PEI is due to a deficiency in pancreatic digestive enzyme production and/or delivery to the small intestine, leading to malabsorption. PEI is most commonly associated with chronic pancreatitis, cystic fibrosis, pancreatic tumours and surgical resection of the pancreas. Symptoms of PEI are non-specific and are shared with other pancreatic and gastrointestinal diseases, meaning that the disease may go undetected in clinical practice. However, PEI is a serious condition that leads to malnutrition-related complications if left untreated, including osteoporosis, coagulation disorders and peripheral neuropathy. PEI is also an independent risk factor for cardiovascular events in patients with chronic pancreatitis and has a significant impact on quality of life. Therefore, an early and accurate diagnosis of PEI is of high clinical importance. PERT is the backbone of treatment for PEI, and has been in use for several decades, with a recent high-quality meta-analysis confirming its effectiveness in patients with chronic pancreatitis. New guidelines from the APC on the management of PEI were published in 2015, and provide recommendations for diagnosis and treatment based on the aetiology of PEI. Careful attention to dosing and administration of PERT is essential in ensuring optimal treatment outcomes.

**Aetiology**

Any pathological events, including extrapancreatic conditions, that interrupt the sequence required for the normal digestion of food by pancreatic enzymes may lead to PEI. Aetiologies include the following:

- **Damage** – the pancreatic parenchyma is no longer able to synthesise the required amounts of digestive enzymes
- **Asynchrony** – dissociation of normal postprandial digestive enzyme secretions and intestinal meal delivery. This can occur in conditions such as short bowel syndrome and Crohn’s disease or after gastric, biliary or pancreatic resections or bypass procedures
- **Obstruction** – pancreatic duct blockage affects the transport of digestive enzymes and other secretions to the duodenum
- **Decreased endogenous stimulation** – decreased stimulation of enzyme production is particularly noted with coeliac disease.

The most dramatic clinical symptom of PEI, steatorrhoea, does not usually manifest until pancreatic lipase levels fall below 5–10% of normal postprandial levels, due to compensatory enzyme mechanisms and the high reserve capacity of the pancreas.

**Prevalence**

PEI is estimated to occur in 94% of patients with chronic pancreatitis, >85% of patients with cystic fibrosis, 74% of patients after pancreatic resection surgery, and 92% of patients with unresectable pancreatic cancer. Malabsorption occurs in up to 80% of patients following upper gastrointestinal surgery, and PEI contributes to pathogenesis, but the causes are most likely multifactorial.

Among the less common aetiologies of PEI, 35–50% of patients with type 1 diabetes have faecal elastase-1 levels <200 µg/g (including 20–30% with levels <100 µg/g), and 20–35% of patients with type 2 diabetes have faecal elastase-1 levels <200 µg/g (including 10–20% with levels <100 µg/g). However, PEI in these patients is typically mild to moderate and not associated with overt steatorrhoea. By definition, all patients with type 3c (pancreatogenic) diabetes, which accounts for 5–10% of diabetes cases in Western populations, have PEI. PEI associated with this form of diabetes is typically more severe.

Patients with coeliac disease may have pancreatic dysfunction, but this is usually transient and normalises with a gluten-free diet. It is estimated that 12–18% of patients with coeliac disease and chronic diarrhoea while on a gluten-free diet have PEI. Low faecal elastase-1 levels have been found in 14–30% of patients with Crohn’s disease and 22% of patients with ulcerative colitis, but this test is known to have poor diagnostic accuracy for PEI in patients with diarrhoea. PEI may also occur in patients with rare genetic diseases such as Schwachman-Diamond syndrome and Johanson-Blizzard syndrome.
There are no reliable estimates of the prevalence of PEI in the general population, although prevalence appears to increase with age.1

**Consequences**

The most common clinical consequence of PEI is fat malabsorption, leading to lower circulating levels of micronutrients, fat-soluble vitamins and lipoproteins and increasing the risk of malnutrition-related complications.7,13 These complications include hypocalcaemia, coagulation disorders, ataxia and peripheral neuropathy, night blindness and xerophthalmia, and contraction or muscle spasms, osteomalacia and osteoporosis.2

