Position Statement: Pancreatic enzyme replacement therapy (PERT) shortage – advice for clinicians on the management of adults with pancreatic exocrine insufficiency

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Position statement and advice for prescribers from the [1]Nutrition Interest Group of the Pancreatic Society of Great Britain and Ireland (NIGPS), [2] Cystic Fibrosis Specialist Group and [3] Gastroenterology Specialist Group, British Dietetic Association.

Endorsed by the British Society of Gastroenterology (Pancreas section); Pancreatic Society of Great Britain and Ireland, Pancreatic Cancer UK, GUTS UK, Cystic Fibrosis Trust, CF Medical Association, Pancreatic Cancer Action, Neuroendocrine Cancer UK and the British Dietetic Association.

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Please ensure you are reading the most up to date version, which is available on the Pancreatic Society of Great Britain and Ireland website:

https://www.psgbi.org/position-statement-pert-shortage/

Introduction

The ongoing supply issues surrounding pancreatic enzyme replacement therapy (**PERT** – under the product brands: **Creon®**, **Nutrizym®** and **Pancrex®**) is predicted to continue until 2026. These intermittent supply issues mean some people are running out of PERT, or experiencing difficulties or delays in accessing PERT. Therefore, there is a need for clinical and symptom management advice that is different to normal clinical practice. This position paper is designed to meet the needs of the clinicians' managing patients with pancreatic exocrine insufficiency (PEI) and provides advice for prescribers, and dietitians. A separate document is available providing advice for patients.

Pancreatic enzyme replacement therapy is prescribed to support adequate digestion in patients with PEI, most commonly due to pancreatic cancer, pancreatitis, pancreatic surgery, cystic fibrosis (CF) and neuroendocrine cancers – also known as neuroendocrine neoplasms (NEN). There are many other clinical situations where patients may have primary or secondary PEI, such as type 3c diabetes or following gastrectomy or gastric bypass surgery (1). Patients who take somatostatin analogues [Lanreotide (Somatuline®) / Octreotide (Sandostatin®)] for the treatment of neuroendocrine tumours (NETs) are also at risk of PEI. Regardless of aetiology, the impact of maldigestion varies from person to person in both the type of symptoms and their severity.

Symptoms of untreated PEI may include bloating, excess wind, diarrhoea, crampy abdominal pain, faecal urgency, steatorrhoea (pale floating stools), hard to manage blood glucose levels, vitamin and mineral deficiencies, weight loss and malnutrition (1). These symptoms are usually managed with PERT and will recur if patients are unable to take adequate doses.

There are many clinical impacts of inadequate PERT, which will affect all patients, and the advice in this document is targeted at all patient groups.

The advice in this paper may be updated as we receive further guidance and expand our experience in managing PEI without adequate PERT. The most up to date version will be available at: https://www.psgbi.org/position-statement-pert-shortage/

Please note the advice in this document is designed for adults with PEI, specialist advice should be sought for children with PEI. Patients with cystic fibrosis will be under the care of a specialist centre, and they should contact their specialist team if they have any concerns.

Customer Services

The two main suppliers of PERT in the UK have set up customer support lines to help identify areas with recent deliveries. However, it is possible these deliveries may have already been allocated to specific patients.

- Viatris (Creon®) 0800 8086410 (for patients and pharmacists)
- Zentiva (Nutrizym®): 08448 793188 (for pharmacists) and 08000 902408 (for patients)

Advice for Prescribers

Imported medications are needed to meet the deficit. Please liaise with your local pharmacy teams, and the medicine management team within your integrated care board (ICB) regarding access to imported medication. There is no evidence to suggest that there is any difference between European and American units of enzymes in these preparations (6)

The shortage has resulted in the need to prioritise some PERT products for specific populations.

Please refer to the latest The Department of Health and Social Care (DHSC) medicines supply notification regarding supply available within the UK. These are updated regularly. During specific periods of shortage supply of paediatric products (Creon Micro and Creon 10,000) may be limited to hospitals only.

- Creon Micro® is prioritised for infants and those with dysphagia who are unable to open the Creon 25,000® capsules.
- Creon 10,000® should be prioritised for children and those unable to swallow larger capsules
- Nutrizym 22® has limited availability and should be prioritised for those unable to tolerate Creon preparations
- Pancrex V® powder should be prioritised for patients receiving enteral feeding

Patients cannot "go without" this medication. This can have significant adverse health effects.

