Surrey Heartlands Integrated Care System
Area Prescribing Committee (APC)

Application for established medicines without APC entry including colour classification

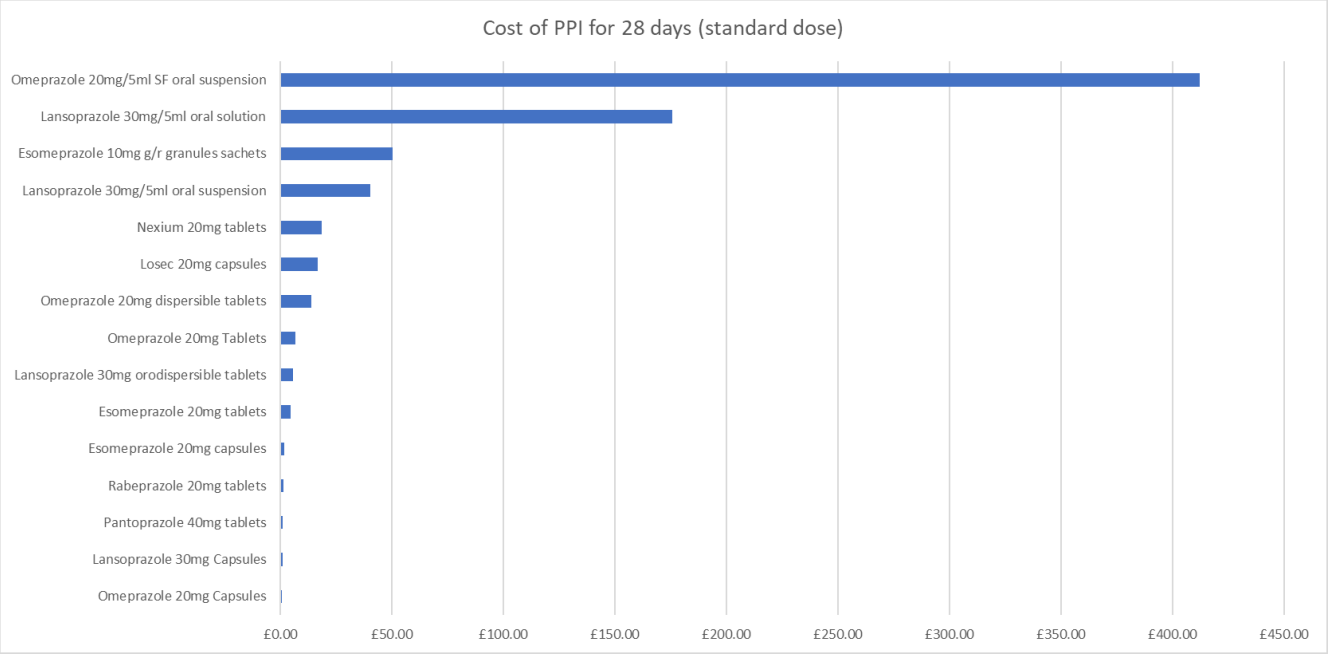
Purpose of this paper:

- **To optimise the use of the most cost-effective oral proton pump inhibitors (PPIs) for use in ADULTS in Surrey Heartlands, taking account of different formulation requirements**
- **To stop the use of Omeprazole Powder for oral suspension[3] in ADULTS**

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 adult patients. Current classifications are by PPI class. This review divides each PPI on 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) • Prevention and treatment of NSAID associated ulcers • Zollinger-Ellison syndrome • Severe Oesophagitis • Acid reflux disease	
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 PCN 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 Appendix 1 Appendix 2 for summary

Costs



Key Considerations

Briefing

There is currently no convincing randomised controlled trial (RCT) evidence that one Proton Pump Inhibitor (PPI) is preferable to another for the management of gastroesophageal reflux disease (GORD), Peptic ulcer disease (PUD) related symptoms or for endoscopically confirmed healing of oesophagitis [1]. - See Appendix 3

In November 2021, as part of a paper to change the traffic light classification of esomeprazole, the broad Green traffic light classification was added to all generic PPIs.