The prevalence of osteoporosis or osteopenia in patients with chronic pancreatitis is 65%.13 PEI is an independent risk factor for cardiovascular disease in patients with chronic pancreatitis.13 PEI contributes to the malnutrition commonly observed in patients with pancreatic ductal adenocarcinoma, and severe PEI is associated with decreased survival in patients with advanced pancreatic cancer.8 Further clinical consequences of PEI can include hyperoxaluria, urinary oxalate stones, renal insufficiency and impairment of cognitive functioning.6

PEI also has a significant negative impact on quality of life, as a result of persistent gastrointestinal symptoms and pain, as well as other factors such as inability to work and financial strain.17

**Diagnosis**

**Clinical presentation**

Symptoms of PEI are nonspecific and vary from patient to patient, depending on severity and aetiology.7 The classic clinical picture is a patient presenting with foul-smelling, loose and fatty stools that are difficult to flush away, weight loss (or lack of weight gain in children), muscle wasting and flatulence.7 Patients may also have abdominal pain and distension, especially after meals.7

Patients with chronic malabsorption may exhibit nail leukonychia due to hypalbuminaemia, ecchymoses due to vitamin K deficiency, ataxia and peripheral neuropathy due to vitamin E deficiency, night blindness and xerophthalmia due to vitamin A deficiency, and contraction or muscle spasms, osteomalacia and osteoporosis due to hypocalcaemia.6

It is important to differentiate malabsorption/ malabsorption due to pancreatic causes from other possible causes, including the following:

- Coeliac disease
- Inflammatory bowel disease
- Inflammatory bowel syndrome
- Microscopic colitis
- Small intestinal bacterial overgrowth
- Short bowel syndrome
- Zollinger-Ellison syndrome
- Bariatric bypass surgery
- Giardiasis.5

**Testing**

Morphological and functional assessments can be used to confirm the diagnosis of PEI.6,13 Computed tomography can identify pancreatic tumours and evidence of chronic pancreatitis (atrophy, calcification). Further investigation may be required with magnetic resonance imaging, endoscopic ultrasound (EUS) and/or secretin-magnetic resonance imaging. The best way to delineate the main pancreatic duct is endoscopic retrograde cholangiopancreatography (ERCP).10,13

Direct pancreatic function tests, including the secretin-cholecystokinin stimulation test and the endoscopic pancreatic function test, are sensitive and specific, but these are too expensive, cumbersome and invasive for routine clinical use.1,13

Indirect functional tests include faecal, breath and blood tests, and these are cheaper and easier to use than direct tests, although they are generally less sensitive and less specific.1,13 The three-day faecal fat test is the “gold standard” for diagnosing steatorrhea, but its use is limited because it is unpopular with patients and lab technicians.13 The faecal elastase-1 test is more popular as a single stool sample is required, but it is best used as screening test for PEI.13 The 13C breath test is a new test which, when PEI is present, demonstrates a reduction in the amount of 13C released after a meal containing triglyceride labelled with 13C.13 Blood tests for magnesius, nutritional markers, bone mineral density and fat-soluble vitamins A, D, E and K are important in the diagnostic workup as they may suggest the presence of PEI.13

The 2015 APC guidelines for the management of PEI classify patients with clinically suspected PEI into three subgroups – PEI definite, PEI possible and PEI unlikely, and present recommendations for diagnosis according to these subgroups (see Table 1).1,7