Logistical recommendations

- Liaise with your ICB (medicines management teams) regarding regional plans for imported medicines and accessing emergency hospital supplies for patients who have run out.
- Allow an override of any electronic systems that block prescription requests if they are placed less than 4 weeks since the previous request.
- Patients should be advised to place their next prescription request as soon as the previous one has been dispensed to allow time for a supply to be sourced.
- If you have an "in house" pharmacy – identify if they are able to place orders that sit on a back-order list at the wholesalers, if not, leave prescriptions on the NHS Spine in order that patients can take these to a pharmacy that can.
- Whilst the supply issues are ongoing, please do **NOT** encourage patients to stockpile these medicines, as this will further drive the shortage.
- Please provide PERT prescriptions on singular prescriptions to allow patients to take prescriptions to a different pharmacy to those who dispense their other medicines.
- In line with the Medicines Supply Notification from the Department of Health and Social Care (issued 16/2/24 MSN/2024/022). Please ensure that only one-month supply is issued at a time. (4).
- If you are hospital based, please liaise with your pharmacy team regarding stock levels and consider issuing "rescue prescriptions" from the hospital **in the event that patients have run out completely**. We recommend no more than 1-2 weeks supply is issued within a rescue prescription. Larger prescriptions risk depleting hospital supplies.

Clinical management suggestions:

- Taking PERT throughout the meal rather than all at the start/ middle/ end improves efficacy.
- For people with CF, please do not change medications, but seek advice from specialist teams.
- Consider prescribing a **proton pump inhibitor** or **H2 receptor antagonist** to reduce acid degradation of the PERT and optimise efficacy in patients where there are not any contra-indications (1).
- Consider prescribing a **multivitamin and mineral** and a **calcium and vitamin D supplement** if patients are not already taking one
- **Anti-spasmodic medication** may help reduce some of the abdominal discomfort (i.e. buscopan®)
- **Anti-diarrhoeal medication** (i.e. loperamide) may reduce the severity of faecal urgency and diarrhoea. **This does not treat malabsorption or malnutrition.**

CAUTIONS – impact on other medication / medical conditions

- **DIABETES**: Be aware that patients on insulin or oral hypoglycaemic agents that can cause hypoglycaemia may experience worsening control and be more susceptible to hypoglycaemia.
    - Please ensure patients with diabetes have adequate testing equipment to allow for increased monitoring.
    - Patients on insulin should (subject to local guidelines) have continuous glucose monitoring devices and these should have the low glucose alarm set.
    - Patients should be encouraged to monitor glucose levels more frequently, especially when undertaking activities such as driving or exercise.
    - Patients who have had a total pancreatectomy are especially vulnerable to hypoglycaemia as they have an absence of glucagon as well as endogenous insulin.
- Please be aware that malabsorptive diarrhoea is osmotic and results in rapid transit time. This may impact the **absorption of other medication** (including medication prescribed for seizure control, anti-hypertensives, arrhythmia drugs, antibiotics and the oral contraceptive pill etc.,)
    - Secondary forms of contraception should be recommended.
    - Please increase monitoring for people with dose sensitive medication.
    - Use loperamide to reduce transit speed where necessary (Not for patients with CF – refer to specialist centre).
- **ANTI-COAGULATION:** Please be aware that Vitamin K is a fat-soluble vitamin and uptake maybe impaired with inadequate PERT – additional monitoring may be needed for patients on anti-coagulation.
- **FALLS:** Uncontrolled PEI results in faecal urgency which is a risk factor for falls in vulnerable patients. Consider the use of loperamide to control faecal urgency where necessary.

CAUTIONS – differential diagnosis

- Distal intestinal obstruction syndrome (DIOS) is a unique feature of CF and is characterised by the accumulation of viscid mucofaecal material in the terminal ileum and caecum. Being a common complication in people with CF, it needs to be considered if someone with CF presents with symptoms following a change in their PERT prescription.
- Be aware that patients with small bowel NENs may be at risk of Carcinoid syndrome, mesenteric fibrosis, short bowel syndrome etc, please refer to their specialist teams if you have concerns.
- Consider that patients with PEI, may also have bile acid malabsorption, small intestinal bacterial overgrowth, coeliac disease etc., please investigate and treat in line with current guidelines (2).

