND*
2. The requested product is being prescribed at a dose and frequency that is within FDA approved labeling OR is supported by compendia or evidence-based published dosing guidelines for the requested indication (see [Summary](#), 5th paragraph); *AND*
3. The member meets the applicable [Medical Necessity Criteria for Initial Clinical Review](#) or [Subsequent Clinical Review](#) listed below.

### Medical Necessity Criteria for Initial Clinical Review

#### Initial Indication-Specific Criteria

##### Exocrine Pancreatic Insufficiency

The Plan considers pancrelipase (Brand Names: Creon; Pancreaze; Pertzye; Viokace; Zenpep) medically necessary when ALL the following criteria are met:

4. The member meets the above [General Medical Necessity Criteria](#); *AND*
5. The member has a documented diagnosis of exocrine pancreatic insufficiency caused by ONE (1) of the following:
  - a. Acute pancreatitis (relapsing or single severe episode); *or*
  - b. Ampullary tumors; *or*
  - c. Celiac disease; *or*
  - d. Chronic pancreatitis; *or*
  - e. Cystic fibrosis; *or*
  - f. Ductal stenosis; *or*
  - g. Duodenal resection; *or*
  - h. Gastrointestinal bypass surgery (e.g., Billroth II gastroenterostomy, Roux-en-y gastric bypass); *or*
  - i. Pancreatectomy; *or*
  - j. Pancreatic cancer; *or*
  - k. Shwachman-Diamond syndrome; *or*
  - l. Somatostatinomas; *or*
  - m. Other medical conditions that lead to pancreatic insufficiency and impair fat digestion (e.g., Zollinger-Ellison syndrome, Crohn's disease, dumping syndrome, loss of the pylorus, longstanding diabetes mellitus, or post-surgery motility disorders such as postcibal asynchrony); *AND*

6. The diagnosis of exocrine pancreatic insufficiency is confirmed by ONE (1) of the following:
  - a. Lab test results (e.g., fecal elastase-1 measurement, fecal chymotrypsin, secretin pancreatic function test); *or*
  - b. Imaging studies (e.g., CT scan, MRI); *or*
  - c. Chart documentation; *AND*
7. Clinical chart documentation indicates the member has been provided individualized dietary advice OR will be referred to a nutritionist; *AND*
8. The member meets ONE (1) of the following:
  - a. The requested product is Creon or Zenpep; *or*
  - b. The requested product is Viokace AND documentation is provided that Viokace will be used with a proton pump inhibitor; *or*
  - c. The requested product is for Pancreaze or Pertzye AND the member is unable to use or has tried and failed ALL of the following<sup>[s]</sup>:
    - i. Creon; *and*
    - ii. Zenpep; *and*
    - iii. Viokace.

If the above prior authorization criteria are met, then the pancrelipase product will be approved for up to 12 months.<sup>[s]</sup>

#### *Continued Care*

#### **Medical Necessity Criteria for Subsequent Clinical Review**

#### **Subsequent Indication-Specific Criteria**

#### Exocrine Pancreatic Insufficiency

The Plan considers pancrelipase (Brand Names: Creon; Pancreaze; Pertzye; Viokace; Zenpep) medically necessary when ALL the following criteria are met:

1. The member meets the above applicable **General Medical Necessity Criteria** and/or **Initial Clinical Review**; *AND*
2. Recent chart documentation (within the past 6 months) shows that the patient is demonstrating sustained improvement or control of symptoms related to maldigestion (e.g., flatulence, steatorrhea, symptoms of abdominal pain, or associated gastrointestinal symptoms [e.g., gain of weight, muscle mass, muscle function, or improvement in fat-soluble vitamin levels]).

If the above reauthorization criteria are met, the requested product will be authorized for up to 12-months.<sup>[s]</sup>

## Experimental / Investigational, or unproven<sup>[s]</sup>

Pancrelipase (Brand Names: Creon; Pancreaze; Pertzye; Viokace; Zenpep) for any other use is considered experimental, investigational, or unproven. Additionally, the safety and efficacy of Viokace in those younger than 18 years of age has not been established.

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#### Clinical Guideline Revision / History Information

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