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People with swallowing difficulties and diagnosed with dysphagia need drinks that flow slowly. Here at Slō Drinks, we specialize in providing drinks that flow slowly for their healthcare and our latest Slō Drink is Pill-Eze.

It is a thickened liquid, which is moderately thick (IDDSI Level 3). As such it makes swallowing pills, capsules and other solid dosage forms easy to swallow for those with the ability to swallow autonomously.

It is not a medicinal product by the UK's MHRA (Medicines and Healthcare Products Regulatory Agency).

Pill-Eze eases the passage of pills through the oesophagus into the stomach. It has a light texture, pleasant mouth feel, and a sweet cherry taste to mask the bad taste of medicines. It has no medicinal after taste.

It is suitable for all degrees of swallowing difficulty and can be used by those diagnosed with dysphagia and prescribed fluids at Levels 1, 2 and 3. It has wide reaching applications and provides benefits to:

- People with difficulty swallowing pills
- All people with pill anxiety
- Adults on multiple medications and/or supplements
- Children having trouble taking solid-form medications or supplements
- People who struggle taking medication due to size, smell or taste of the tablet

Safe ingredients

Pill-Eze contains only safe ingredients based on the latest WHO, EMA and FDA guidelines (Administration, 2015a, 2015b, 2015c, 2015d, 2015e, 2015f; Committee on Drugs, 1997; Committee for medicinal products for human use: European Medicines Agency, 2006; Committee for Medicinal Products for Human Use., 2014; Committee on Fetus and Newborn, Committee on Drugs, n.d.; Council, 1993; EU (European Union), 2003; European Commission, 2003; European Medicines Agency. Committee for Medicinal products for Human Use (CHMP), 2005; European Parliament and Council Directive, 1995; Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2005, 2011; Scientific Committee on Food (SCF), 2000; Union, 2003) Pill-Eze is free of ingredients commonly used in medicinal oral liquids and gels that can have toxicological effects, induce allergic reactions or cause irritation of the gastro-intestinal tract.

Compatibility with medicines

Often patients use food and beverages to aid the intake of their medication, without seeking advice from health professionals (Lau ETL, Steadman KJ, Mak M, Cichero JAY, 2015; Marquis et al., 2013).

A benefit of this practice is it helps patients take their medication and is usually very low cost. However, combined administration of medication with foods or beverages can pose several risks, including (GRiP, 2015) such as:

- Jam (high sugar content)
- Compote (high sugar content)
- Yoghurt (acidic, dairy product)

- Interaction of the medication with the food or beverage, affecting the chemical stability of the medication e.g. temperature or the microorganisms in food and beverages
- Interaction of the medication with the food or beverage, increasing or decreasing bioavailability (JannMW, Bean J., 1986)
- Foods or beverages can greatly differ in pH, taste-masking properties, viscosity, etc. (Administration,2015e)
- Not all foods and beverages are suitable for all patients (e.g. high sugar content or specific allergies)

Because of these associated risks, the European Medicines Agency now requires the Pharmaceutical Industry to study the compatibility of new medication with food and beverages if they want to recommend this as a suitable option to manipulate medication for administration in patients with swallowing difficulties (EMA, 2013).

This information, however, is not available for most medicines on the market today but is available for these medicines in Pill-Eze.

Pill-Eze is based on starch, which means that it is virtually chemically inert and therefore compatible with almost all medicines.

The chemical compatibility of Pill-Eze with over 100 commonly used medicines has been demonstrated by independent, GLP and ISO9001 certified laboratories. An overview with the compatible APIs is provided in section 6.0.

As such it can be used with a huge range of medications, including extended-release formulations: **providing they are not crushed prior to ingestion**

Quality

Pill-Eze is manufactured in compliance with the highest pharmaceutical standards, in a GMP and ISO 13485 certified facility.

Manufacture & Distribution

Pill-Eze is intellectual property of Slõ Drinks Ltd, 4 Greek Street, Stockport, SK3 8AB (UK).

Manufactured for Slõ Drinks Ltd in the Netherlands.

Slõ Drinks is the sole distributor.

Pill-Eze is based on starch, which means that it is virtually chemically inert and therefore chemically compatible with almost all medicines. It is formulated using only safe and well-tolerated ingredients to make it suitable for the widest range of patients.

Presentation

Pill-Eze is supplied in a pump dispenser and spoon.
At IDDSI 3, flow rate it is suitable for those on IDDSI 1 and 2 fluids.