**Table 1.** Australian Pancreatic Club 2015 recommendations for diagnosis of PEI according to aetiology.1,7

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>PEI definite</th>
<th>PEI possible</th>
<th>PEI unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pancreatectomy</td>
<td>Mild and moderate chronic pancreatitis</td>
<td>Irritable bowel syndrome</td>
<td></td>
</tr>
<tr>
<td>Severe chronic pancreatitis</td>
<td>After severe acute pancreatitis</td>
<td>Coeliac disease</td>
<td></td>
</tr>
<tr>
<td>Tumour destroying head of pancreas</td>
<td>After Whipple procedure</td>
<td>Inflammatory bowel disease</td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis destroying head of pancreas</td>
<td>Cystic fibrosis</td>
<td>Weight loss in older people</td>
<td></td>
</tr>
<tr>
<td>Gastroctomy with postprandial asynchrony</td>
<td>Vitamin A, E, D, K deficiency</td>
<td>Type 2 diabetes</td>
<td></td>
</tr>
<tr>
<td>Biliary resection</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Diagnosis**

In the presence of severe steatorrhea and weight loss, diagnosis can be made on clinical grounds alone.6,13

In the presence of moderate pancreatic structural changes, a diagnosis of PEI is suggested if nutritional impairment and diarrhoea are also present.13

Symptoms of PEI occur in < 10% of patients. Tests of lower sensitivity and specificity may result in under- or over-diagnosis.13

Probability of a positive objective test for PEI is 100%.

Probability of a positive objective test for PEI is 30-70%.

Probability of a positive objective test for PEI is < 10%.

**EXPERT COMMENTARY**

Because PEI is often insidious, there is the need for a high index of suspicion. In practice it is often overlooked, and as a result PERT can be too little and too late. Identifying those at risk of PEI requires vigilance and the APC guidelines (as shown in Table 1) are helpful by categorising patients into those with definite and possible PEI.

The panel of tests recommended when the diagnosis of PEI is sought is important, and should be kept close to hand. The metabolic and nutritional consequences of PEI have been emphasised in the text. Involvement of a dietitian with expertise in pancreatic disease is encouraged for patients with definite PEI, and the diagnostic tests should be repeated at regular intervals (3-6 monthly) for the early detection of these metabolic and nutritional consequences.

Faecal elastase-1 should be done in all patients with possible PEI, but it should not be used as the final or only arbiter of whether a patient requires PERT. It is a useful guide, but many patients have subclinical PEI before the test is positive. This means that a trial of supplemental PERT is often offered to patients without a diagnostic faecal elastase-1 test.
Management

The primary goal of treatment for PEI is to restore normal digestion in order to maintain adequate nutrition. In addition, symptoms must be alleviated and malnutrition-related disease progression prevented. Key aspects of PEI management will be discussed and include the following:

- PERT
- Lifestyle modification, including alcohol abstinence, smoking cessation and consumption of a well-balanced diet
- Trial of acid-suppressing agents in patients with continued symptoms despite high doses of PERT
- Diet adjustments, including smaller frequent meals, normal fat intake and supplementation of fat-soluble vitamins A, D, E and K
- Patient follow-up to detect nutritional deficiencies, symptoms of maldigestion, treatment of associated diseases and adherence with PERT

PERT

PERT is the backbone of treatment for PEI. APC 2015 guidelines state that steatorrhea, either proven or implied, must be present before PERT is initiated – a decrease in pancreatic enzyme secretion alone does not mandate treatment. However this is debated, as it is possible to have the consequences of PEI without overt symptoms. Thus steatorrhea and a positive faecal elastase-1 test result are not absolute requirements for PERT. If the presence of steatorrhea cannot be confirmed by faecal elastase-1 testing, other diagnostic tests can be undertaken. Its presence can often be inferred by the clinical context, imaging and patient characteristics, including suggestive changes in stool habit, weight loss, measured deficiencies in fat-soluble vitamins and osteoporosis.

The guidelines present recommendations for the use of PERT according to PEI aetiology (see Table 2).

