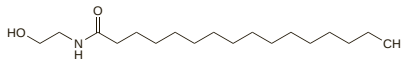
Palmidrol *(rINN)*

Palmidrolum. *N*-(2-Hydroxyethyl)palmitamide.

Пальмидрол

$C_{18}H_{37}NO_2$ = 299.5.

CAS — 544-31-0.



Profile

Palmidrol is a naturally occurring lipid compound that may be isolated from soybean lecithin, egg-yolk, or peanut meal. It has been used as an immunostimulant. It is given orally in doses of 1 g two or three times daily for the treatment of respiratory-tract infections.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Palmitan†.

Pancreatic Enzymes

Pancreatin *(BAN)*

Haimajauhe (pancreas powder); Kasos milteliai (pancreas powder); Pancréas, poudre de (pancreas powder); Pancreatina; Pancreatinum; Pancreatis pulvis (pancreas powder); Pankreaspulver (pancreas powder); Pankreatiini; Pankreatin; Pankreáz-por (pancreas powder).

CAS — 8049-47-6.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US* as pancreatin or another pancreatic exocrine extract or both.

Ph. Eur. 6.2 (Pancreas Powder; Pancreatis Pulvis; Pancreatic Extract BP 2008). It is prepared from the fresh or frozen pancreases of mammals. It contains various enzymes having proteolytic, lipolytic, and amylolytic activities. Each mg of pancreas powder contains not less than 1 Ph. Eur. unit of total proteolytic activity, not less than 15 Ph. Eur. units of lipolytic activity, and not less than 12 Ph. Eur. units of amylolytic activity. A slightly brown, amorphous powder. Partly soluble in water; practically insoluble in alcohol. Store in airtight containers.

BP 2008 (Pancreatin). A preparation of mammalian pancreas containing enzymes having protease, lipase, and amylase activity. Each mg of pancreatin contains not less than 1.4 FIP units of free protease activity, not less than 20 FIP units of lipase activity, and not less than 24 FIP units of amylase activity. It may contain sodium chloride. A white or buff amorphous powder, free from unpleasant odour. Soluble or partly soluble in water forming a slightly turbid solution; practically insoluble in alcohol and in ether. Store at a temperature not exceeding 15°.

USP 31 (Pancreatin). A substance containing enzymes, principally amylase, lipase, and protease, obtained from the pancreas of the hog or of the ox. It is a cream-coloured, amorphous powder, having a faint, characteristic, but not offensive odour. Its greatest activities are in neutral or faintly alkaline media; more than traces of mineral acids or large amounts of alkali hydroxides make it inert. An excess of alkali carbonate also inhibits its action.

Pancreatin contains, in each mg, not less than 25 USP units of amylase activity, not less than 2 USP units of lipase activity, and not less than 25 USP units of protease activity. Pancreatin of a higher digestive power may be labelled as a whole-number multiple of the 3 minimum activities, or may be diluted with lactose, or with sucrose containing not more than 3.25% of starch, or with pancreatin of lower digestive power. Store in airtight containers at a temperature not exceeding 30°.

Pancrelipase *(USAN)*

Pancrelipasa.

CAS — 53608-75-6.

Pharmacopoeias. In *US*.

USP 31 (Pancrelipase). A substance containing enzymes, principally lipase, with amylase and protease, obtained from the pancreas of the hog. It is a cream-coloured, amorphous powder having a faint characteristic, but not offensive odour. Its greatest activities are in neutral or faintly alkaline media; more than traces of mineral acids or large amounts of alkali hydroxides make it inert. An excess of alkali carbonate also inhibits its action. Pancrelipase contains, in each mg, not less than 24 USP units of lipase activity, not less than 100 USP units of amylase activity, and not less than 100 USP units of protease activity. Store in airtight containers preferably at a temperature not exceeding 25°.

Units

The Ph. Eur. and USP units of protease activity depend upon the rate of hydrolysis of casein, those of lipase activity depend upon the rate of hydrolysis of olive oil, and those of amylase activity depend upon the rate of hydrolysis of starch. Because of differences in the assay conditions, the Ph. Eur. and USP units are not readily comparable.

FIP units of protease, lipase, and amylase activity are approximately equivalent to Ph. Eur. units.

Adverse Effects and Precautions

Pancreatic enzyme supplements commonly cause gastrointestinal adverse effects such as abdominal discomfort and nausea and vomiting. They may also cause buccal and perianal irritation, particularly in infants. Colonic strictures (fibrosing colonopathy) have occurred, mainly in children with cystic fibrosis receiving high doses of pancreatin preparations; the use of high doses in patients with cystic fibrosis should preferably be avoided (see Effects on the Gastrointestinal Tract, below). Adequate hydration should be maintained at all times in patients receiving higher strength preparations.

Hypersensitivity reactions have been reported; these may be sneezing, lachrymation, or skin rashes. Hyperuricaemia or hyperuricosuria have occurred with high doses. There have been occasional reports of the contamination of pancreatin preparations with *Salmonella* spp.

