Surrey Heartlands Integrated Care System
Area Prescribing Committee (APC)

Application for established medicines without APC entry including colour classification

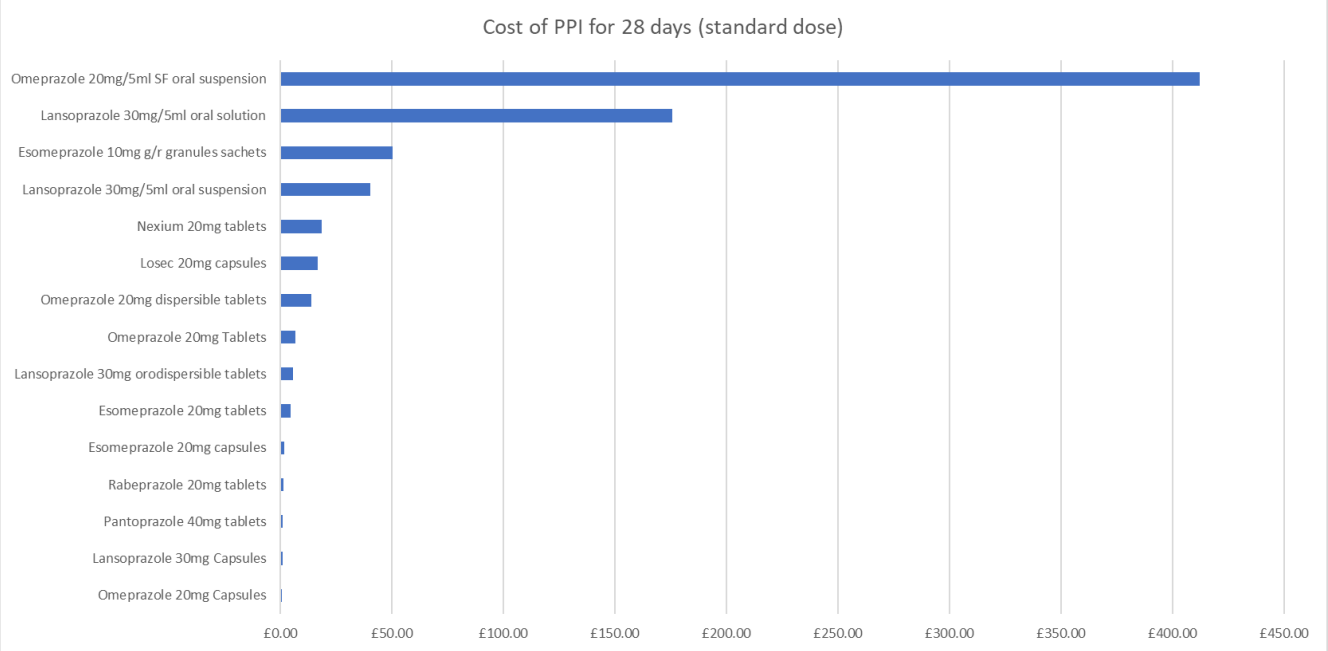
Purpose of this paper:

- **To optimise the use of the most cost-effective oral proton pump inhibitors (PPIs) for use in CHILDREN in Surrey Heartlands, taking account of different formulation requirements**
- **To restrict the use of Omeprazole powder for suspension to children <10kg, with enteral < 8Fr enteral feeding tubes**

Does diagnosis require Specialist? N

Medicine details		
Name, (brand name) and manufacturer if branded product	This paper will describe the place in therapy for all PPIs in children. Current classifications are by PPI class. This review divides each PPI into their different formulations.	
Licensed indication	• Short-term treatment of gastric and duodenal ulcers • In combination with antibacterials for the eradication of Helicobacter pylori (H. Pylori) • Dyspepsia • Gastro-oesophageal reflux disease (GORD) with severe symptoms • Endoscopically confirmed erosive ulcerative, or structuring oesophagitis • Prevention and treatment of NSAID associated ulcers • Zollinger-Ellison syndrome • Degradation of pancreatic enzyme supplements in children with cystic fibrosis.	
Formulation	Specific formulations to be approved or decision made to be non-formulary due to very big range of costs with no clinical benefit, or even harm.	
Usual dosage	As per BNF	
Traffic Light Status *Please use APC decision making criteria to inform reasons for change* 20160526_colour classification guideline	**Current status**	**Proposed status**
	Esomeprazole **Green** Nexium Non-formulary Lansoprazole **Green** Zoton Non-formulary Omeprazole **Green** Losec Non-formulary Pantoprazole **Green** Protium Non-formulary Rabeprazole **Green** Pariet Non-formulary	See Table below (Appendix 1)