<table>
<thead>
<tr>
<th>PEI aetiology</th>
<th>Recommendations for use of PERT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pancreatitis</td>
<td>The use of PERT in the initial stages of acute pancreatitis is not recommended.</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: 1b</td>
</tr>
<tr>
<td></td>
<td>All patients recovering from acute pancreatitis should undergo a nutritional assessment and those</td>
</tr>
<tr>
<td></td>
<td>with continuing symptoms suggestive of ongoing malabsorption should be considered for PERT.</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: 5</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>PERT can improve the symptoms of PEI in patients with chronic pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: 1b</td>
</tr>
<tr>
<td></td>
<td>PERT can improve quality of life in patients with chronic pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: 1b</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Aggressive nutritional management with a high-energy, high fat diet and PERT is recommended for</td>
</tr>
<tr>
<td></td>
<td>cystic fibrosis patients with documented fat malabsorption or PEI found on pancreatic function</td>
</tr>
<tr>
<td></td>
<td>testing</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: 1b, 2b</td>
</tr>
<tr>
<td>Bowel resection</td>
<td>PERT should be considered for those with clinical evidence of PEI and its ongoing requirement</td>
</tr>
<tr>
<td></td>
<td>reviewed regularly because of possible intestinal adaptation</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: 3c</td>
</tr>
<tr>
<td>Gastric surgery</td>
<td>After gastric surgery, patients whose wellbeing is not severely affected do not require long</td>
</tr>
<tr>
<td></td>
<td>term PERT</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: 5</td>
</tr>
<tr>
<td></td>
<td>PEI can contribute to maldigestion and weight loss, and impact on quality of life in gastric</td>
</tr>
<tr>
<td></td>
<td>surgery patients with more severe bowel symptoms. Adequate and appropriate PERT should be</td>
</tr>
<tr>
<td></td>
<td>trialled here and continued if patients respond and experience improved wellbeing, bearing in</td>
</tr>
<tr>
<td></td>
<td>mind the risk of a placebo effect</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: 3b</td>
</tr>
<tr>
<td>Pancreatectomy</td>
<td>Patients having total or subtotal pancreatectomy, including pancreatic head resection, require</td>
</tr>
<tr>
<td></td>
<td>PERT postoperatively</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: 2b</td>
</tr>
<tr>
<td></td>
<td>PERT is required in patients after pancreatecto-gastrostomy because of the effect of acid on</td>
</tr>
<tr>
<td></td>
<td>endogenous enzymes</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: 2b</td>
</tr>
<tr>
<td>Unresectable pancreatic cancer</td>
<td>PERT and dietary guidance from a dietician should be used to treat PEI in patients with</td>
</tr>
<tr>
<td></td>
<td>unresectable pancreatic cancers from the time of diagnosis in order to maintain weight and</td>
</tr>
<tr>
<td></td>
<td>improve quality of life</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: 2a</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Rarely is there a need to use PERT in patients with diabetes. Limited randomised controlled</td>
</tr>
<tr>
<td></td>
<td>trial data do not support treating patients with PERT simply on the basis of very low faecal</td>
</tr>
<tr>
<td></td>
<td>elastase-1 levels (&lt;100 mg/g)</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: 2b</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>After establishing impaired pancreatic secretion in coeliac disease patients, or where</td>
</tr>
<tr>
<td></td>
<td>pancreatic function testing is not feasible, a trial of PERT might be an option</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: 3b</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>PERT may lead to clinically significant improvements in diarrhoea-predominant irritable bowel</td>
</tr>
<tr>
<td></td>
<td>syndrome where there is evidence of pancreatic exocrine insufficiency</td>
</tr>
<tr>
<td></td>
<td>Level of evidence: 3b</td>
</tr>
</tbody>
</table>

Table 2. Australian Pancreatic Club 2015 recommendations for use of PERT according to PEI aetiology. Also provided is the level of evidence on which the recommendations are based: 1b, individual randomised controlled trials (with narrow confidence interval); 2a, systematic reviews (with homogeneity) of clinical studies; 2b, individual cohort study or low quality randomised controlled trials; 3b, individual case-control study; 3c, critical review of the literature, including multiple experimental and observational studies; 5, expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”.