It was recognised at the time, that different formulations had a very significant impact on expenditure, and it was agreed that a further paper would be presented to rationalise the most cost-effective formulations for specific patient populations.

Decisions on traffic light classification will be based on the least expensive medicines in class, with the least expensive formulation which is licensed for specific routes of administration.

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.

It is expected that new patients will be started on the 1st choice PPIs, and that patients on expensive formulations will be switched to less expensive formulations where appropriate. Where the cost differences are small, there is no recommendation switch to first line choices.

Where there are several formulations of the same product, e.g. tablets and capsules, only the least expensive will be considered formulary, and the more expensive, non-formulary.

The specific patient populations which will be addressed are:

- Adults with no swallowing difficulties
- Adults who cannot/do not like to swallow solid dosage forms but do not have swallowing difficulties

- Adults with swallowing difficulties and
- Adults with enteral feeding tubes

As PPIs are non-irritant, the considerations for people who cannot/do not like to swallow tablets and those with swallowing difficulties will be the same.

Paediatric selections will be addressed in a separate paper.

PPIs acid-labile weak bases which are deactivated by gastric acid. The PPIs are packaged in a variety of delivery systems [2]. 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 patients with enteral feeding tubes.

Omeprazole Powder for oral suspension [3] 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 [4] License for this product was granted on the basis of established use of the unlicensed liquids[5]. 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. This paper will recommend that the licensed omeprazole powder for oral suspension is considered non-formulary for adults? and should not be prescribed in primary. (Proposed use in children will be very restricted). All other unlicensed PPI oral suspensions should also not be prescribed in primary care.

NB: This paper does not address the safety concerns about PPI prescribing and the benefit of routine re-appraisal as to whether ongoing treatment is required – See BNF

Summary:

There is currently no convincing RCT evidence that one Proton Pump Inhibitor (PPI) is preferable to another for the management of GORD or PUD related symptoms or for endoscopically confirmed healing of oesophagitis [1].
It is therefore important to prescribe the formulation of the least acquisition cost which meet patient's individual requirements. The requirements which will be addressed are:

- Adults with no swallowing difficulties
- Adults who cannot/do not like to swallow tablets but do not have swallowing difficulties
- Adults with swallowing difficulties and
- Adults with enteral feeding tubes

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 [2]. Omeprazole Powder for oral suspension[3] 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[4]

The different PPIs available for prescribing and their respective formulations are listed in Appendix 1, with the recommended traffic light classifications and prescribing restrictions. Appendix 2 summarises the preferred PPI formulation for different patient requirements.

The briefing explains why omeprazole liquid is less clinically suitable for prescribing. See above.

Cost implications to the local health economy
Surrey Heartlands spend around £650,000 per year on PPIs for adults and children. This figure is around £300,000 for adults and all children over the age of 5. For adults there is a potential saving of £120,000 per year offset by the cost of alternative formulations. See below for more detail: • Switching dispersible omeprazole to dispersible lansoprazole could potentially save £78,000 per year • Switching omeprazole suspension to dispersible omeprazole or even more economically, and with smaller granule sizes, dispersible lansoprazole, could potentially save £390,000 per year • Switching from brand preparations to their generic version could potentially save £24,000 per year • Switching from omeprazole tablets to omeprazole capsules could potentially save £50,000 per year
Impact to current prescriber or medication initiator
• There is no place in therapy, in adults, for PPI liquids including licensed omeprazole powder for suspension because of cost of these formulations, and the likelihood is that these formulations are less effective and less safe than the enteric coated formulations. Switch all patients on these formulations to suitable alternatives. • 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 • 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
• No impact is expected. • 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
Additional comments
A separate paper will address the use of PPIs in paediatric patients. 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. 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
2. 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/

3. eSPC, Omeprazole 4 mg/ml, Powder for Oral Suspension, Rosemont Pharmaceuticals Limited, https://www.medicines.org.uk/emc/product/11032/smpc ,
4. 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
5. Written communication from the MHRA, see appendix 3

Prepared by: Reham Al-Shwaikh

Declaration of Interest:

None

Date: 05/08/2022

Reviewed by:

Declaration of Interest:

None

Date:

VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
1.0	*05/08/22*	*Reham Al-Shwaikh*		
	08/08/22	*Carina Joanes*		*Peer review*
2.0	*26/08/22*	*Reham Al-Shwaikh*		*Amended following consultation*

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: PPI cost and place in therapy

PPI	Formulation	Pack Size	Cost per 28 days	Traffic light classification	Patients with no swallowing difficulties	Patients with swallowing difficulties	Patients with enteral feeding tubes	Place in Therapy	Comments
Lansoprazole	15mg gastro-resistant capsules	28	£0.84	Green	Yes	Yes (see comments)	Yes (see comments).	1st line	Some capsules are licensed to be opened and have their contents mixed with water, apple/tomato juice, or sprinkled on soft food (e.g. yogurt, apple puree) to help people with swallowing difficulties. Some brands are licensed for enteral feeding tubes 14F or larger (check SPC)
Omeprazole	20mg gastro-resistant capsules	28	£0.84	Green	Yes	Yes (see comments)	Non-formulary	1st line	Most capsules can be opened, and granules dispersed in water (check individual SPC)
Omeprazole	10mg gastro-resistant capsules	28	£0.85	Green	Yes	Yes (see comments)	Non-formulary	1st line	Most capsules can be opened, and granules dispersed in water (check individual SPC)
Lansoprazole	30mg gastro-resistant capsules	28	£1.07	Green	Yes	Yes (see comments)	Yes (see comments)	1st line	Some capsules are licensed to be opened and have their contents mixed with water, apple/tomato juice, or sprinkled on soft food (e.g. Yogurt, apple puree) to help people with swallowing difficulties. Some brands are licensed for enteral feeding tubes 14F or larger (check SPC)
Pantoprazole	20mg gastro-resistant tablets	28	£1.07	Green	Yes	Non-formulary	Non-forumulary	2nd line	Suitable for patients that cannot have animal-derived products
Pantoprazole	40mg gastro-resistant tablets	28	£1.11	Green	Yes	Non-formulary	Non-formulary	2nd line	Suitable for patients that cannot have animal-derived products
Rabeprazole	10mg gastro-resistant tablets	28	£1.26	Green	Yes	Non-formulary	Non-formulary	2nd line	Crushing is not recommended as stomach acid can destroy the active drug. Suitable for patients that cannot have animal-derived products.
Rabeprazole	20mg gastro-resistant tablets	28	£1.49	Green	Yes	Non-formulary	Non-formulary	2nd line	Crushing is not recommended as stomach acid can destroy the active drug. Suitable for patients that cannot have animal-derived products.
Esomeprazole	20mg gastro-resistant capsules	28	£1.77	Green	Yes	Yes (see comments)	Yes (see comments)	3rd line	Most (but not all) brands of esomeprazole tablets, capsules and granules for oral suspension are licensed for administration via gastric tubes. They will disperse in water for administration. For patients with fine-bore enteral tubes, consider switching to lansoprazole Fastabs®, which have smaller micro-granules.
Esomeprazole	40mg gastro-resistant capsules	28	£2.07	Green	Yes	Yes (see comments)	Yes (see comments)	3rd line	Most (but not all) brands of esomeprazole tablets, capsules and granules for oral suspension are licensed for administration via gastric tubes. They will disperse in water for administration. For patients with fine-bore enteral tubes, consider switching to lansoprazole Fastabs®, which have smaller micro-granules.
Omeprazole	40mg gastro-resistant capsules	7	£2.60	Green	Yes	Yes (see comments	Non-formulary	1st Line	Most capsules can be opened, and granules dispersed in water (check individual SPC)
Lansoprazole	15mg orodispersible tablets	28	£3.55	Green (R)	Non-formulary	Yes (see comments)	Yes (see comments)	1st line for restrictions	Restricted for use in adults with swallowing difficulties/cannot swallow tablets. Licensed for administration via nasogastric feeding tubes.
Esomeprazole	20mg gastro-resistant tablets	28	£4.75	Not for new initiation	Not for new initiation	Not for new initiation	Not for new initiation	Consider Switching to suitable alternative	
Esomeprazole	40mg gastro-resistant tablets	28	£4.77	Not for new initiation	Not for new initiation	Not for new initiation	Not for new initiation	Consider Switching to suitable alternative	
Lansoprazole	30mg orodispersible tablets	28	£5.77	Green (R)	Non-formulary	Yes (see comments)	Yes (see comments)	1st line for restrictions	Restricted for use in adults with swallowing difficulties/cannot swallow tablets. licensed for administration via nasogastric feeding tubes.