Advice for managing symptoms in those who are unable to access adequate supplies

- Liaise with your local ICB regarding accessing hospital supplies - each region should have a process in place for this.
- Be aware that in those with diabetes, this can lead to potentially life-threatening hypoglycaemia and is an urgent issue that **needs to be rectified on the same day.**
- In patients who are experiencing loose bowel motions or faecal urgency due to lack of PERT, and who do not have cystic fibrosis and where an infective, inflammatory (underlying inflammatory bowel disease) or obstructive cause has been ruled out - please consider prescribing loperamide at a starting dose of 2mg in the morning and working up to 2mg before meals (TDS) if needed. Higher doses may be needed and should be assessed individually. This will slow the gut transit time down and help alleviate symptoms but **will not treat malabsorption**.
- If patients are unable to access any PERT and are losing weight or have intractable or unmanageable abdominal symptoms, we suggest reducing their oral intake of food significantly and prescribing peptide based oral nutritional supplements instead (**Vital 1.5kcal®**, **Survimed OPD 1.5kcal®**, **Peptisip Energy HP®**). Please note this should be used for a short period until further supplies of PERT can be obtained. We recommend you only prescribe one-week supply at a time, due to the cost of these products. Please note standard oral nutritional supplements are **NOT** suitable without PERT (i.e., Altraplen® Aymes®, Ensure®, Foodlink® Fortisip®, Fresubin®).

This table suggest the number of nutritional supplement drinks that should be prescribed for patients not able to absorb food and without access to PERT.

Body weight	**Supplements needed per day (Vital 1.5kcal® or Survimed OPD 1.5kcal® or Peptisip Energy HP®**
Below 40kg	Contact a dietitian
40 - 50kg	4 x 200ml bottles = 1200kcal
50 - 60kg	5 x 200ml bottles = 1500kcal
60 - 70kg	6 x 200ml bottles = 1800kcal
70 - 80kg	7 x 200ml bottles = 2100kcal
80 - 90kg	8 x 200ml bottles = 2400kcal
Over 90kg	Contact a dietitian

- This may under-estimate energy needs, however it should be sufficient for short term nutritional support. If needed for longer and the patient is rapidly losing weight or is very active, add in one more bottle per day. If they gain weight and were not intending to – reduce by 1 bottle per day.
- Small amounts of fruit and vegetables can be consumed alongside these drinks.
- For those who do not have diabetes, sugary drinks and sweets can also be consumed.
- Fruit, vegetables and sugary drinks should not worsen symptoms but will not provide any protein, so should only be used to improve satiety and quality of life.

IMPORTANT

For patients with CF please contact the patients' CF Specialist team. For all other patients please contact your local tertiary hepato-pancreatico-biliary (HPB) / pancreatic / neuroendocrine unit. Depending on the local service available, this may be either the specialist HPB / pancreatic / NEN dietitian or pancreatologist. The Specialist Pharmacy Service Medicines Supply Tool can be accessed by Prescribers for more information on supply at: https://www.sps.nhs.uk

Advice for Dietitians

In addition to the above advice, please consider the following:

- Remind patients to spread the dose of their PERT out throughout their meals to optimise absorption – taking some PERT at the beginning, some in the middle and some towards the end of their meal.
- Remind patients to store their enzymes properly – all products should be stored below 25 degrees, and some require refrigeration. Excess heat causes irreversible denaturation.
- Only dose escalate PERT in nutritionally compromised patients – liaise with medical teams to access loperamide for those who are weight stable to minimise any diarrhoea (Not appropriate for patients with CF or some patients with NENs). Ensure obstructive / infectious causes have been ruled out first. Refer patients not responding to treatment back to their managing physician to ensure other causes of diarrhoea have been excluded.
- Use peptide based oral nutritional supplements (ONS). i.e., **VITAL 1.5 kcal®** / **Survimed OPD 1.5kcal®/ Peptisip Energy HP®** in place of polymeric supplements to reduce the need for PERT with polymeric ONS. **Peptamen® Vanilla** contains less energy (1kcal/ml), but these could be used if supplies of **VITAL 1.5 kcal®** / **Survimed OPD 1.5kcal®/ Peptisip Energy HP®** are limited.
- Consider fat free ONS sipped slowly without PERT if the patient is weight stable. If the patient experiences significant abdominal symptoms or weight loss despite this, please swap to peptide based ONS. PERT is still be required for polysaccharide and protein digestion. Fat free ONS are not nutritionally complete and should not be used a sole source of nutrition.
- Use **ProSource Jelly®** / **ProSource Plus®** for additional protein (as these are peptide based).
- Medium chain triglyceride (MCT) lipid products (**Liquigen®** / **MCT oil®**) could be used alongside fat free ONS in patients who need higher energy ONS. Please note that **Elemental 028®** contains 35% MCT and still requires PERT for lipid absorption. **Emsogen®** can also be considered, as this should not require PERT, but is low in energy and protein, this can be concentrated if tolerated.
- Consider 10-20% reduction in dietary fat for patients who are symptomatic.
- Consider reducing dietary fibre if large doses are consumed (>40g fibre per day) as high fibre diets can reduce the efficacy of PERT.
- Ensure patients with diabetes on **insulin** or medications associated with hypoglycaemia (i.e. **Gliclazide**) are regularly monitoring their blood glucose levels and aware of how to treat a hypo.
- Please ensure patients with signs of malabsorption and taking anti-coagulation are highlighted to their managing physician as Vitamin K absorption may be impaired.
- Seek advice from specialist centres for specific advice for patients with CF.
    - CF Dietitians will review and optimise PERT dosing and adherence.
    - CF Dietitians will optimise vitamins and minerals and adjust as appropriate.
- Patients with intractable malabsorption may need peptide enteral, or in severe cases parenteral nutrition.
- If you work in a tertiary pancreatic / NEN centre, please liaise with your pharmacy team regarding stock levels and consider issuing “rescue prescriptions” from the hospital in the event that high priority patients have run out completely. We recommend no more than 1-2 weeks supply issued within a rescue prescription if possible. Larger prescriptions risk depleting hospital supplies.

Nutritional composition of additional products

Liquigen® 30mls = 136kcal, 0g protein, 97.4% MCT. ACBS approved. 250ml bottle, once open store in a refrigerator and use within 14 days. Suitable for vegans and vegetarians.

Nutricia MCT oil® 100mls = 855kcal, 0g protein, 99.9% MCT. ACBS approved. 500ml bottle, once open, reseal and use within 1 month. Suitable for vegans and vegetarians.

Vital 1.5kcal® 300kcal, 13.5g protein (as peptide), 64% MCT. ACBS approved. 200ml bottle, suitable for vegetarians (not vegan), once open store in a refrigerator and discard after 24 hours

Peptisip Energy HP® 300kcal, 15g protein (as peptide), 60% MCT, ACBS approved, 200ml bottle, suitable for vegetarians (not vegan), once open store in a refrigerator and discard after 24 hours.

Survimed® **OPD 1.5kcal** drink – 300kcal, 15g protein (as peptide), 50% MCT, ACBS approved, 200ml bottle, once open store in a refrigerator and discard after 24 hours.

Emsogen® 438 kcal, 12.5g protein per 100g,(as amino acid), 83% MCT, 88kcal per 100mls, 2.5g protein, ACBS approved. Note this is a low energy, low protein supplement drink. Standard concentration is 20% w/v (1 x 100g sachet in 500mls water). This can be concentrated further if tolerated, but patients may require additional fluids afterwards. Milkshake / coffee syrups can be added to flavour.

ProSource Jelly® 90kcal, 20g protein (as peptide), 0g fat, <1g carbohydrates, ACBS approved. 118g serving, serve chilled.

ProSource Plus® 100kcal, 15g protein (as peptide), 0g fat, 11g carbohydrates. ACBS approved. 30ml serving, flavoured products can be taken as a shot, unflavoured can be added to drinks or food.

Peptamen Vanilla® 200kcal, 8g protein (as peptide), 68% MCT, ACBS approved. 200ml bottle, best served chilled, once open refrigerate and consume within 24 hours.

References / sources of further information

1) Phillips ME, Hopper AD, Leeds JS, *et al* Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines *BMJ Open Gastroenterology* 2021 ;**8:**e000643. doi: 10.1136/bmjgast-2021-000643
2) https://bnf.nice.org.uk/drugs/pancreatin/ accessed 16/3/24
3) https://cks.nice.org.uk/topics/diarrhoea-adults-assessment/ accessed 16/3/24
4) Medicine Supply Notification: Creon 25000 MSN/2024/022 Issued 16/02/24
5) A5_Hypo_TREND.pdf (trenddiabetes.online) accessed 16/3/24
6) https://lp.thieme.de/emag/CP/11525-Drug-Report-Pankreatin-2024/#6
7) NPSA https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103253 accessed 11/6/24

Appendix 1: Table 3: High fat foods and their lower fat alternatives

	Reduce your portion sizes of these	Have these instead
Fats and oils	Butter, lard, Ghee, Margarine, cooking oils	Small portions of low-fat spreads Use spray on cooking oils if needed
Dairy products	Full fat milk / yoghurt Cream Crème Fraiche Cheese	Semi-skimmed or skimmed milk. Low fat yoghurts Use small amounts of grated cheese instead of slices of cheese – choose stronger cheeses to maximise taste. To increase your protein intake make skimmed milk powder up using skimmed milk and use in place of milk throughout the day
Meat and Fish	Fried foods or foods cooked in batter Skins / visible fat on meat Tinned fish, tinned in oil	Meat and fish cooked without added oil Tinned fish, tinned in spring water / brine
Plant based protein sources	Nut butters	Pulses (e.g. lentils, chickpeas, beans (note portion sizes in table 4) Quorn® / Tofu – up to 100g
Fruit & vegetables	No restrictions for low fat, see Table 4 for fibre suggestions	
Carbohydrate based foods	Croissants, pastries Chips / Fried Roast potatoes	Bread, Breakfast cereals Potatoes, rice, pasta, cooked without added fat
Sauces / Condiments	Cheese based sauces Creamy sauces (bearnaise, hollandaise etc.,) Large portions of mayonnaise	Tomato based sauces, gravy, mustard, tomato ketchup, soy sauce, mint jelly, vinegar or low-fat salad dressings

Appendix 2: Table 4: Fibre content of high fibre foods. Aim for less than 40g fibre per day

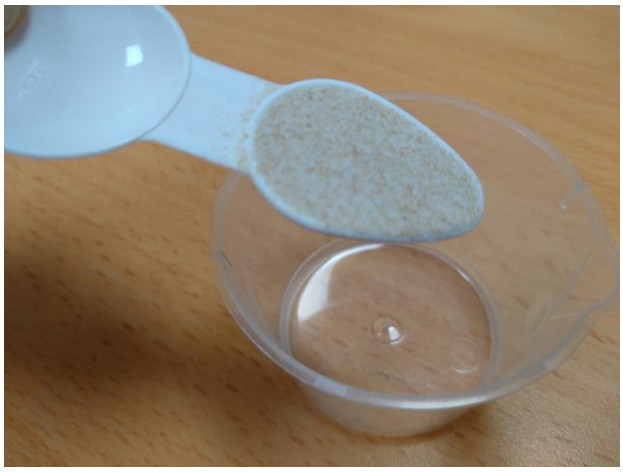
Very high fibre foods		**High fibre foods**			
Food	**Portion providing 10g fibre**	**Food**	**Portion providing 5g fibre**	**Food**	**Portion providing 5g fibre**
All bran®	40g	Whole wheat pitta	1 large	Weetabix®	2 biscuits
Brown pasta	250g (cooked)	Rye based crackers (i.e. Ryvita®)	4 biscuits	Shredded wheat®	2 biscuits
Baked Beans	300g	Branflakes®/ Sultana Bran®, Fruit n/Fibre®	30g bowl	Porridge / Readybrek®	Large bowl (60g oats)
Dried apricots / prunes	120g	Jacket potato with skin	1 medium	Pasta (white)	250g (cooked)
Nuts and seeds	150g	Wholemeal spaghetti	150g (cooked)	Wholemeal bread	100g
Dried lentils / chick peas /Mung beans	100g (weight before cooking)	Baked beans	150g	Quorn®	75g
Dried soya beans / red kidney beans	70g (weight before cooking)	Green beans / peas (fresh or frozen)	120g	Spinach	5 tablespoons
Desiccated coconut	70g	Sweetcorn	7 tablespoons	Avocado pear	1 whole fruit

Appendix 3: Guide to making up powdered enzymes

Appendix 2: Guide to making up powdered enzymes (Pancrex® V powder) for administration through a gastric feeding tube (NG,PEG or RIG) for patients who are eating.

Step 1) You will need a medicine spoon, cooled, boiled water and a pot for mixing in.

Step 2) Wash your hands. If you have eczema or sensitive skin you may wish to wear gloves for this, as Pancrex® V powder can be irritant to sensitive skin.



Step 3) The 2.5ml end of a measuring spoon measures 2g of Pancrex® V powder (50,000 units of lipase) - measure your dose of powder and place in a small bowl or cup for mixing.

Step 4) Start eating your meal.

Step 5) Once you are halfway through your meal - add 20mls cooled boiled water to the powder and mix with the medicine spoon until the powder is dissolved, don't worry if some seems to stick to the edges.

Step 6) Draw the mixture up into an enteral syringe, if some powder is stuck to the edges, squirt the mixture back into the bowl to knock it off and draw it up again.

Step 7) Flush through your feeding tube and then flush with water as normal.

You will need to do this each time you eat, the powder will only mix with the food in your stomach. If you spend more than 30 minutes eating your meal, you should take another dose.

Appendix 4: Content of imported pancreatin products

There are multiple options for imports. These are a selection of products available.

CREON®

Creon can be imported in the same doses as licenced in the UK, we recommend this is done to reduce confusion for patients. (10,000 and 25,000)

PANGROL®

Enteric coated capsules with mini tabs

Preparation	Pack size	Presentation	Amylase	Protease	Lipase
Pangrol 10,000	200	Capsule	9000	500	10,000
Pangrol 25,000	200	Capsule	22,500	1250	25,000

Viokace®

Tablet presentation. Please note these contain Lactose.

Preparation	Pack size	Description	Amylase	Protease	Lipase
Viokace® Tablets Made by Nestle (Imported by Target)	100	Tablets – tan, round, biconvex VIO9111 on one side and 9111 on the other	39,150	39,150	10,440
	100	Tan, oval, biconvex with V16 on one side and 9116 on the other	78,300	78,300	20,880

Appendix 5: Conversion charts

Conversion charts to support the use of Creon 25,000 in patients prescribed other medications (2)

Creon® 25,000 Dose	Equivalent in Nutrizym® 22	Equivalent in Creon® 10,000	Equivalent in Pancrex® 340mg (8,000 units lipase)	Equivalent in Pancrex® 125mg (2,950 units lipase)	Equivalent in Creon® Micro*	Pancrex® V powder*
1 x Creon 25,000	1 x Nutrizym 22	3 x Creon 10,000	3 x Pancrex 8,000	8 x Pancrex 2,950	5 scoops Creon Micro	½ x 2.5ml spoon
2 x Creon 25,000	2 x Nutrizym 22	5 x Creon 10,000	6 x Pancrex 8,000	16 x Pancrex 2,950	10 scoops Creon Micro	1 x 2.5ml spoon
3 x Creon 25,000	3 x Nutrizym 22	8 x Creon 10,000	9 x Pancrex 8,000	24 x Pancrex 2,950	15 scoops Creon Micro	1½ x 2.5ml spoon
4 x Creon 25,000	4 x Nutrizym 22	10 x Creon 10,000	12 x Pancrex 8,000	32 x Pancrex 2,950	20 scoops Creon Micro	2 x 2.5ml spoon
5 x Creon 25,000	5 x Nutrizym 22	13 x Creon 10,000	15 x Pancrex 8,000	40 x Pancrex 2,950	25 scoops Creon Micro	2 ½ x 2.5ml spoon
6 x Creon 25,000	6 x Nutrizym 22	15 x Creon 10,000	18 x Pancrex 8,000	48 x Pancrex 2,950	30 scoops Creon Micro	3 x 2.5ml spoon

**Mix with a mildly acidic puree (fruit yoghurt / apple sauce), rinse mouth with water and ensure thorough mouth care as at risk of ulceration if powder / granules get stuck in the gums / under dentures*