Costs



Key Considerations

Briefing

Initial management of GORD in children is clearly described in NICE CKS[9]

NICE NG1[1] and ESPGHAN[2] recommend a 4 to 8 week trial with Proton Pump Inhibitors (PPIs) in children with symptoms of Gastro-oesophageal reflux disease (GORD). If symptoms do not resolve or reoccur, consider referral to a specialist for possible endoscopy. When symptoms persist despite adequate medical treatment, (re-) evaluate treatment compliance and differential diagnoses. Most frequently, failure of treatment will be due to one of these two causes[2]. See appendix 2

In adults, long-term PPI use has been associated with several adverse effects: increased risk of gastrointestinal and respiratory tract infection, vitamin B12 deficiency*, hypomagnesaemia*, bone fractures, acute and chronic kidney failure, and rebound hyperacidity after discontinuation. There is limited data to determine if the same adverse effects are seen in children, however until the evidence base develops further it should be assumed that children are equally at risk from these long-term adverse effects[3].

*Consider blood monitoring if symptoms of deficiency develop.

All patients on PPIs should be regularly reviewed, and the **medicines discontinued if they are no longer deemed to be necessary**. This is particularly true in the management of gastro-oesophageal reflux in neonates and infants, where PPI treatment should be reserved for cases with evidence of pathological exposure to acid reflux episodes and/or oesophagitis[3]. See appendix 3

Clinically there is no clear evidence that one PPI is more effective than another[3]. The main PPIs prescribed in children are omeprazole, lansoprazole and esomeprazole. Individual patient choice will depend on several factors, including route of administration, patient age /weight, cost and palatability[3]..

Despite the evidence not supporting differences between the PPIs, historically there is a practice to select different products as demonstrated by the range of products in use.

PPIs are acid-labile which means that they are deactivated by gastric acid. The PPIs are packaged in a variety of delivery systems [4]. These include enteric-coated tablets, gelatine capsules with enteric coated granules inside, oro-dispersible tablets formulated with enteric coated granules or coated granules supplied as a powder for suspension. The size of these individually enteric coated granules are different between formulations and brands, and this will make a difference when considering the best product for children with enteral feeding tubes.

Omeprazole Powder for oral suspension [5] relies on formulation with an alkali to protect the product from degradation instead of enteric coating, but there are no bioavailability studies to support this. It is very likely that the amount available for absorption is very low [6] License for this product was granted on the basis of established use of the unlicensed liquids[7]. The use of the unlicensed PPI liquids had already been considered by the APC in December 2019, as part of the Ranitidine Recall advice paper presented, and not recommended for use, and in September 2022, in a review paper of PPIs in adults.
It is recognised that the individual coated granules in the PPI dispersible tablets and in capsules may get stuck in enteral feeding tubes, especially in fine bore tubes, (<8FR), which are most commonly used in children and infants <10Kg. A newer formulation, esomeprazole gastro-resistant granules for oral suspension (sachet) is formulated with very small enteric coated beads in a suspension which thickens when added to water, is licensed for administration through feeding tubes French size 6 or larger and therefore is being presented as the preferred product for children 10-20Kg with enteral feeding tubes. It is licensed for children over 1 year of age, which tends to be associated with that weight range.

This paper will recommend that the licensed omeprazole powder for oral suspension is considered **BLUE** for children <10kg with enteral feeding tubes (<8Fr), and non-formulary in all other circumstances. All other unlicensed PPI oral suspensions should not be prescribed in primary care. Clinicians should understand that the efficacy of the omeprazole solution is uncertain because of acid breakdown, and they need to be aware of the sodium, potassium and alkali content of this medicine.

