The Pharmacoeconomics of Proton Pump Inhibitors Prescribing in Ireland

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Abstract

Objectives: The purpose of this study was to determine cost-saving measures in the treatment of patients with conditions requiring proton pump inhibitor (PPI) maintenance therapy, and to examine factors that contribute to inappropriate PPI prescribing. **Methods:** Cost-Minimisation Analysis was used as the method of pharmacoeconomic evaluation for this study, an appropriate method given the National Institute for Clinical Excellence guidelines from July 2000, which concluded that all five PPIs on the market have equal efficacy. **Results:** Despite its higher cost, the original PPI omeprazole (Losec®) is still the most frequently prescribed PPI. In PPI maintenance therapy, substitution with any generic form of omeprazole (Losamel, Ulcid, Lopraz, or Losepine) is more cost-effective than using the brand-name omeprazole. Furthermore, in prescribing maintenance therapy for specific indications such as GORD, duodenal ulcer, and NSAID-induced peptic ulcer, rabeprazole (Pariet), lansoprazole (Zoton), or pantoprazole (Protium), respectively, are more cost-effective options compared with brand-name omeprazole. **Conclusion:** Substitution with these PPIs would be expected to produce savings of over six million euro per year.

Introduction

The secretion of hydrochloric acid (HCl), or gastric acid, into the stomach lumen is influenced by various physiological and neuroendocrine mechanisms. Physiologically, there are three overlapping phases of gastric acid secretion: cephalic, gastric, and intestinal. The cephalic phase is mediated by acetylcholinergic and vagal mechanisms and is stimulated by anticipation, taste and smell chemoreceptor activation, and swallowing. The gastric phase is primarily characterized by the release of gastrin from G cells found in the antrum of the stomach. The intestinal phase accounts for a minimal proportion of gastric acid secretion. The function of gastrin is to increase gastric acid secretion, and its release is stimulated by stomach distension and by the chemical effects of food products, including amino acids and peptides. In particular, phenylalanine and tryptophan are potent stimulators of gastrin secretion.

Stimulation of parietal cells in the gastric mucosa results in gastric acid secretion via up-regulation of the hydrogen-potassium adenosine triphosphotase enzyme system (H^+/K^+ ATPase), also known as the proton pump.[1] The three major stimuli of parietal cells are acetylcholine (ACh), gastrin and histamine, as shown in Figure 1.[2]

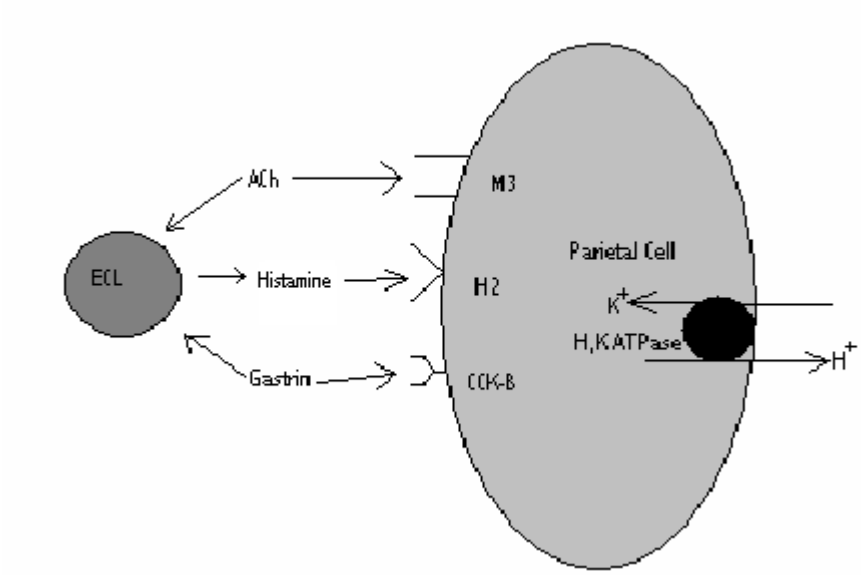

Figure 1: The regulation of acid secretion[3]