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Before prescribing Pradaxa please review the data sheet for information on dosage, contraindications, precautions, interactions and adverse effects on the Medsafe website www.medsafe.govt.nz. Boehringer Ingelheim, Auckland Ph: 0800 802 461. Medicine classification: Prescription medicine. TAPS TM

Good evidence confirms the danger of using a cell phone while driving. The health media should ensure adequate coverage of the abundance of evidence confirming the danger of using a cell phone while driving and potentially distracting drivers which compromises road safety. This highlights the need for public education and awareness raising, steps that need to be taken by the health media to protect their audience.

This paper did not address the potential harms of medical interventions. The health media should ensure adequate coverage of the abundance of evidence confirming the danger of using a cell phone while driving and potentially distracting drivers which compromises road safety. This highlights the need for public education and awareness raising, steps that need to be taken by the health media to protect their audience.

In the Natural Health section, data from around half a million people in the UK Biobank suggest that coffee drinkers are 3.2% (95% CI, 1.32) more likely to be alive than non-drinkers. This risk peaked at 5–7 years after smoking cessation and fell only gradually thereafter. The increase in risk was modified by the amount of weight gained; quitters who did not gain weight were not at higher risk (p<0.001). Interestingly, gaining weight after quitting smoking did not influence the reduction in mortality; the hazard ratios for death from CVD were 0.69 (95% CI, 0.52–0.91) for those who gained ≤19 kg, 0.83 (95% CI, 0.61–1.12) for those who gained 19–29 kg, and 0.99 (95% CI, 0.78–1.26) for those who gained ≥30 kg. The difference between the groups remained significant for at least 10 years after smoking cessation.

In conclusion, there is evidence that cigarette smoking is associated with an increased risk of death from CVD, and this risk persists for at least 10 years after quitting. The risk is modified by the amount of weight gained, and it is not influenced by weight gain after quitting smoking.
Effectiveness
PERT has been used in the treatment of PEI for several decades, and many clinical trials have been conducted. The primary endpoint for assessing efficacy in clinical trials is usually the coefficient of fat absorption, but this does not directly translate to clinical symptoms. European guidelines for enteral nutrition in patients with pancreatitis recommend clinical endpoints such as improvement in steatorrhea and maintenance of body weight.

In practice, there is room to improve efficacy. Steatorrhea is difficult to resolve completely with PERT and a 60-70% reduction is all that is usually achieved. Recent studies from the Netherlands indicated that 68-70% of patients with PEI secondary to chronic pancreatitis or pancreatic surgery had steatorrhea-related symptoms while receiving PERT. The important reasons for this suboptimal efficacy are insufficient use of PERT, suboptimal scheduling in relation to meals or insufficient control of gastric acid output. Furthermore, persistent deficits in blood nutritional parameters, fat-soluble vitamins and bone mineral density have been found in patients with chronic pancreatitis despite receiving PERT.

Careful attention to dosing and administration of PERT is crucial in achieving the best outcome for patients with PEI, with individual titration necessary. Determining response to treatment is further complicated by the lack of practical, objective outcome measures, and no clear guidance on this issue is offered by the APC. Most guidelines recommend a re-evaluation of symptoms and body weight and a re-evaluation of serum tests of malnutrition.

The PERT preparation Creon® has been well studied in randomised controlled trials of patients with chronic pancreatitis, patients with cystic fibrosis aged ≥7 years and following pancreatic surgery. Creon® has also been studied in open-label trials of patients with cystic fibrosis aged 1 month to 6 years. Trials of Creon® and other PERT formulations have shown that this treatment improves the coefficient of fat absorption and clinical symptoms in patients with PEI secondary to chronic pancreatitis, cystic fibrosis and following pancreatic surgery. However, most trials have enrolled relatively small numbers of patients and were of short duration. A recently published, high quality meta-analysis has confirmed the effectiveness of PERT for the treatment of PEI in patients with chronic pancreatitis. The meta-analysis included quantitative data from 14 randomised controlled trials, published between 1979 and 2012. PERT significantly improved the coefficient of fat absorption compared with placebo (83.2 ± 5.5 vs 67.4 ± 7.0; p=0.0001; I² = 86%). PERT also improved the coefficient of nitrogen absorption, reduced faecal fat excretion, faecal nitrogen excretion, faecal weight and abdominal pain. Quality of life was significantly improved in a 1-year extension to one of the randomised controlled trials.