For all other children and infants, it is expected that a formulation including enteric coated granules will be used as this is more likely to deliver the PPI to the absorption site in the proximal small bowel, without degradation by the stomach acid.
The preferred PPIs for use in children have been selected for different age groups, taking into consideration the enteric coated granule (bead) sizes, see Appendix 2, the algorithm for prescribing PPIs in children.
It is expected that children on omeprazole oral suspension or any other liquid PPI preparations (unlicensed) should be reviewed for the need to continue PPI therapy, and, if yes, they should be switched to a suitable enteric coated formulation, unless they have an enteral <8Fr nasogastric feeding tube, see Appendix 3 for deprescribing advice.

Sodium bicarbonate can sometimes be used for flushing out blocked tubes if flushing with warm water using the push and pull technique has not worked. This should only be done in secondary care.

Summary:

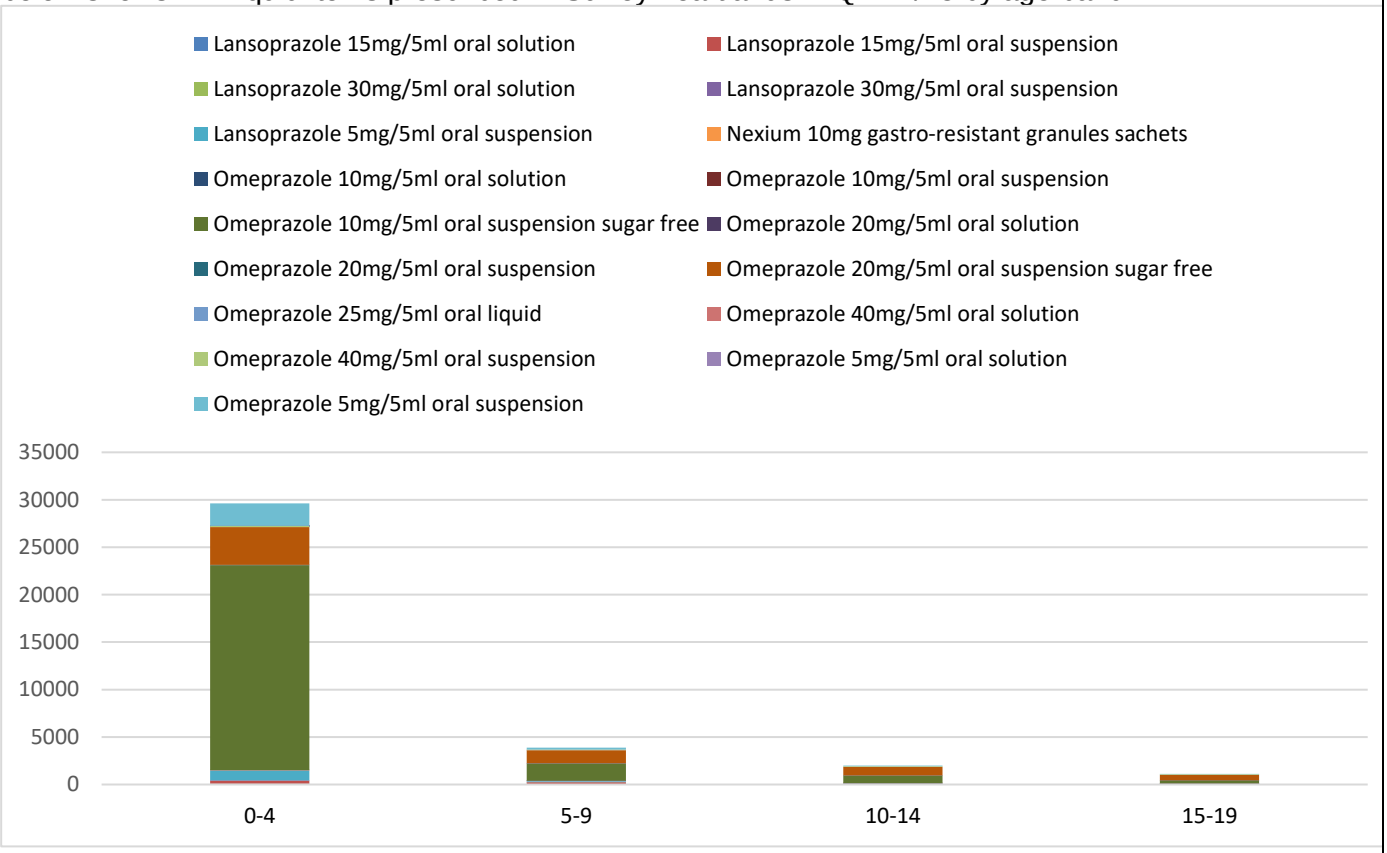
There is currently no convincing randomised control trial (RCT) evidence that one Proton Pump Inhibitor (PPI) is preferable to another for the management of GORD or Peptic Ulcer Disease (PUD) related symptoms or for endoscopically confirmed healing of oesophagitis [1].