Effects on folic acid. Pancreatic extract significantly inhibited folate absorption in healthy subjects and in pancreatic insufficient patients.[1] Testing *in vitro* showed that pancreatic extract formed insoluble complexes with folate. It was suggested[1] that patients being treated for pancreatic insufficiency should be monitored for folate status or given folic acid supplementation, particularly if pancreatic enzymes and bicarbonate (or cimetidine) were being used together in the treatment regimen.

1. Russell RM, *et al*. Impairment of folic acid absorption by oral pancreatic extracts. *Dig Dis Sci* 1980; **25:** 369–73.

Effects on the gastrointestinal tract. ***FIBROSING COLONOPATHY.*** After the introduction of high-strength pancreatic enzyme preparations, there were a number of reports[1-6] of colonic strictures in children with cystic fibrosis who received these formulations, and the problem, now dubbed fibrosing colonopathy, was reviewed.[7,8] Fibrosing colonopathy has also been reported[9] in an adult who was not thought to have cystic fibrosis, but who had been taking high doses of pancreatic enzyme supplements, including 2 with methylacrylic acid copolymer (MAC) coatings, for 5 years after surgical removal of the pancreas.

The pathogenesis and aetiology of this condition still remain unclear. Dose-related thickening of the colon wall has been described,[10] and an inflammatory or immune-mediated mechanism has been suggested.[11,12] It has also been suggested that the type of preparation used may have a role. An analysis[13] of cases of fibrosing colonopathy occurring in the UK between 1984 and 1994 demonstrated that there was a dose-related association between the high-strength preparations and this adverse effect although there was some criticism and debate surrounding the methodology of this particular analysis.[14-16] A subsequent case-control study[17] of patients in the US presenting between 1990 and 1994 concluded that there was a strong association between high daily doses of pancreatic enzymes, in any form, and the development of fibrosing colonopathy; no significant differences were observed between the various high- and low-strength preparations used. Re-analysis[18] of the UK data found a highly statistically significant association with the intake of preparations using MAC for enteric coating, but no evidence that a high intake of lipase in the absence of MAC was a risk factor for the disease. However, at least one case has been reported with a preparation that did not contain this material.[19]

As a result of these problems, high-strength preparations were withdrawn in the USA, while in the UK, the CSM recommended[20] that unless special reasons exist, patients with cystic fibrosis should not use high-strength pancreatin preparations, and that all patients treated with these products should be monitored carefully for gastrointestinal obstruction. The CSM later elaborated on these recommendations:[21] they advised that *Nutrizym 22*, *Pancrease HL*, and *Panzytrat 25 000* [now discontinued in the UK] should not be used in children with cystic fibrosis who were aged 15 years or less; that the total daily dose of pancreatic enzyme supplements for patients with cystic fibrosis should not exceed a lipase activity of 10 000 units/kg; and that patients on any pancreatin preparation should be reviewed to exclude colonic damage if new abdominal symptoms or a change in symptoms occurred. Other risk factors identified were male sex, more severe cystic fibrosis, and the concomitant use of laxatives.[21] The US Cystic Fibrosis Foundation has made recommendations for the management of patients who do not respond adequately to moderate doses of pancreatic enzymes,[22] and similar recommendations have been made in the UK.[23]