In unresectable pancreatic cancer, PERT reduced weight loss in a randomised, double-blind, placebo-controlled trial, although these findings were not borne out in a more recent randomised, open-label trial. A newly published retrospective study has shown that PERT improves survival in patients with unresectable pancreatic cancer, particularly those with a significant weight loss.

A randomised, double-blind crossover trial in patients after total gastrectomy demonstrated that PERT improved stool consistency and decreased faecal fat excretion in patients with considerable steatorrhea. However, another similarly controlled trial showed only marginal improvements in symptoms and steatorrhea with PERT after total gastrectomy.

Safety
PERT is well tolerated. The most commonly reported adverse events are gastrointestinal disorders and allergic skin reactions, reflecting the porcine origin of PERT. Many randomised controlled trials have shown that patients with chronic pancreatitis receiving PERT have a quality of life that is not inferior to that of placebo. The New Zealand Data Sheet for Creon® notes that unusual abdominal symptoms or changes in abdominal symptoms should be medically assessed to exclude the possibility of fibrosing colanopathy.

Dosing and administration
Two preparations of PERT have approval for use in New Zealand and are funded by Pharmac – Creon® (available in two different strengths) and Panzytrat®. Both contain porcine pancreatic enzymes. Minimum pancreatic enzyme activity levels are shown in Table 3.

<table>
<thead>
<tr>
<th>Enzyme activity (Ph Eur Units)</th>
<th>Creon® 10,000</th>
<th>Creon® 25,000</th>
<th>Panzytrat® 25,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipase</td>
<td>10,000</td>
<td>25,000</td>
<td>25,000</td>
</tr>
<tr>
<td>Amylase</td>
<td>8000</td>
<td>18,000</td>
<td>22,500</td>
</tr>
<tr>
<td>Protease</td>
<td>600</td>
<td>1000</td>
<td>1250</td>
</tr>
</tbody>
</table>

Creon® and Panzytrat® have a pH-sensitive coating to allow the pancreatic enzymes to mix with chyme, while being protected from inactivation by gastric acid. Intact enzymes then pass into the alkaline pH of the duodenum where the enteric coating rapidly dissolves and the enzymes are released. A low duodenal pH, for example in patients with bicarbonate deficiency, may affect the dissolution of the enteric coating and reduce the effectiveness of PERT. Acid suppression with H₂-antagonists and proton pump inhibitors may be tried in patients who do not achieve an adequate response to PERT, although this is not an approved indication for these agents. To ensure that the alkalinity of acid-suppressing agents does not destroy the enteric coating of PERT, at least 1 hour should elapse between the administration of both agents.

The possibility of small intestinal bacterial overgrowth should be considered in patients with a poor response to PERT despite dose titration and acid suppression.
Recommended dosing

The following recommendations are offered by the manufacturer of Creon®:

For children and adults with PEI associated with cystic fibrosis:

- Starting dose 1000 units lipase/kg bodyweight per meal (patients aged <4 years) or 500 units lipase/kg bodyweight per meal (patients aged ≥4 years)
- Adjust dose according to disease severity, control of steatorrhoea and maintenance of good nutritional status
- Maximum dose 4000 units lipase/g dietary fat intake OR 10,000 units lipase/kg bodyweight per day.12

For adults with PEI associated with other conditions:

- Starting dose 25,000-40,000 units lipase with each meal; half of meal dose with each snack
- Assess patient for clinical response and adherence with therapy
- If necessary, increase dose to 80,000 units lipase with each meal and half of meal dose with each snack
- Maximum dose 10,000 units lipase/kg bodyweight per day.22

The following recommendations are offered by the manufacturer of Panzytrat®:

For children and adults with PEI:

- Starting dose 50,000 lipase units/day for infants aged ≤18 months
- Starting dose 100,000 lipase units/day for children
- Starting dose 150,000 lipase units/day for adults
- Adjust dose according to individual severity of PEI; in the case of total pancreatic insufficiency this may be up to 400,000 lipase units/day.29