Omeprazole	20mg gastro-resistant tablets	28	£6.80	Non-formulary	Non-formulary	Non-formulary	Non-formulary	Switch to suitable alternative	
Omeprazole	10mg gastro-resistant tablets	28	£8.48	Non-formulary	Non-formulary	Non-formulary	Non-formulary	Switch to suitable alternative	
Omeprazole	10mg dispersible gastro-resistant tablets	28	£9.30	Non-Formulary	Non-Formulary	Non-Formulary	Non-Formulary	Switch to suitable alternative	
Omeprazole	20mg dispersible gastro-resistant tablets	28	£13.92	Non-Formulary	Non-Formulary	Non-Formulary	Non-Formulary (see comments)	Switch to suitable alternative	Licensed for enteral feeding tubes however the granules in lansoprazole orodispersible tablets are smaller and therefore more appropriate to be used in enteral feeding tubes
Lansoprazole	30mg/5ml oral suspension	100ml	£17.01	Non-Formulary	Non-Formulary	Non-Formulary	Non-Formulary	Switch to suitable alternative	
Esomeprazole	10mg gastro-resistant granules sachets	28	£25.19	Green (R)	Non-formulary	Yes	Yes	3rd line	Only for patients with dysphagia or enteral feeding tubes (6F or larger) when opening capsules is not clinically appropriate
Omeprazole	40mg gastro-resistant tablets	7	£27.2	Non-Formulary	Non-Formulary	Non-Formulary	Non-Formulary	Switch to suitable alternative	
Omeprazole	40mg dispersible gastro-resistant tablets	7	£27.92	Non-formulary	Non-formulary	Non-formulary	Non-formulary	Switch to suitable alternative	
Lansoprazole	15mg/5ml oral solution	100ml	£93.35	Non-Formulary	Non-Formulary	Non-Formulary	Non-Formulary	Switch to suitable alternative	
Lansoprazole	30mg/5ml oral solution	100ml	£123.05	Non-Formulary	Non-Formulary	Non-Formulary	Non-Formulary	Switch to suitable alternative	
Omeprazole	10mg/5ml SF Powder for Oral suspension	75ml	£212.92	Non-Formulary	Non-Formulary	Non-Formulary	Non-Formulary	Switch to suitable alternative	
Omeprazole	20mg/5ml SF Powder for Oral suspension	75ml	£412.00	Non-Formulary	Non-Formulary	Non-Formulary	Non-Formulary	Switch to suitable alternative	
Branded PPI's	Zoton, Losec, Pariet, Nexium, Protium all formulations, all strengths			Non-Formulary	Non-Formulary	Non-Formulary	Non-Formulary	Switch to suitable alternative	

All licensed PPI's (with the exception of omeprazole oral powder for solution and other unlicensed PPI solutions) are equal in terms of clinical efficacy. The formulary recommendations are based primarily on cost. Where indicated for the purpose of administration through enteral feeding tubes, the size of the enteric coated granules in the formulation are also considered. The omeprazole powder for oral solution (and all other unlicensed PPI solutions) have not been selected as they have been demonstrated to be clinically inferior.