1. Smyth RL, *et al.* Strictures of ascending colon in cystic fibrosis and high-strength pancreatic enzymes. *Lancet* 1994; **343:** 85–6.
2. Oades PJ, *et al.* High-strength pancreatic enzyme supplements and large-bowel stricture in cystic fibrosis. *Lancet* 1994; **343:** 109.
3. Campbell CA, *et al.* High-strength pancreatic enzyme supplements and large-bowel stricture in cystic fibrosis. *Lancet* 1994; **343:** 109–110.
4. Mahony MJ, Corcoran M. High-strength pancreatic enzymes. *Lancet* 1994; **343:** 599–600.
5. Knabe N, *et al.* Extensive pathological changes of the colon in cystic fibrosis and high-strength pancreatic enzymes. *Lancet* 1994; **343:** 1230.
6. Pettei MJ, *et al.* Pancolonic disease in cystic fibrosis and high-dose pancreatic enzyme therapy. *J Pediatr* 1994; **125:** 587–9.
7. Taylor CJ. Colonic strictures in cystic fibrosis. *Lancet* 1994; **343:** 615–16. Correction. *ibid.*; 1108.
8. Taylor CJ. The problems with high dose pancreatic enzyme preparations. *Drug Safety* 1994; **11:** 75–9.
9. Bansi DS, *et al.* Fibrosing colonopathy in an adult owing to over use of pancreatic enzyme supplements. *Gut* 2000; **46:** 283–5.
10. MacSweeney EJ, *et al.* Relationship of thickening of colon wall to pancreatic-enzyme treatment in cystic fibrosis. *Lancet* 1995; **345:** 752–6.
11. Croft NM, *et al.* Gut inflammation in children with cystic fibrosis on high-dose enzyme supplements. *Lancet* 1995; **346:** 1265–7.
12. Lee J, *et al.* Is fibrosing colonopathy an immune mediated disease? *Arch Dis Child* 1997; **77:** 66–70.
13. Smyth RL, *et al.* Fibrosing colonopathy in cystic fibrosis: results of a case-control study. *Lancet* 1995; **346:** 1247–51.
14. Dodge JA. Concern about records of fibrosing colonopathy study. *Lancet* 2001; **357:** 1526–7.
15. Dodge JA. Further comments on fibrosing colonopathy study. *Lancet* 2001; **358:** 1546.
16. O'Hara D, Talbot IC. Further comments on fibrosing colonopathy study. *Lancet* 2001; **358:** 1546.
17. FitzSimmons SC, *et al.* High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. *N Engl J Med* 1997; **336:** 1283–9.
18. Prescott P, Bakowski MT. Pathogenesis of fibrosing colonopathy: the role of methacrylic acid copolymer. *Pharmacoepidemiol Drug Safety* 1999; **8:** 377–84.
19. Taylor CJ, Steiner GM. Fibrosing colonopathy in a child on low-dose pancreatin. *Lancet* 1995; **345:** 1106–7.
20. Committee on Safety of Medicines/Medicines Control Agency. Update: bowel strictures and high-potency pancreatins. *Current Problems* 1994; **20:** 13. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015632&RevisionSelectionMethod=LatestReleased (accessed 06/08/08)
21. Committee on Safety of Medicines/Medicines Control Agency. Fibrosing colonopathy associated with pancreatic enzymes. *Current Problems* 1995; **21:** 11. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON2023217 (accessed 06/08/08)
22. Borowitz DS, *et al.* Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. *J Pediatr* 1995; **127:** 681–4.
23. Littlewood JM. Fibrosing colonopathy in cystic fibrosis: commentary, implications of the Committee on Safety of Medicines 10 000 IU lipase/kg/day recommendation for use of pancreatic enzymes in cystic fibrosis. *Arch Dis Child* 1996; **74:** 466–8.

MOUTH ULCERATION. In 3 children taking preparations of pancreatic extracts (*Pancrex V powder*, *Pancrex V Forte*), severe mouth ulceration and angular stomatitis, causing dysphagia, loss of weight, and pyrexia, were attributed to digestion of the mucous membrane due to retention of the preparations in the mouth before swallowing.[1]

1. Darby CW. Pancreatic extracts. *BMJ* 1970; **2:** 299–300.

Hypersensitivity. A successful desensitisation regimen has been described[1] for a child with cystic fibrosis who vomited within 1 to 2 hours after ingestion of pancreatic enzymes, suggestive of a type I hypersensitivity reaction.

1. Chamarthy LM, *et al.* Desensitization to pancreatic enzyme intolerance in a child with cystic fibrosis. Abstract: *Pediatrics* 1998; **102:** 134–5. Full version: http://pediatrics.aappublications.org/cgi/reprint/102/1/e13.pdf (accessed 14/07/06)

Uses and Administration

Pancreatic enzymes (as pancreatin or pancrelipase) hydrolyse fats to glycerol and fatty acids, break down protein into peptides, proteoses and derived substances, and convert starch into dextrins and sugars. They are given by mouth in conditions of pancreatic exocrine deficiency such as pancreatitis and cystic fibrosis. They are available in the form of powder, capsules containing powder or enteric-coated granules (which may be opened before use and the contents sprinkled on soft food), enteric-coated tablets, or granules. If pancreatic enzymes are mixed with liquids or food the resulting mixture should not be allowed to stand for more than 1 hour before use. Histamine H_2-receptor antagonists, such as cimetidine or ranitidine, have been given an hour before a dose in an attempt to lessen destruction of the pancreatic enzymes by gastric acid, or proton pump inhibitors such as omeprazole may be used; alternatively, antacids may be given with the dose.

The dose of pancreatic enzymes is adjusted according to the needs of the individual patient and will also depend on the dosage form. In the UK, proprietary preparations generally provide about 5 000 to 10 000 units of lipase activity per dose-unit and usual doses, given with each meal, range from about 5 000 to 56 000 units of lipase activity (with varying proportions of protease and amylase activity, depending on the preparation). In the USA, doses providing up to 40 000 USP units of lipase activity may be given with each meal. So-called high-strength or high-potency preparations are available for those receiving high doses, and typically contain about 20 000 to 40 000 units of lipase activity per dose unit, but their use has been associated with the development of fibrosing colonopathy in children with cystic fibrosis (see Effects on the Gastrointestinal Tract, above). Such preparations are consequently not recommended for children in the UK and authorities there consider the total daily dose of pancreatic supplements for patients with cystic fibrosis should not exceed a lipase activity of 10 000 units/kg.

Purified lipase preparations have also been used. A recombinant human bile-salt stimulated lipase is under investigation for the treatment of fat malabsorption in patients with exocrine pancreatic insufficiency and cystic fibrosis.

Pancreatin is also used to remove protein deposits from the surface of soft contact lenses (p.1622).