PPIs are membrane permeable, acid-labile weak bases. In order to prevent premature activation and degradation by luminal gastric acid, these drugs are packaged in a variety of delivery systems. These include enteric-coated tablets, gelatine capsules, or coated granules supplied as a powder for suspension [4]. Omeprazole Powder for oral suspension[5] relies on formulation with an alkali to protect the product from degradation, but there are no bioavailability studies to support this, and it is very likely that the amount available for absorption is very low[6]

Appendix 2 provides an algorithm for formulation selection for children of different ages, with and without enteral tubes in situ.
When PPIs are prescribed in children, it is important to review the need for continued therapy regularly. Appendix 3 provides support for deprescribing PPIs in children.

Cost implications to the local health economy

Surrey heartlands spend around £340,000 per year on high cost PPIs in children 0-19 years old. Graph below shows PPI liquid items prescribed in Surrey heartlands in Q1 22/23 by age band.



Impact to current prescriber or medication initiator

- Where patients have enteral feeding tubes it is important to share good practice on the methods for administering dispersed soluble tablets or the contents of capsules to minimise the risk of enteral tubes being blocked, for example link[8]
- There are other formulations for which there is also no place in therapy which should be switched to more cost-effective options. However, this should be done in line with local priorities.

Impact to proposed prescriber or medication initiator

Initiation: make sure initiation is with the product of lowest acquisition cost considering patients ability to swallow/enteral feeding tube. There is no evidence of clinical benefit between different PPIs.

Impact to patients

- Patients on liquid formulations should get better bioavailability when switched to enteric coated alternatives but may experience a loss of brief relief from the alkaline in the suspension.
- Omeprazole powder for oral suspension (4mg/ml) contains 3.75mmol of sodium per 5ml dose, and 6.95mmol of potassium per 5ml dose. To be taken into consideration by patients with reduced kidney function or patients on a controlled sodium and/ or potassium diet. This is not the case for dispersible tablets.
- Discontinuation of the use of the oral suspension will reduce the risk of it being used inadvertently in patients who should not have the additional sodium and potassium This paper will recommend that the licensed omeprazole powder for oral suspension is considered **BLUE** for children <10kg, with

enteral <8Fr nasogastric feeding tubes as they are likely to be under a specialist who can recommend the suspension to be prescribed in primary care.
Additional comments
OptimiseRx messages will need to accurately describe each classification for each formulation – work will be done with the Optimise team to ensure messages are put in place.
Identified lead for development of necessary documents e.g. shared care agreement
Name: **Designation:** **Organisation:** **Estimated date of preparation:**

References:

1. Gastro-oesophageal reflux disease in children and young people: diagnosis and management. NICE guideline [NG1] Last updated: 09 October 2019. Available at:https://www.nice.org.uk/guidance/ng1/chapter/1-Recommendations#pharmacological-treatment-of-gord (Accessed – 9th October 2022)
2. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines. ESPGHAN guidelines 2017. Available at: https://www.espghan.org/knowledge-center/publications/Gastroenterology/2017_Pediatric_Gastroesophageal_Reflux_Clinical_practice_guidelines (Accessed - 9th October 2022)
3. Guideline for the Initiation and Monitoring of Proton Pump Inhibitors in Children, Nottingham Children's Hospital, NUH available through the Nottinghamshire Formulary (link), accessed 11/2022, adopted with permission from Andrew Wignell, Divisional Lead Pharmacist (Family Health), Advanced Pharmacist Practitioner (Paediatric Critical Care), Nottingham University Hospitals NHS Trust
4. Pump Inhibitors: A Comprehensive Review, Gut Liver. 2017 Jan; 11(1): 27–37. Published online 2016, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5221858/
5. eSPC, Omeprazole 4 mg/ml, Powder for Oral Suspension, Rosemont Pharmaceuticals Limited, https://www.medicines.org.uk/emc/product/11032/smpc ,
6. Northern Neonatal Formulary 2013 and earlierhttps://www.wiley.com/en-gb/Neonatal+Formulary%3A+Drug+Use+in+Pregnancy+and+the+First+Year+of+Life%2C+7th+Edition-p-9781118819517
7. Comparative effectiveness of proton pump inhibitors, Therapeutics Initiative, Evidence Based Drug Therapy, The University of British Columbia, Canada, https://www.ti.ubc.ca/wordpress/wp-content/uploads/2016/06/99.pdf 25 Years of Proton
8. NHS Greater Glasgow and Clyde, October 2018: Patient Information Leaflet: Instructions For The Administration Of Lansoprazole Orodispersible Tablets Via A PEG tube (ggcmedicines.org.uk) (accessed October 2022)
9. NICE CKS GORD in children July 2022: GORD in children | Health topics A to Z | CKS | NICE (Accessed 29/11/22)

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Declaration of Interest:

None

Date: 01/11/2022

Reviewed by: Clare Johns

Declaration of Interest:

None

Date:

VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
1.0	*01/11/22*	*Reham Al-Shwaikh,*	*Draft*	
1.1	*04/11/22*	*Carina Joanes*	*Draft*	
1.2	*10/11/22*	*Clare Johns*	*Draft*	*For QA review*
2.0	14/11/22	Reham Al-Shwaikh and Carina Joanes	Final	