Intended use and purpose

People with swallowing difficulties and diagnosed with dysphagia struggle swallowing pills, capsules and other solid dosage forms. Swallowing difficulties can impair daily life and can lead to non-adherence to therapy (Marquis et al., 2013).

Frequently patients resort to chewing, crushing or splitting their tablets or capsules, or use food and beverages to aid the intake of their medication, without seeking advice from health professionals (Lau ETL, Steadman KJ, Mak M, Cichero JAY, 2015; Marquis et al., 2013). This can pose serious risks, including:

- Destruction of a pill coating, leading to dose-dumping or inactivation of the medication (Marquis Etal., 2013)
- Interaction of the medication with the food or beverage, increasing or decreasing Bioavailability (Marquis et al., 2013)

Complications of difficulties include chest infection, and in some cases death due to choking on food, or as a result of aspiration pneumonia (Lau ETL, Steadman KJ, Mak M, Cichero JAY, 2015; Marquis et al., 2013).

Pill-Eze makes it easy to swallow solid dosage forms of all shapes and sizes. These include but are not limited to medical pills and (liquid) capsules intended to be swallowed. E.g.

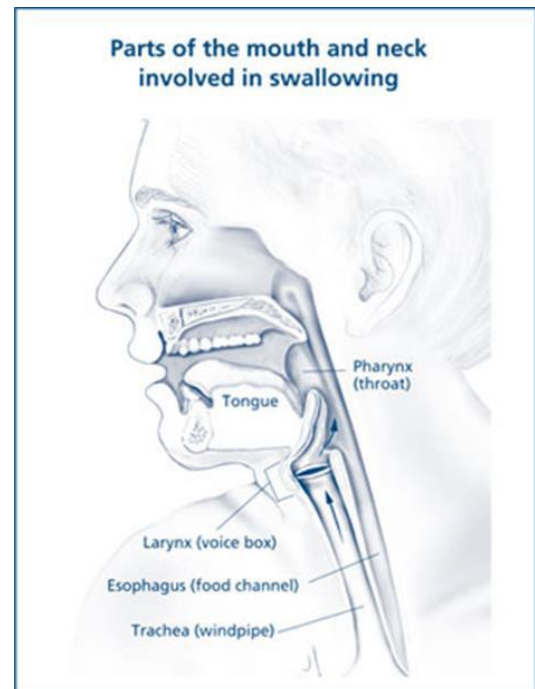
- Vitamin preparations
- Food supplements
- Other solid dosage forms intended to be swallowed.

Pill-Eze can be used to facilitate the swallowing of intact solid dosage forms, as well as aid the intake of crushed pills or opened capsule contents.

! When crushing pills or opening capsules, it is essential to check if this practice is supported by the original manufacturer of the solid dosage form in the patient information leaflet and with a Pharmacist.

The normal swallowing process consists of four phases (Lau ETL, Steadman KJ, Mak M, Cichero JAY, 2015; Marquis et al., 2013).

1. The **oral preparation phase** in which the object to be swallowed is brought into the mouth cavity, chewed if necessary, and wetted with saliva.
2. The **oral transport phase** in which the wetted object to be swallowed is transported towards to throat opening by the use of the tongue.
3. The **pharyngeal phase** in which the object to be swallowed is transported from the throat opening into the oesophagus.
4. The **oesophageal phase** in which the object is transported down the oesophagus into the stomach by peristaltic movements.



This process can be disturbed at one or more time points, which can lead to dysphagia. Possible swallowing disorders include, but are not limited to (Lau ETL, Steadman KJ, Mak M, Cichero JAY, 2015; Marquis et al., 2013):

- Inability to completely close the mouth.
- Pain during chewing, swallowing or passage through the oesophagus.
- Inability to swallow due to neurological conditions.
- Reduced muscle power in the mouth and throat.
- Swallowing apraxia (disorganized anterior to posterior tongue movement).
- Insufficient wetting of the object to swallow, due to reduced saliva production.
- Passage disorders (the object is not sufficiently passed into the oesophagus and remains stuck in the throat opening). After the swallowing reflex, the remainders can accidentally pass into the airways.
- Reflux (the swallowed object flows back from the stomach through the oesophagus into the mouth cavity).

Pill-Eze is believed to aid the swallowing processes and eases the passage of medicines through the oesophagus into the stomach in several ways:

- Pill-Eze is a lightly viscous liquid that is easier to swallow than non-viscous liquids such as water. This is due to the fact that non-viscous liquids are turbulent and fast flowing, and therefore more difficult to control during the passage of the throat opening. This results in impaired airway protection, especially in patients with dysphagia. Thicker liquids flow more slowly, allowing individuals time to coordinate safe swallowing (Marquis et al., 2013).
- Pill-Eze lubricates the object to be swallowed, making it slippery and reducing the resistance and preventing friction with the mucous membranes during the swallowing process. This eases the passage of the object into the oesophagus.
- In the oesophagus the object lubricated with Pill-Eze is more easily pushed down with the peristaltic movements of the oesophagus towards the stomach.

- The starch used in Pill-Eze gives the liquid thixotropic and pseudo plastic behaviour, meaning that the liquid increases in viscosity when no stress (movement) is applied and decreases in viscosity when under stress (Marquis et al., 2013).
- Because of these properties Pill-Eze likely forms a small viscous adhesive layer on the (still standing) surface of the solid object, while being low viscous on the outer layer which is constantly exposed to movement. This will further aid the easy passage and prevents friction with the mucous membranes during the swallowing process.

To use Pill-Eze to aid the intake of solid medication, follow these steps:

1. Place the medication on a spoon, crush the tablet or open the capsule only if necessary*.
2. Add 5 ml (one pumps) of Pill-Eze onto the spoon to cover the medication.
3. Take the medication and finish by drinking water.**

*When crushing tablets or opening capsules it is recommended to carefully read the patient information leaflet (PIL) and/or consult a health professional.

** Finish by drinking water if this is recommended in the PIL.



! Warnings:

- Read Instructions before use
- Check the consistency and ingredients are suitable for the drinker
- Keep out of reach of children
- Not suitable for pre-matures, neonates and children that cannot swallow independently
- Do not use in combination with effervescent pills
- Not recommended to crush coated or any sustained-release medication
- Do not use in case of hypersensitivity for one of the ingredients
- If the drinker is pregnant or breast-feeding, has appendicitis, has narrowing of intestines, a bowel blockage or scheduled for surgery within 2 weeks of drinking check with a healthcare professional this is suitable.
- Avoid contact with the eyes
- Store at (or below) room temperature 25 °C, do not freeze. Keeping in the top part of a fridge enhances the mouth feel.
- Do not use a bottle more than 12 months after first use and not after the indicated expiry date.
- Not to be used as a source of nutrition.
- For oral consumption only.
- Store in a cool dry place and use by the best before date on the sachet.
- It can cause flatulence or bloating.
- For 2 years+.

Description

Pill-Eze is a sweetened, hazy white, translucent syrup. It is packaged in 250ml and 500ml PET bottles. Technical features are:

Ingredients	Purified water, modified food starch, cherry flavour, sodium citrate, citric acid, sucralose sodium benzoate (<0.1%), malic acid and simethicone.
IDDSI flow rating	IDDSI 3
Appearance:	Hazy, white, translucent syrup
Flavour:	Cherry
pH:	4.0-5.0
Osmolality:	<50 mOsmol/Kg
Shelf life after unopened:	36 months
Shelf life after opening:	12 months
Storage conditions:	Store below 25°C
Viscosity at 1rpm:	500-900
Viscosity at 10rpm:	100-3000

Claim	Justification of claim
Pill-Eze eases swallowing of solid dosage forms, including pills and capsules.	In vivo tests (see Chapter 7. Clinical evidence). Literature data (Lau ETL, Steadman KJ, Mak M, Cichero JAY, 2015; Marquis et al., 2013; Notterman, Nardi, & Saslow, 1986)
Pill-Eze can be used for both intact pills and capsules, as well as crushed pills or opened capsules contents.	Active ingredient stability analysis by external, independent laboratory (see Compatibility information).
Pill-Eze is suitable for everyone that can swallow independently, from the age of 2.	At 2 years old 46% of children are able to swallow mini-tablets (3 mm) (Marquis et al., 2013). In general most children can swallow independently when of school age (Marquis et al., 2013). All ingredients used in Pill-Eze are considered safe for ages 2+.(Cichero, 2013; Effectieve Ouderen Zorg, 2011; Jann MW, Bean J., 1986; Lau ETL, Steadman KJ, Mak M, Cichero JAY, 2015; Marquis et al., 2013; Notterman et al., 1986; Overbeeke-Bakker M.J. van, Hutten, 2006).
Pill-Eze contains safe ingredients.	Pill-Eze has a safe ingredient selection, based on literature references for ingredient safety and avoidable ingredients (Cichero, 2013; Diamond & Lavallee, 2010; Effectieve Ouderen Zorg, 2011; Ivanovska, Rademaker, van Dijk, & Mantel-Teeuwisse, 2014; Jann MW, Bean J., 1986; Lau ETL, Steadman KJ, Mak M, Cichero JAY, 2015; Marquis et al., 2013; Notterman et al., 1986; Overbeeke-Bakker M.J. van, Hutten, 2006; Thompson, 1998; Thomson et al., 2009).
Pill-Eze can be used for all patients, including diabetics, children above 2, hospitalized patients, oncology patients, elderly, lactose-intolerant patients, and patients on a ketogenic diet.	Pill-Eze has a safe ingredient selection, based on literature references for ingredient safety and avoidable ingredients (Cichero, 2013; Diamond & Lavallee, 2010; Effectieve Ouderen Zorg, 2011; Ivanovska et al., 2014; Jann MW, Bean J., 1986; Lau ETL, Steadman KJ, Mak M, Cichero JAY, 2015; Marquis et al., 2013; Notterman et al., 1986; Overbeeke-Bakker M.J. van, Hutten, 2006; Thompson, 1998; Thomson et al., 2009).
Pill-Eze has a minimized risk for gastrointestinal side effects.	Osmolality of <50 mOsmol/kg. Liquids with an Osmolality above 400 mOsmol/kg may cause gastrointestinal side effects in the GI tract(Lau ETL, Steadman KJ, Mak M, Cichero JAY, 2015; Marquis et al., 2013).
Pill-Eze has a pleasant taste and mouth feel.	In vivo tests.
Pill-Eze can improve patient compliance.	A pleasant taste and easy administration process are known to improve patient compliance (Lau ETL, Steadman KJ, Mak

Precautions	Justification of claim
It is not recommended to crush coated or any sustained-release medication.	Coatings often protect the active ingredient from degradation. When sustained-release medication is crushed, dose dumping can occur leading to higher than intended drug blood levels (Marquis et al., 2013). Manufacturer information (Lau ETL, Steadman KJ, Mak M, Cichero JAY, 2015; Marquis et al., 2013).
Pill-Eze should not be used by children that cannot swallow independently.	Taking pills by children that cannot swallow independently, can lead to choking or aspiration (Marquis et al., 2013).
Pill-Eze should not be used by people suffering from severe swallowing problems (Dysphagia IDDSI Level 4).	Taking pills by people that suffer from severe swallowing problems, (IDDSI 4 Level) can lead to choking or aspiration.(Cichero et al., 2013)
Pill-Eze should not be used in pre-matures and neonates.	Even though the WHO mentions an acceptable daily intake of 5 mg/kg bodyweight sodium benzoate, it is known that this ingredient can cause metabolic acidosis and neurotoxicity in pre-term neonates and infants (< 6 month) due to immature metabolism capacity (Lau ETL, Steadman KJ, Mak M, Cichero JAY, 2015; Marquis et al., 2013; Notterman et al., 1986). The concentration sodium benzoate in Pill-Eze is low (<0.1%) compared to the concentrations reported in literature during fatal accidents (Marquis et al., 2013), and much lower than concentrations to which neonates are still being exposed in hospital settings today (Marquis et al., 2013). However, as precaution it is not recommended to use Pill-Eze in this age group.
Keep out of reach of children.	Pill-Eze is a pleasant tasting, sweet liquid, that can be attractive to children. Though not expected to be harmful, the accidental intake of large quantities of Pill-Eze is best avoided.
Not suitable for the administration of effervescent tablets.	Effervescent tablets should usually be dissolved in large quantities of water (Marquis et al., 2013). A minimal amount of a viscous liquid like Pill-Eze will not be suitable for completely dissolving such tablets.
Do not use in case of known hypersensitivity to any of the ingredients.	Even though all ingredients used in Pill-Eze are considered safe by world leading references (Cichero, 2013; Effectieve Ouderen Zorg, 2011; Jann MW, Bean J., 1986; Lau ETL, Steadman KJ, Mak M, Cichero JAY, 2015; Marquis et al., 2013
Avoid contact with the eyes	The product contains some acidic ingredients, this might irritate the eyes

The use of starch as thickener means that Pill-Eze is virtually chemically inert and therefore compatible with a broad range of medication.

Pill-Eze is buffered to a pH of 4.2 (comparable to the pH of the stomach), to ensure maximum compatibility.

To scientifically support this claim, over 100 scientific compatibility studies in collaboration with independent, GLP and ISO9001 certified laboratories. Quantification of active ingredient degradation was performed by high performance liquid chromatography (HPLC), though stability indicating methods according to the official USP or Ph.Eur monographs with minor modifications when necessary.