ACh released from parasympathetic neurons directly stimulates parietal cells through muscarinic subtype 3 (M3) receptors, and indirectly through activation of enterochromaffin-like cells (ECLs). ECLs release histamine, which activates histamine 2 (H_2) receptors, resulting in parietal cell stimulation. Gastrin primarily acts via stimulation of ECLs, but it can also directly stimulate parietal cells by binding to cholecystokinin-B (CCK_B) receptors. M3 and CCKb are G-protein coupled receptors (Gq), and their stimulation results in activation of phospholipase C, formation of inositol triphosphate and intracellular calcium release.[4] The majority of H_2 receptors couple with G_s, leading to activation of adenylate cyclase, resulting in elevated cyclical adenosine monophosphate concentrations.[5]

Stimulation of parietal cells induces structural and morphological changes. Parietal cells contain intracellular membrane regions called tubulovesicles, which retain H^+/K^+ ATPase pumps beneath the apical surface of the parietal cell in the unactivated state. Following activation, the tubulovesicles bind to the cell surface, resulting in translocation and insertion of the H^+/K^+ ATPase into the apical region of the parietal cell through a fusion-based mechanism, thereby creating a pathway through which acid secretion can take place.[6,7,8] Electron micrographs reveal dilated canalicular spaces, expanded apical membrane surfaces, and reduction of cytoplasmic tubulovesicles when parietal cells become activated.[8,9,10]

Structurally, PPIs contain a pyridine moiety, making them protonatable weak bases, with pKas of between 4.0-5.0.[11] In the unprotonated state, they are prodrugs and accumulate in regions where the pH is less than 4; the only area where this occurs is the canaliculi of active gastric parietal cells. PPIs are enteric-coated to protect them from premature activation by gastric acid.[12] After absorption in the duodenum, the PPI is transported to the parietal cell canaliculus, where it is protonated and converted to the active form of the drug, which forms a covalent disulphide bond with a cysteine residue in the H^+/K^+ ATPase proton pump. This irreversibly inhibits the terminal step in the acid secretory pathway, thereby reducing gastric acid secretion.[12,13]

PPIs are used to inhibit gastric acid secretion in a number of conditions: gastro-oesophageal reflux disease (GORD), duodenal ulcer, gastric ulcer, NSAID-induced ulcer, erosive esophagitis, hypersecretory syndromes including Zollinger-Ellison syndrome, and in combination therapy for the eradication of *Helicobacter pylori*. Each year approximately 40% of the population will suffer from symptoms of dyspepsia, including abdominal distension, early satiety, fullness, epigastric or retrosternal burning, anorexia, vomiting and nausea.[14] The goal of treatment is to maintain control of symptoms using the minimum effective dose of acid suppression. The standard method of treating dyspepsia is known as the 'step-up' approach, which begins with lifestyle modification and antacids. If this step fails, H_2 antagonists or motility drugs are started, followed by PPIs if necessary. The initial treatment dose of a PPI is used to bring the symptoms of dyspepsia under control, but once control has been achieved, the PPI dose is lowered in a 'step-down' approach. The majority of patients requiring long-term PPI therapy can achieve symptom control using the maintenance dosage. Long-term therapeutic dosages are only indicated in severe oesophagitis.[15]

This study examines expenditure on long-term PPI maintenance therapy in community drug schemes from 2000 to 2004. The three main community schemes, which account for about 95% of government drug expenditure, are the General Medical Services scheme (GMS), the Drugs Payment scheme (DP), and the Long Term Illness scheme (LTI), each responsible for expenditures of €550.89 million, €192.37 million, and €61.64 million, respectively, over the period from 2000 to 2003.[16]

PPIs accounted for 10.5% of total expenditure under the General Medical Services and Drugs Payment schemes in 2002, and the original PPI Losec (omeprazole) was the number-one selling drug in that year.[16] The four other PPIs on the market are lansoprazole (Zoton), rabeprazole (Pariet), esomeprazole (Nexium), and pantoprazole (Protium).[17] Branded generic forms of omeprazole are also available: Losamel, Ulcid, Lopraz and Losepine. Late in 2005, lansoprazole went off patent and generic brands Lansiop and Lanzol have recently been marketed.

In July 2000, the U.K.'s National Institute for Clinical Excellence (NICE) issued guidelines on PPI use.[18] These guidelines state that all five PPIs are of equal efficacy, so the least expensive PPI licensed for a given indication should be prescribed. Furthermore, PPIs should be prescribed in a 'step down' manner; that is, the dose should be lowered to a maintenance level after healing has been achieved, to control symptoms or prevent reoccurrence, depending on the condition. The guidelines also specify that patients diagnosed with non-ulcer dyspepsia (e.g. gastritis, duodenitis, hiatus hernia) should not be prescribed PPIs, and that long-term PPI therapy should only be implemented when a confirmed clinical diagnosis has been established.

Methodology

There are four main types of pharmacoeconomic evaluation: Cost Minimisation Analysis, Cost Effectiveness Analysis, Cost Utility Analysis, and Cost Benefit Analysis.[19,20] Cost Minimisation Analysis is used to define the most economical treatment among different alternatives already shown to have equal efficacy. It is a relatively straightforward and simple method; in practice, however, it is very difficult to find a situation where true equality in efficacy and safety exist, and consequently, this method is rarely applicable. However, since there is no difference in efficacy between the PPIs licensed for a given indication per NICE guidelines, all PPIs for an indication can be considered equal and the least expensive PPI should be used. Therefore, CMA is a suitable method of economic evaluation to identify the most appropriate PPI.

Data analyzed for this project was obtained from GMS Payment Board annual reports, 2000 to 2004, and from the GMS prescription files, which contain the following information for each prescription reimbursed:

- Date dispensed, dosage and expenditure
- ATCG Code (Anatomical Therapeutic Code Guideline; identifies drug, including therapeutic class, anatomical area, therapeutic indication)
- Patient number
- Patient gender
- GP number
- Pharmacy code

To limit the analysis to patients on maintenance therapy, only data from patients receiving PPI therapy for three consecutive months was used.

A table was compiled illustrating the different licensed indications and doses for each PPI. The cost per tablet for four weeks therapy at maintenance and treatment doses was then calculated using current retail prices. The most frequently prescribed drug was substituted using CMA with each of the other PPIs to determine potential cost savings. The percentage of prescriptions for each PPI at the higher treatment dose was determined, which prevented overestimation of potential savings for each drug. The potential savings by substitution was then calculated. Using this data, each PPI was ranked according to cost for each indication.

Results

The data collected from the GMS annual reports and prescription files shows that spending on PPIs in Ireland is increasing annually, more than doubling between 2000 and 2004[16]. Figure 2 demonstrates the overall increase in PPI expenditure, while Figure 3 compares the relative increases among the five different PPIs. The number of prescriptions mirrors the upward trend in expenditure, but the differences between Figure 3 and Figure 4 reflect the difference in price of each PPI. For example, use of the relatively inexpensive lansoprazole is increasing, as indicated by the growing number of prescriptions, but it does not contribute to the increase in expenditure to a similar degree. Overall, omeprazole is still the most frequently prescribed PPI. While its contribution to the total number of prescriptions is decreasing, it maintains a fairly consistent lead in its share of expenditure.