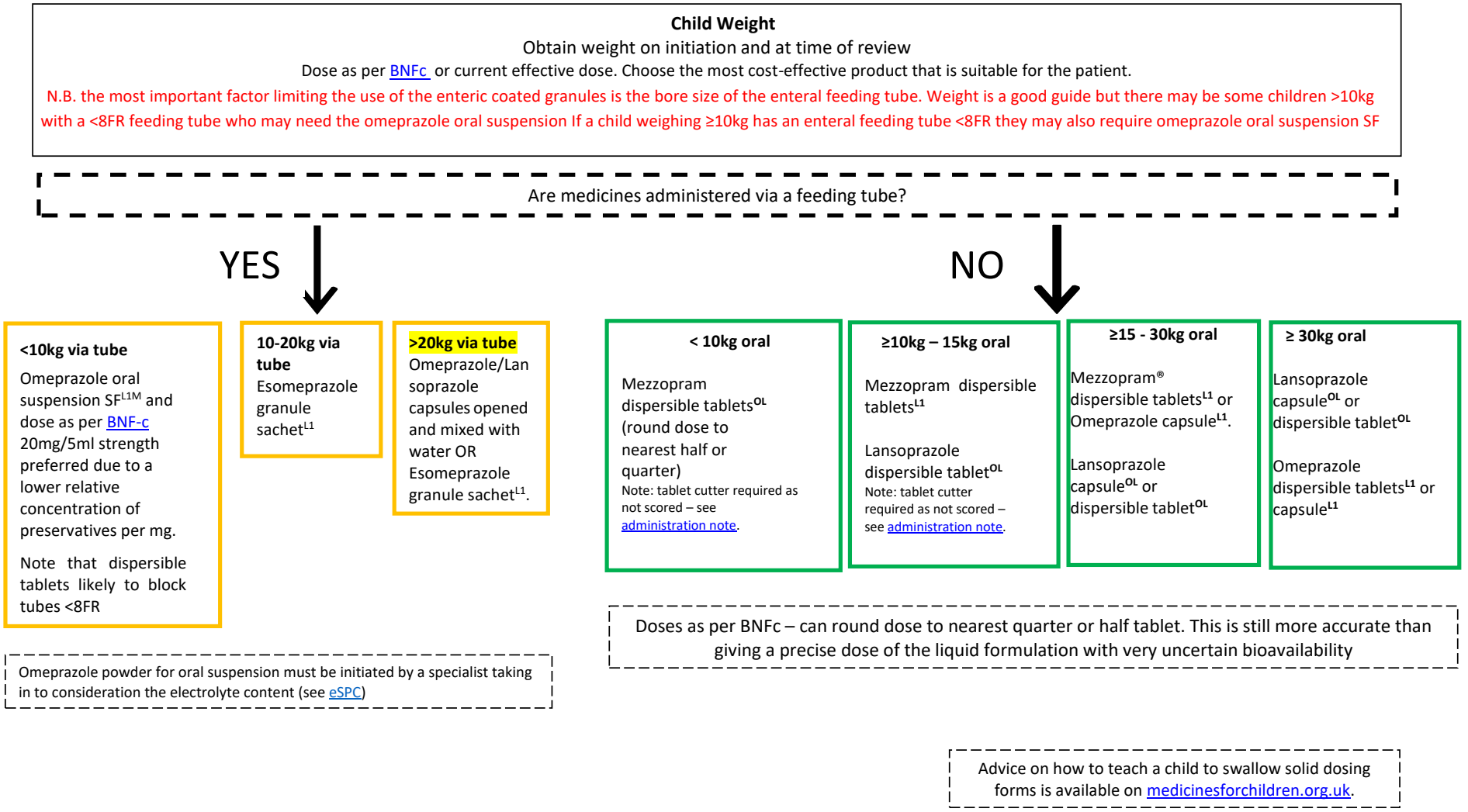
GREEN - Non-Specialist Drugs GPs (or non-medical prescribers in primary care) are able to take full responsibility for initiation and continuation of prescribing
BLUE - Specialist Input WITHOUT Formal Shared Care Agreement Prescribing initiated and stabilised by specialist but has potential to transfer to primary care WITHOUT a formal shared care agreement
AMBER - Specialist Initiation WITH Shared Care Guidelines Prescribing initiated and stabilised by specialist but has potential to transfer to primary care under a formal shared care agreement
RED - Specialist ONLY drugs Treatment initiated and continued by specialist clinicians
Non-Formulary Not recommended for use in any health setting across Surrey and NW Sussex health economy

Appendix 1: Cost and Place in Therapy for PPIs in Children

PPI	Formulation	Cost per 28 days	Licensing	Traffic light classification	Children who cannot swallow tablets	Children with enteral feeding tubes	Place in Therapy	Comments
Omeprazole	10mg and 20mg gastro-resistant capsules	10mg - £0.98 20mg - £1.02	Licensed in children >1 year and >10kg	GREEN [R]	most brands can be opened (licensed) and mixed with water or a slightly acidic fluid e.g. fruit juice, apple sauce.	No	1st Line	Bead size: Large (~1mm)
Omeprazole	10mg, 20mg and 40mg dispersible gastro-resistant tablets. (Mezzopram® is preferred due to smaller granule sizes) Losec Mups® should not be prescribed unless Mezzopram is out of stock.	10mg - £6.58 20mg - £9.86 40mg - £19.72	Licensed in children >1 year and >10kg	GREEN [R]	Disperse the tablets in water, then mix with orange/apple/ pineapple juice, apple sauce or yoghurt	No	1st Line	Bead size: Small (~0.2mm). Tablets are not scored but can easily be halved or quartered with a sharp knife. Neutral taste. Cordial can be added to water if needed.
Omeprazole	20mg/5ml and 10mg/5ml oral suspension SF	20mg/5ml 2x75ml - £402.20 10mg/5ml 2x75ml - £207.86	Licensed in children >1month	BLUE with no information sheet (on recommendation)	No	Yes for tube feeds <8FR	1st line for restrictions (<10kg <8Fr)	No enteric coating so possibly more likely to be degraded by stomach acid. 20mg/5ml is preferred strength as proportion of sodium and potassium per dose is less. To be switched to Mezzopram® when enteral feeding tube removed or larger guage in use. **NON-FORMULARY for all other indications/patients**
Lansoprazole	15mg and 30mg capsules	15mg - £1.00 30mg - £1.25	Not licensed in children however established use: Lansoprazole | Drugs | BNFC | NICE	GREEN [R]	Some capsules are licensed to be opened and have their contents mixed with water, apple/tomato juice or sprinkled on soft food (e.g. yoghurt, apple puree) for people with swallowing difficulties	No	2nd Line	Bead size: Large (~1mm)
Lansoprazole	15mg and 30mg orodispersible tablets **(Zoton FasTab®)**	15mg - £3.15 30mg - £4.63	Not licensed in children however established use: Lansoprazole | Drugs | BNFC | NICE	GREEN [R]	Orodispersible tablets dispere in the mouth to release gastro-resistant granules. Lansoprazole is NOT absorbed sublingually. The gastro-resistant granules must be swallowed for the medicine to be effective. The FasTabs® can also be administered in apple or orange juice.	No	2nd line	Bead size: Small ~0.2mm
Esomeprazole	10mg gastro-resistant granules sachets **(Nexium®)**	£25.19	Licensed in children >1year and >10kg	GREEN [R]	No	Yes (see product spc)	1st line for restrictions (enteral feeding tubes 6F or larger)	Bead size: Small ~0.2mm Sachet contains beads and a thickening agent, Tastes slightly sweet and unoffensive. For use in enteral feeding tubes FR<6

Appendix 2: Algorithm for prescribing PPIs in children. See updated version on PAD uploaded separately

Algorithm for prescribing PPIs in Children



L1 – licensed for children over 1 year of age and ≥10kg
L1M – licensed for children over 1month of age
OL – Off-Label

Appendix 3: Deprescribing PPIs in children

Why is the medication prescribed? Does the patient still need to be on treatment?
NICE NG1 & ESPGHAN recommend that after 4 to 8 weeks treatment, a trial off the medication should be attempted.

Consider stopping*/reducing the dose if:

- Indication still unknown
- Started for infant reflux and patient now eating some solids
- Gastro-oesophageal reflux disease (GORD) treated for 4-8 weeks (oesophagitis healed, symptoms controlled)
- Completed *Helicobacter pylori eradication* (in combination with antibiotics)
- Symptom-free for over 3 months
- Started as cover for NSAID/steroid/antiplatelet which is now stopped

* If patient has been on omeprazole for >6 months, reduce dose over 2-4 weeks before stopping to reduce risk of rebound symptoms.

Monitor at 2-4 weeks & at 12 weeks for: heartburn, dyspepsia, regurgitation, epigastric pain, loss of appetite, weight loss, and agitation. Advise parents / carers to contact the GP if the symptoms reoccur before the review date.

Recommend reducing the dose

Stop treatment and monitor for return of symptoms.

Treatment **should not be stopped** if the child has been diagnosed with:

- Benign gastric ulcer
- Duodenal ulcers
- On-going, uncontrolled GORD
- Acid related dyspepsia
- Zollinger-Ellison Syndrome
- Eosinophilic oesophagitis
- Previous dystonic crises/status dystonicus
- Fat malabsorption despite pancreatic enzyme replacement therapy in cystic fibrosis
- Gastro-protection whilst co-prescribed a potentially ulcerogenic medicine: NSAID; antiplatelets; anticoagulants; corticosteroids; SSRIs; NSAID + SSRIS and/or aspirin.
- Barrett's oesophagus
- Severe oesophagitis
- History of bleeding GI ulcer

Continue treatment but optimise formulation choice (see above algorithm)