Active ingredients were obtained from raw material when available or crushed tablets or capsule contents when not otherwise obtainable.

The use of raw materials was preferable, as the stability of the active ingredient is most important and the composition of tablets and capsules can vary per manufacturer.

An overview of all active ingredients that are shown to be chemically compatible for at least 7 days with Pill-Eze is listed overleaf.

So far no incompatibilities have been observed in any of the studies. However, it is reasonable to expect incompatibility with crushed pills or capsule contents that contain iodine, as this can provoke a chemical interaction with starch.

In general, it is also not recommended to crush coated or any sustained-release medication. Coatings often protect the active ingredient from degradation at acidic environments. When sustained-release medication is crushed, dose dumping can occur leading to higher than intended drug blood

Demonstrated compatible active pharmaceutical ingredients

Paracetamol (acetaminophen)	Glycopyrrolate (glycopyrronium bromide)	Penicillamine
Acetazolamide	Griseofulvine	Pentoxiphylline
Allopurinol	Haloperidol	Phenobarbital
Alprazolam	Hydrochlorothiazide	Phenytoin
Amiodarone HCl	Hydrocortisone	Prednisolone sodium phosphate
Amitriptyline HCl	Hydrocortisone hemisuccinate	Pregabalin
Amlodipine (as besylate)	Hydrocortisone sodium phosphate	Propranolol HCl
Atenolol	Imipramine HCl	Propylthiouracil
Atropine sulfate	Isoniazid	Pyridoxine HCl (Vit. B6)
Baclofen	Itraconazole	Quinidine sulfate
Caffeine	Ketoconazole	Ranitidine HCl
Captopril	Ketoprofen	Riboflavin (Vit. B2)
Carbamazepine	Labetalol HCl	Rifampin (rifampicin)
Carvedilol	Lamotrigine	Sertraline HCl
Celecoxib	Levodopa and carbidopa	Sildenafil citrate
Ciprofloxacin	Levofloxacin	Simvastatin
Chloral hydrate	Lisinopril	Spirolactone
Chloroquine phosphate	Loperamide HCl	Spirolactone and hydrochlorothiazide
Clomipramine HCl	Lorazepam	Sulfadiazine
Clonazepam	Mebeverine HCl	Sulfasalazine
Cholecalciferol (Vit. D3)	Melatonin	Tacrolimus
Cyanocobalamine (Vit. B12)	Methotrexate	Terbinafine HCl
Cyclosporin A	Metoprolol tartrate	Tetracycline HCl
Dapsone	Metronidazole benzoate	Thiamine HCl (Vit. B1)
Dexamethasone	Midazolam HCl	Tiagabine HCl
Diclofenac sodium	Minocycline HCl	Topiramate
Diltiazem HCl	Nadolol	Tramadol HCl
Dipyridamole	Naltrexone HCl	Trimethoprim
Domperidone	Naproxen	Ursodiol (ursodeoxycholic acid)
Enalapril maleate	Nifedipine	Valsartan
Flecainide acetate	Nitrofurantoin	Vancomycin HCl
Folic acid	Ondansetron HCl	Verapamil HCl
Gabapentin	Oseltamivir phosphate	Zonisamide
Glutamine	Oxandrolone	

Pill-Eze is a thickened liquid at IDDSI 3, Moderately thick flow rate.

Administered orally and intended to facilitate safer swallowing of pills, capsules and other solid dosages by those who have swallowing difficulties and diagnosed with dysphagia.

Pill-Eze has no therapeutic function and is only used during the administration of the medication.

It is not connected to any other medical devices, nor is it powered by an electrical power source ('active device').

It does not fit the categories 'Surgically invasive device' or 'Implantable device'. Pill-Eze use is to be considered transient ("Normally intended for continuous use for less than 60minutes"), in which continuous is defined as 'an uninterrupted actual use of the device for the intended purpose'. Based on rule 5 for 'Invasive devices'.

Pill-Eze **could be** considered as an invasive medical device ("A device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body") based on the European Directive 93/42/EEC, Annex IX Classification Criteria (14 June 1993) 'Definitions for the classification rules'.

However, like all other SIō Drinks which allow the safer swallowing of fluids and oral nutritional supplements, Pill-Eze only allows the safer swallowing of pills and capsules and we are therefore seeking for them to be added to the same classification of Food for Special Medical Purposes.

The UK's MHRA (Medicines and Healthcare Products Regulatory Agency) is of the opinion that "Pill-Eze" *does not fall within the definition of a medicinal product.*"