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Appendix 2: Summary of preferred PPI formulation for different patient requirements

Summary

- For people with no swallowing difficulties:
  - 1st Line: Lansoprazole capsules/Omeprazole capsules
  - 2nd line: Pantoprazole tablets (Suitable for patients that cannot have animal-derived products)
  - 2nd line: Rabeprazole tablets (Suitable for patients that cannot have animal-derived products)
  - 3rd line: Esomeprazole capsules – not for new initiation

- For patients who cannot swallow tablets/have swallowing difficulties:
  - 1st Line: lansoprazole orodispersible tablets
  - 2nd line: lansoprazole capsules/omeprazole capsules (opened, and granules dispersed in water/yoghurt/apple puree)
  - 3rd line: esomeprazole granule sachets

- For patients with enteral feeding tubes:
  - 1st line: lansoprazole orodispersible tablets
  - 2nd line: lansoprazole capsules
  - 3rd line: esomeprazole granule sachets

All other formulations are non-formulary for adults. See table for priority switching

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Appendix 3: Similarity between different drugs in class(2)

Table 2

Pharmacokinetic Properties of Proton Pump Inhibitors

	Omeprazole	Esomeprazole	Lansoprazole	Dexlansoprazole	Pantoprazole	Rabeprazole
Bioavailability, %	30–40	64–90	80–85	-	77	52
Time to peak plasma level (tmax, hr)	0.5–3.5	1.5	1.7	1–2, 4–5	2–3	2–5
Protein binding, %	95	97	97	96	98	96.3
Half-life, hr	0.5–1	1–1.5	1.6	1–2	1–1.9	1–2
Primary excretion	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic
Liver metabolism	CYP2C19	CYP2C19	CYP2C19	CYP2C19 CYP3A4	CYP2C19 CYP3A4	CYP2C19

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Appendix 4: Written communication from MHRA

From: ……..
Hi there,
I have long had an interest in the pharmaceutics and pharmacology of Omeprazole oral suspension/ solution, and was surprised that this product has received a license, even though I accept that the unlicensed preparation was in use in significant quantities:
https://www.medicines.org.uk/emc/product/11031/smpc

Omeprazole is very acid labile and, the unlicensed solutions, there was more than 50% of the active ingredient lost to acid degradation before absorption (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 , and this despite giving neonates a significant dose of bicarbonate, sodium and potassium.
If the same theory is applied to adults, the amount of proportional buffer to the omeprazole by suspending it in an alkali, it is highly likely that the buffer solution will be diluted out in the much larger volume of stomach acid and therefore be even less bioavailable. It is also true that in this population the 'dose' of alkali, sodium and potassium is less clinically significant.
I am writing to you to enquire whether the manufacturers submitted any evidence for bioavailability specific to this formulation? I am in the process of writing a paper for the Area Prescribing Committee.
I have contacted Rosemont in June 2020 who informed me that the only information they have is that in the SPC. I have read the SPC very carefully and the evidence seems to be extrapolated as a 'me too' submission even though pharmaceutically it is such a different product.
I would be very grateful if I could be informed whether there was any additional basis for granting the license. If not, may I suggest that this is looked at again? There are two licensed products that should be used in preference – lansoprazole capsules which are licensed to be opened, and esomeprazole granules. These include enterically coated granules that protect the contents from the stomach acid.

Best regards……..……

From: MHRA Customer Services <MHRACustomerServices@mhra.gov.uk>
Dear ……
Apologies for the delay in reply. We have reviewed your request and can provide the following information below.
The approval of Omeprazole of 2 mg/ml Oral Suspension by the EU concerned member states (CMSs) was based on the assessment of the application by the reference member state (RMS), in this case, the Netherlands. As described in the public assessment report (PAR), the weakness of the supportive paediatric clinical study data in children under one year old was recognised by the RMS, that it was largely due the small number subjects investigated. This was acknowledged by the CMSs. However, in addition to the submitted study data, the decision by the member states to finally approve was in addition based on account of the experience with the innovator product. The applicant had demonstrated that the pharmacokinetic profile of the generic product is similar to the pharmacokinetic, pharmacodynamic, efficacy and safety profile of the reference product. In particular, the pharmacokinetic and pharmacodynamic data for young infants (<1 year) were supportive for omeprazole dosing recommendation of a milligram-per-kilogram weight basis in these patients.
Kind regards,
……
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