For patients with PEI associated with cystic fibrosis:

- The dose should not exceed that required for adequate fat absorption, taking into account the size and composition of meals. Increases in dose should be conducted under medical supervision with the aim of improving symptoms, and should not exceed 15,000-20,000 lipase units/kg bodyweight per day.29

The APC recommendation for dietary protein intake in patients with PEI is 1.0-1.5 g/kg bodyweight/day.22,29 Although total daily energy requirements can vary greatly between individuals, guidelines from the Spanish Pancreatic Club suggest a target of 30 kcal/kg bodyweight/day.2,31

Method of administration

PERT should be taken either during or immediately after meals.22,29 Capsules should be swallowed intact, without crushing or chewing, and with plenty of fluid.22,29 For patients unable to swallow capsules, advice for Creon® is to open capsules and mix the contents with acidic soft food or liquid, such as apple sauce, yogurt or fruit juice with a pH of <5.5 (apple, orange or pineapple juice).22 Advice for Panzytrat® in patients unable to tolerate capsules is to open and swallow the unchewed contents of the capsules.29

Crushing or chewing capsules or their contents, or mixing with food or fluid with a pH >5.5, can dissolve the protective enteric coating, leading to early release of enzymes in the oral cavity, reduced effectiveness and irritation of the oral mucosa.22,29

Nutritional management

Given that the main consequence of PEI is malabsorption of fat, and therefore vitamins and trace elements, routine nutritional assessment to ensure early detection of malnutrition is essential.1,7,13 Such assessments should be carried out by a dietician, and should include the following:

- Aetiology of PEI – nutritional management varies according to diagnosis, particularly for meal size, frequency and the potential need for nutritional supplementation
- Diet history – to establish baseline diet, how the patient eats and define alcohol habits. Zero alcohol intake is recommended for patients with PEI; this is particularly important for patients with PEI secondary to chronic pancreatitis
- Malnutrition assessment – should include anthropometric measures such as mid-arm circumference, mid-arm muscle circumference, triceps skinfold or subjective global assessment in addition to body mass index
- Nutritional deficiencies – screening for markers such as magnesium, fat-soluble vitamins, vitamin B12, iron and lipoproteins should be conducted at diagnosis so that appropriate supplements can be given and their status monitored
- Bone health – bone mineral density should be measured using dual-energy X-ray absorptiometry at diagnosis and every 2 years, with vitamin D and calcium supplementation given and referral to a bone specialist made when necessary
- Fat requirement – low fat or reduced fat diets are not recommended for patients receiving optimised PERT. A target of 30% total energy from dietary fat is considered appropriate, but a higher fat content may be recommended for some patients who are having difficulty gaining or maintaining weight. Adverse symptoms such as steatorrhoea need to be closely monitored.1,7,13

The following recommendations are offered by the manufacturer of Creon®:

- Adjust dose according to disease severity, control of steatorrhoea and maintenance of good nutritional status
- Maximum dose 4000 units lipase/g dietary fat intake OR 10,000 units lipase/kg bodyweight per day.12
- Assess patient for clinical response and adherence with therapy
- If necessary, increase dose to 80,000 units lipase with each meal and half of meal dose with each snack
- Maximum dose 10,000 units lipase/kg bodyweight per day.22

CONCLUSIONS

While there is clear evidence for the effectiveness of PERT in the treatment of PEI in patients with chronic pancreatitis, cystic fibrosis and after pancreatic surgery, more randomised controlled trials are needed for patients with PEI associated with other conditions. Long-term studies across all areas are needed to establish the effects of PERT on morbidity and mortality, and to determine optimal PERT regimens.7,8,10

New biotechnology-derived PERT formulations that avoid the use of animal products have recently been approved by the US Food and Drug Administration, and more are in clinical development.9 These new formulations are liquid- rather than capsule-based, making them potentially more palatable in those who find it difficult to swallow capsules.7
REFERENCES:


