

Title	Pancreatic Enzyme Replacement Therapy
Version	2.0

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1. Introduction

More than 85% of UK cystic fibrosis patients have Pancreatic Insufficiency (PI) as confirmed by faecal elastase testing. Pancreatic Enzyme Replacement Therapy (PERT) is required for these patients to maintain adequate nutritional status.

PERT preparations are made from porcine extracts. They contain lipase, protease and amylase enzymes and aid the digestion of fat, protein and carbohydrate. Most preparations contain enteric-coated microspheres resistant to acid digestion which can achieve up to 90% fat digestion.

2. Assessment for Pancreatic Insufficiency

2.1 Faecal 1 Elastase measurement is the Gold Standard test. Faecal elastase is a specific human protease synthesised by the acinar cells of the pancreas. It correlates to pancreatic exocrine function and pancreatic enzyme production. It can be used to test for PI even if PERT has been started. (See 2. 4)

2.2 Testing: a cherry-sized, non-watery sample of stool is required. Tests can be done at age 3 days in term infants and age 2 weeks in preterm infants.

2.3 Interpretation of faecal elastase level

- Normal function >500mcg/g faeces
- Borderline normal 200-300mcg/g faeces
- Weak/mild PI 100-200mcg/g faeces
- PI <100mcg/g/faeces
- CF normally <15mcg/g faeces

2.4 PERT may be started in advance of the faecal elastase result in infants presenting through newborn screening programmes, particularly in those with two CFTR mutations associated with PI and with obvious signs of maldigestion. In infants with a non-typical genotype, and later diagnosis children and adults, faecal elastase levels should be checked prior to commencing PERT unless there are obvious signs and symptoms of malabsorption.

3. Symptoms of Pancreatic Insufficiency

- Greasy oily, bulky, loose stools
- Stool colour pale / yellow / orange
- Excess odour and flatulence
- Abdominal pain
- Faltering growth
- Frequent stools

Average stools per day:

Infant stool	Variable according to feed, typically 1 – 4 per day
Toddlers	2 – 3 stools per day.
Children / adults	1 – 2 stools per day.

4. Recommended Enzyme Preparations

4.1 Enteric-coated micropheres

- Creon Micro for children
- Creon 10,000
- Creon 25,000

See Appendix 1 for details on each preparation's content.

4.2 Non-enteric coated powdered form

- Pancrex V powder (only used if problems with enteric-coated enzymes)

5. Dosage, Administration, Titration

5.1 Dosage

Currently safe maximum doses should be:

- 10,000 iu lipase/kg/day*
- 2,500 iu lipase/kg/day per meal (and half for snacks)
- 500-4000 iu lipase per g/fat

*NB. In infants where a higher proportion of energy is derived from fat or those following a high fat diet or on tube feeds, IU lipase/kg may exceed 10,000. Dietary fat should not be limited to keep Creon intake < 10,000 iu lipase/kg in this situation as it may negatively impact on intake/growth, but the individual should be closely monitored.

Initial Dosage of Enzymes

- Infants – Breast feeding – ¼-½ scoop Creon micro with short feeds (<20mins) and ½- 1 scoop with longer feeds (>20 mins).
- ½ scoop Creon micro with 90-120mls milk (standard formula).
If using a hydrolysed-milk a smaller dose is needed, Approx. ½-1 scoop with 100mls high energy infant formula.
- Children/adults, 1 -3 capsules Creon 10,000 with meals 1 with snacks
- If changing to Creon 25000 start with a ratio of 1 Creon 25,000: 2 Creon 10,000 capsules.

5.2 Administration of enzymes

PERT is needed to digest all foods and drinks containing fat, protein and starch (and to aid prescribed fat-soluble vitamin digestion). They are not needed for foods containing predominantly simple sugars (see section 7)

Infants – Milk Feeds

- Give at the start or during a feed.
- For larger volume or longer feeds it may be best to split the total dose and give at the start and during the feed.
- Mix with a little apple puree or milk from a teaspoon.
- Do not put into a bottle.
- Do not put directly into mouth as this can lead to aspiration of beads into lungs.
- Check the micro-spheres do not remain in the infant's mouth post-feed.

Infants- Weaning

- Start weaning at 4-6 months; enzyme dose does not increase until symptoms start.
- Enzymes can be mixed with apple puree, yoghurt or a small amount of food.
- Enzymes need to be taken in 1-2 swallows > 20 minutes will deactivate enzymes.
- Hot food will deactivate enzymes.
- Adjust dose according to symptoms.
- If still feeding over 30 minutes more enzymes are needed.

Children / Adults

- Whole capsules can be given around 2-5 years of age at the beginning and during meals and snacks.
- If still feeding over 30 minutes more enzymes are needed.
- Use swallowing enzymes diet sheet.
- If enzymes not taken can still be given within 10 minutes after eating.

Enteral Feeding

- Estimate dose required by assessing usual enzyme requirement per gram of fat.
- The timing of enzyme varies; the majority are given before and during the feed, sometimes enzymes are needed at the end of the feed.

Giving enzymes via enteral tubes

- Non enteric coated enzyme powder can be used down feeding-tube of less than size 15 French:
 - Dose of Pancrex – suggest starting at approx.. 2000iu lipase per g of fat.
 - Pancrex V powder is normally given 2-3 hourly – evenly spaced over the course of continuous feeds or immediately prior to short bolus feeds.
 - Pancrex V powder will likely require dilution to acquire correct lipase dose, particularly in neonates/ infants and young children.
 - Dilute 1 x 2.5ml purple scoop of Pancrex (2g) in a specified volume of water and provide dosage guidance. (See appendix 2 for worked example).
- In older children and adults if patient's current enzyme:fat ratio known, consider using this as starting point for Pancrex dosing.
- If using a tube greater than or equal to a 15 French, Creon micro or Creon 10,000 can be considered discuss with CF Dietitian.

5.3 Titration

Increase doses very slowly until symptoms resolve. Increasing too quickly may cause constipation.

Unresolved malabsorption

If malabsorption continues despite increasing enzymes to the maximum level further investigation is needed. **See Table 1 and 2.**

Table 1

Some concurrent gastro-intestinal disorders which may cause malabsorption which will not respond to increasing enzymes.

Coeliac disease
Lactose malabsorption
Enteric bacterial infection Parasites-giardiasis
Bacterial overgrowth of small intestine
Biliary disease
Short bowel syndrome
Crohn's disease Pseudomembranous colitis

Table 2

Factors contributing to a poor response to PERT.

Enzyme factors

Outdated prescription.
Enzymes not stored in a cool/dry environment.

Dietary factors

Excessive fluid intake e.g. juice/ tea.
Patient or parental perception that enzymes are not needed with milk or snacks.
'Grazing' eating behaviour / high fat 'fast foods'.

Low adherence to the prescribed enzyme regimen

Toddler refusal.
Chaotic household / multiple meal givers.
Anger / and or desire to be 'normal' / Perceived people's views.
Teenage desire to be slim.

Acid intestinal environment

Poor dissolution of enteric coating.
Microcapsule released all at once.
(*H₂ blockers, sodium bicarbonate may help*).

Poor absorption

Due to abnormal intestinal mucins / motility.
Decrease in bile acid pool (*taurine supplements may help*).

6. **Side-effects of Pancreatic Enzyme Therapy**

- Excess enzyme therapy may cause diarrhoea, abdominal pain, soreness and, or itching around anus.

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- Increasing enzyme dose should be gradual as too rapid an increase may cause constipation.
- Certain enzyme preparations that contain a eudragit-coating have been implicated in the causation of fibrosing colonopathy, which results in colonic strictures. This condition has only been seen in children. Children at the greatest risk of this condition are:
 - a. Age < 12 years old
 - b. Intake of > 6000 iu lipase/kg/meal for over 6 months
 - c. Past history of meconium ileus /DIOS/ Inflammatory bowel disease.

Patients on these preparations should be changed to a non eudragit-coated capsule (see Appendix 1)

7. Foods Not Requiring Enzyme Replacement

- Fruit / fruit juice / squash / fizzy drinks.
- Sugar, glucose, sweets (boiled and jelly) jelly.
- Vegetables (excluding potato, pulses and avocado).

8. Standards for Monitoring Enzyme Replacement Therapy

- Check dosage of lipase / kg / day at least annually, or when changes to Creon doses are made.
- Check enzyme dose vs fat content of meal or snack.
- If IU lipase / kg / day > 10,000 monitor closely.
- If maldigestion continues, check other potential causes (See page 4).
- Check bowel motion at clinic visit (Stool type, fatty, floating, colour, smell, presence of visible oil, frequency, flatulence).
- Ask re abdominal pain, discomfort, bloating, presence of mucus or blood* Be aware of conditions which may present similarly to low enzyme adherence e.g. IBD, Coeliac, Bowel cancers.
- Check adequacy of fluid intake.

9. References

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Appendix 1 Pancreatic Enzyme Preparation Composition

Pancreatic Enzyme Preparation	Lipase content per capsule	Protease content per capsule	Amylase content per capsule	Description	Legal Classification
Creon Micro for Children	Per scoop 5000	200	3600	Brown pancreatin Gastro-resistant	P
Creon 10 000	10 000	600	8000	Brown/clear capsules containing granules of enteric coated pancreatin	P
Creon 25 000	25 000	1000	18000	Orange/clear capsules containing enteric coated granules of pancreatin	POM
Pancrex V Forte Capsules	8000	430	9000	Non enteric coated	P
Pancrex V Powder	50,000 (per 2.5ml scoop)	2800	60000	Powder preparation can be swallowed dry or mixed with a little milk or water	P
* Pancrease HL	25 000	1250	22 500	<i>White capsules containing light brown enteric coated minitablets of pancreatin</i>	<i>POM > 15 years</i>
* Nutrizym 22	22 000	1100	19 800	<i>Red/yellow capsules containing enteric coated minitablets of pancreatin</i>	<i>POM > 15years</i>

P Pharmacy prescription
POM Prescription-only Medicine

* These preparations are not recommended as they contain eudragit-coating which has been implicated in the causation of fibrosing colonopathy. Patients on these preparations should be changed to a non eudragit-coated capsule.

Appendix 2

Pancrex V powder worked example for infants/young children:

- Pancrex V Powder = 25,000 iu lipase per 1g.
- Commonly used ward measurement scoops- small purple SHS 2.5ml scoop = 2g Pancrex.
- Equal to 50,000 iu lipase.
- For infant therefore receiving 1 x scoop Creon Micro per bottle feed orally (5000 iu lipase).
- Equivalent Pancrex V powder dose prepare as follows:
 - 1 x 2.5ml scoop Pancrex V powder, dissolved in 10mls water = 5,000 iu lipase per ml. Therefore 1 ml required with each bottle equivalent enteral feed bolus.
 - Dilution can be altered accordingly e.g. 1 x 2.5ml scoop Pancrex dissolved in 20mls water = 2,500 iu lipase/ml.
 - Note once dissolved mixed solution should be given within 30 minutes.