Figure 2: Total PPI expenditure on the GMS 2001-2004

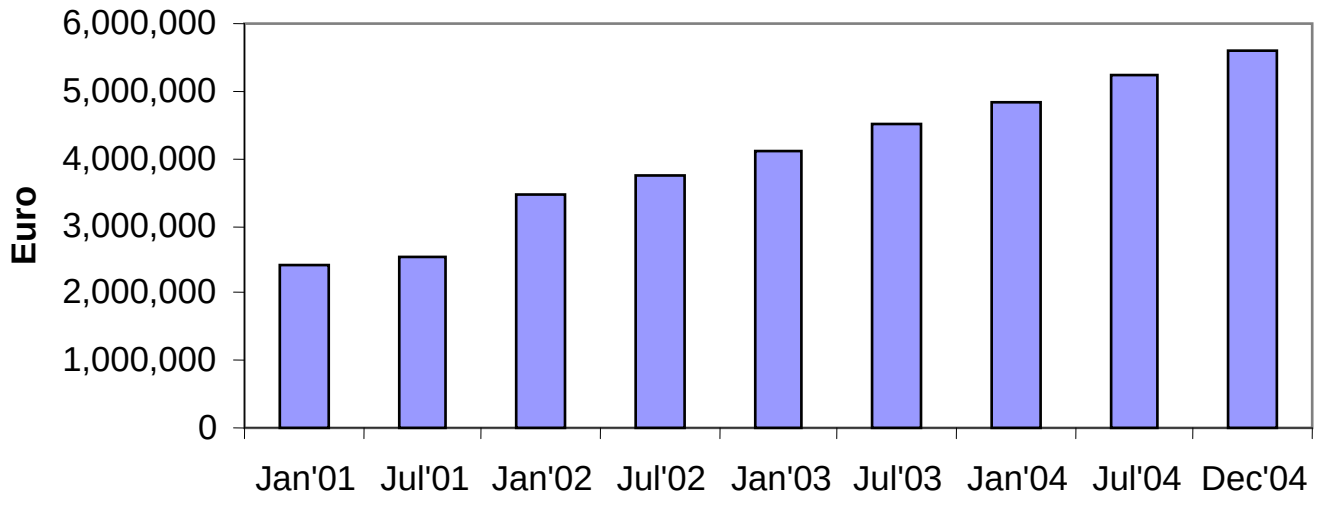

Figure 3: PPI expenditure on the GMS 2001- 2004

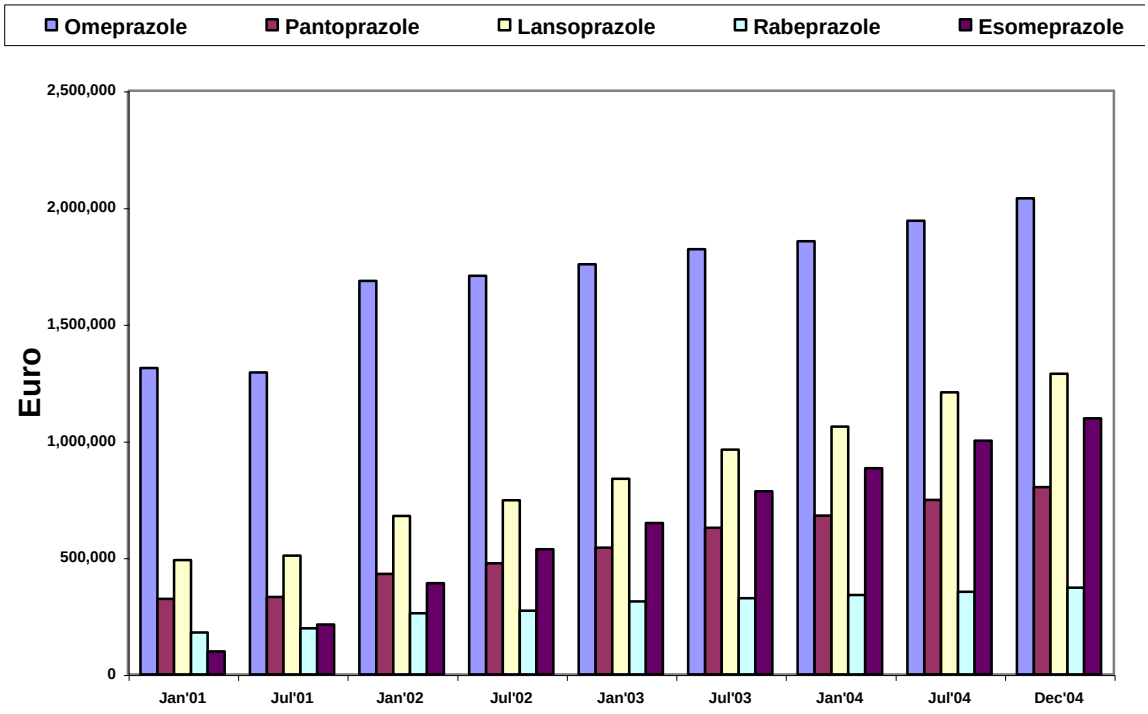

Figure 4: Total number of PPI prescriptions on the GMS between 2001-2004

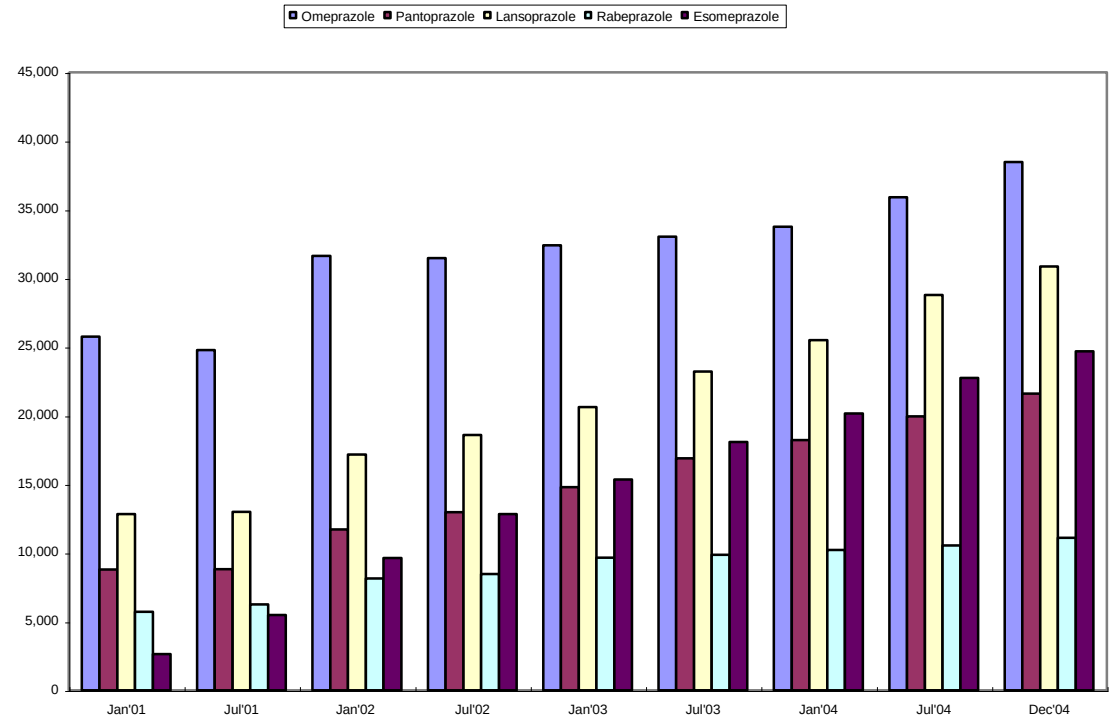

Table 1 displays the conditions for which each PPI is licensed, and whether it is licensed for treatment or for maintenance therapy. Omeprazole and lansoprazole are licensed for treatment and long-term maintenance for all three indications, while esomeprazole is only indicated for treatment and maintenance therapy of GORD. The doses for each drug and condition, for both treatment and maintenance, are compiled in Table 2, while the cost per tablet for four weeks therapy at maintenance and treatment doses using current retail prices is detailed in Table 3.

Drug	Indication				
	GORD		Duodenal Ulcer		NSAID PU
	Tx	Maintenance	Tx	Maintenance	Tx
Omeprazole (Losec, Losamel,Losepine Ulcid & Lopraz)	√	√	√	√	√
Lansoprazole	√	√	√	√	√
Rabeprazole	√	√	√	X	X
Pantoprazole	√	√	√	X	√
Esomeprazole	√	√	X	X	X

Table 1: Indication for each PPI for treatment and maintenance[17]

Drug	Dosage				
	GORD		Duodenal Ulcer		NSAID PU
	Tx	Maintenance	Tx	Maintenance	Tx
Omeprazole (Losec, Losamel,Losepine Ulcid & Lopraz)	20 mg/d	10-20 mg/d	20 mg/d 40 mg/d	10-20 mg/d	20 mg/d
Lansoprazole	30 mg/d	15-30 mg/d	30 mg/d	15 mg/d	15-30 mg/d
Rabeprazole	20 mg/d	10-20 mg/d	20 mg/d	X	X
Pantoprazole	40 mg/d	20 mg/d	40 mg/d	X	20 mg/d
Esomeprazole	20-40 mg/d	20 mg/d	X	X	X

Table 2: Dosage of each PPI for treatment and maintenance[17]

Omeprazole				
Losec	10 mg/d	10 mg x 28 =	€ 26.35	€ 0.94 / tab
	20 mg/d	20 mg x 28 =	€ 49.61	€ 1.77 / tab
	40 mg/d	40 mg x 14 =	€ 49.57	€ 3.54 / tab
Losamel	20 mg/d	20 mg x 30 =	€ 41.46	€ 1.38 / tab
Losepine	10 mg/d	10 mg x 28 =	€ 19.00	€ 0.68 / tab
	20 mg/d	20 mg x 28 =	€ 37.98	€ 1.36 / tab
Lopraz	10 mg/d	10 mg x 28 =	€ 18.95	€ 0.68 / tab
	20 mg/d	20 mg x 28 =	€ 28.95	€ 1.03 / tab
	40 mg/d	40 mg x 14 =	€ 35.50	€ 2.54 / tab
Lansoprazole				
Zoton	15 mg/d	15 mg x 28 =	€ 21.48	€ 0.77 / tab
	30 mg/d	30 mg x 28 =	€ 42.69	€ 1.52 / tab
Rabeprazole				
Pariet	10 mg/d	10 mg x 28 =	€ 20.68	€ 0.74 / tab
	20 mg/d	20 mg x 28 =	€ 32.42	€ 1.16 / tab
Pantoprazole				
Protium	20 mg/d	20 mg x 28 =	€ 21.22	€ 0.76 /tab
	40 mg/d	40 mg x 28 =	€ 39.30	€ 1.40 / tab
Esomeprazole				
Nexium	20 mg/d	20 mg x 28 =	€ 31.43	€ 1.12 / tab
	40 mg/d	40 mg x 28 =	€ 48.50	€ 1.73 / tab

Table 3: Cost of individual PPIs as per MIMS Ireland (December 2005 Edition)[21]

Given that omeprazole was shown to be the most commonly prescribed PPI, it was substituted with each of the other PPIs to determine potential cost savings using the prices calculated in Table 3. The percentage of prescriptions for each PPI at the higher treatment dose was determined, which prevented overestimation of potential savings for

each drug, and is shown in the first column of Table 4. The second column of Table 4 shows that by substituting the generic Lopraz for brand-name Losec in maintenance therapy, savings of over 6 millions euros per year would be expected. In fact, substitution with any of the generic forms of omeprazole is more cost-effective than using Losec. Furthermore, substitution of Losec with any other PPI would produce significant savings. In addition, substituting more cost-effective drugs based on indication, including rabeprazole (Pariet) for GORD, lansoprazole (Zoton) for duodenal ulcer, and pantoprazole (Protium) for NSAID-induced peptic ulcer will produce additional savings, as shown in the cost-effectiveness ranking in Table 5.

Drug	**Percentage of prescriptions at maintenance dose**	**Total savings when substituted for Losec (in euro)**
Generic omeprazole (Lopraz)	100%	6,843,000
Rabeprazole	19%	6,829,000
Generic omeprazole (Ulcid)	100%	6,419,000
Pantoprazole	34%	5,728,000
Lansoprazole	28%	4,233,000
Esomeprazole	52%	3,356,000
Generic omeprazole (Losamel)	100%	3,136,000

Table 4: Potential annual savings through substitution of alternative PPIs for brand-name omeprazole in maintenance therapy

	GORD		Duodenal Ulcer		NSAID PU
1	Losepine/Lopraz	1	Losepine/Lopraz	1	Losepine/Lopraz
2	Rabeprazole	2	Lansoprazole	2	Pantoprazole
3	Pantoprazole	3	Losamel	3	Lansoprazole
4	Lansoprazole	4	Losec	4	Losamel
5	Losamel			5	Losec
6	Esomeprazole				
7	Losec				

Table 5: Cost-effective drug list based on indication

Discussion

The objective of this study was to apply pharmacoeconomic evaluation to PPI prescribing in Ireland to ascertain whether any potential savings could be made.

The findings from this study demonstrate that omeprazole is the most frequently prescribed PPI. However, it remains the most expensive PPI, despite many licensed generic brands. Losepine and Lopraz, generic brands of omeprazole, are the most cost-effective PPI's for all indications. Substitution of Losec with these brands would produce savings in excess of 6.8 million euro (Table 5). Generic prescribing of drugs has long been advocated as good practice for all clinicians, not just to minimize expenditure but also to prevent medication errors. However, as demonstrated in Tables 3 and 5, it does not always optimize savings, as the generic brand of omeprazole, Losamel, is still more expensive than some of the other branded PPIs. Currently, legislation in Ireland restricts pharmacists from generic substitution without approval from the clinician. The council of the Pharmaceutical Society of Ireland issued the following statement in reference to generic substitution in pharmacies, "The community pharmacist has a complete responsibility for dispensing a prescription accurately and in accordance with the prescriber's instructions. In normal circumstances, where a doctor specifies a particular brand, the pharmacist is not entitled to substitute a generic 'equivalent', or even another branded product deemed to be equivalent, without the doctor's approval. In an emergency, where the prescriber is not readily contactable, the pharmacist may exercise his professional judgment in the best interest of the patient"[22]. While this issue may be addressed in the upcoming Pharmacy Act, at present the responsibility for generic prescribing lies with the doctor.

Following Losepine and Lopraz, the next most cost-effective PPI's were rabeprazole, lansoprazole, and pantoprazole for GORD, duodenal ulcer disease, and NSAID-induced ulcer respectively. Substitution of these PPIs in place of Losec in the treatment of the aforementioned conditions could result in savings of four to six million euro. A number of factors have been identified by GPs as important considerations when prescribing PPIs. These include guidelines, clinical investigations, marketing, prescribing behaviour and cost. The influence of aggressive marketing by pharmaceutical companies has been postulated as a significant cause of increased PPI prescribing.[23]

Another important finding from this study relates to the sizeable proportion of prescriptions for PPI maintenance therapy which were written at a treatment dose. All prescriptions for omeprazole were written at the correct maintenance dose, perhaps reflecting greater compliance of prescribers with its dosing schedule. However, for the remaining PPIs a great variation in the percentage of prescriptions at maintenance dose was observed: 52% for esomeprazole, 34% for pantoprazole, 28% for lansoprazole and 19% for rabeprazole. Thus, patients initially prescribed the higher, treatment dose are not

being prescribed the less expensive, maintenance dose once symptomatic control has been attained. There are two possible explanations which may account for this. Firstly, the lower dose may not be effective for symptom control in a proportion of patients and secondly, GPs may not be routinely reviewing treatment and decreasing doses as appropriate.

Conclusions

Expenditure on community drug schemes in Ireland is increasing rapidly, as illustrated in figures 2 and 3, with PPIs accounting for a considerable portion. A dramatic decrease in drug expenditure could be achieved through changes in PPI prescribing practices. As PPIs are equally effective, costs can be lowered without compromising clinical efficacy, through generic prescribing and prescribing the more cost-effective drug for certain indications. Use of the generic brands of omeprazole Losepine and Lopraz for all indications would achieve maximum savings. Expenditure could also be minimised by using rabeprazole for GORD, lansoprazole for duodenal ulcer, and pantoprazole for NSAID-induced ulcers. Generic prescribing is a simple and safe way to combat costs and all prescribers should be strongly urged to examine their prescribing practices.

According to the NICE guidelines, 70 to 80% of patients taking PPIs should be prescribed a maintenance dose.[18] Doctors should be informed of these guidelines and encouraged to periodically review the patient's symptoms and 'step down' treatment when appropriate. The results of this study highlight the potential for cost savings to be made by generic substitution, facilitating the most efficient use of the limited drugs budget.

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