Chapter 9

General discussion
In the first part of this thesis the clinical and pharmacoeconomic aspects of the use of proton pump inhibitors were investigated. The second part of this thesis was dedicated to pharmacoeconomic aspects of *Helicobacter pylori* eradication. Thirdly the pharmacoeconomics of *Helicobacter pylori* vaccination was discussed. All 3 parts are discussed separately in the following section.

9.1.1 Proton pump inhibitors

The first part of this thesis was concerned with the differences in clinical effectiveness between the 5 PPIs currently available in the Netherlands. Currently there are 5 different PPIs are available in the Netherlands: omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole (the s-isomer of omeprazole). This difference in clinical effectiveness is then translated into the potential consequences on the use and the costs of the PPIs. Not only are the five branded products of importance, but also the newly introduced generic, omeprazole, which was launched in April of 2002 following the patent expiry of Losec®.

Omeprazole was the first available drug in this class and therefore most of the comparisons between the PPIs include omeprazole. There are differences in the mechanism of action in terms of specific binding sites on the proton pump for the different PPIs. All PPIs bind to the proton pump at the cysteine site 813. In addition, pantoprazole also binds on the adjacent cysteine site 822, whereas omeprazole binds to cysteine 892. The newer PPIs lansoprazole and rabeprazole bind to two additional sites, cysteine 892 and 321 [1]. PPIs bind only to the activated proton pumps and should therefore be administered 30-60 minutes before a meal for optimal effectiveness [2]. The differences in the pharmacokinetics of the various PPIs do not seem to influence the overall clinical effectiveness. Most of the PPIs are eliminated renally (70-90%) with the exception of lansoprazole, which is predominately excreted through the bile [3].
The onset of action for all PPIs is between 1-2 hours, in particular, lansoprazole 30mg having the most rapid onset of action (1.0 hour), whereas pantoprazole 40mg and rabeprazole 20mg are slowest (1.75 hour) [4]. Although rabeprazole has the longest time to onset, it reaches the highest 24-h median pH (3.4) within the first day. This indicates that rabeprazole reaches the maximum effect before the other investigated PPIs. This strong first-day effect of rabeprazole has been documented in the literature [5]. An important factor for clinical effectiveness of PPIs is the duration of intragastric pH above 3 or even better 4. This time is called the “holding time” for PPIs. Generally the longer this “holding time” the better. In a study where 5 PPIs were compared: omeprazole capsule, omeprazole MUPS, pantoprazole, lansoprazole and rabeprazole, the holding time for the first day dosing was shown. Rabeprazole was superior to the other PPIs used [4]. However in a recent five-way crossover study where omeprazole MUPS, pantoprazole, lansoprazole, rabeprazole and esomeprazole were compared it was shown that on day 5 esomeprazole had the superior holding time for pH>4 [6]. In these studies different dosages of PPIs were used. It is unclear how the dosages used affect the results found. Although there is a defined daily dose for all PPIs, it is debatable whether this dosage is the optimal dosage for a maximum effect.

Another difference can be found in the different enzymes which are involved in the metabolism of the different PPIs. For omeprazole, pantoprazole, lansoprazole and esomeprazole the most important metabolic pathway is the cytochrome P450 2C19 (CYP2C19) enzyme. Fast metabolizers (with highly active CYP2C19) will yield lower plasma levels and thus lower efficacy will be reached in those patients [7,8]. The CYP3A4 pathway, an isoenzyme, is also an important pathway in the PPI metabolism. Lansoprazole is mainly metabolised by the CYP3A4 isoenzymes [9]. Esomeprazole is metabolised more slowly and more predicatively than the R-isomer of omeprazole. Rabeprazole is unique as it is metabolised through a non-enzymatic pathway and the isoenzymatic CYP2C19
and CYP3A4 pathways are secondary [10,11]. Genetic testing prior to starting a PPI might be useful in the future to optimize PPI therapy [12].

The difference in metabolic pathways also impacts the potential for drug interactions. Many medications are metabolised through the CYP450 pathways, and the potential for interaction is therefore dependent on the extent in which the PPI is metabolised via the CYP450 system. Omeprazole has the greatest interaction potential, whereas rabeprazole due to its alternative pathway has the least interaction potential.

The existence of limited differences between the various PPIs raises the question whether switching patients from one PPI to another, results in a positive effect on the budget. This question has been addressed in chapter 3 with a pharmacoeconomic comparison between omeprazole and pantoprazole. At the time of the study, omeprazole was still under patent protection. A total of €40.8 million could be saved if 90% of the patients of omeprazole switched to pantoprazole. During the study, omeprazole was still under patent protection, the recent introduction of generic omeprazole is likely to result in even greater savings.

The current agreement between industry, pharmacists, government and insurance companies, generic prices are 40% lower compared to the prices of the branded products [13]. A potential danger for this cost-savings with the introduction of generics is therapeutic substitution, which is the switching of one chemical entity in a given therapeutic class to another (e.g., a switch from omeprazole to pantaprazole). Therapeutic substitution is a phenomenon which is not uncommon in daily practice. There are many reasons for therapeutic substitution, including an adverse reaction to one of the drugs in the therapeutic group, which is unlikely to occur with one of the alternatives in that therapeutic class (e.g., reactions to adjuvant components in a tablet) or it may result from a lack of effect with the first drug used in that therapeutic class. After the patent expiry of omeprazole more
patients switched from omeprazole to another PPI. Many explanations for this change in switching behaviour may exist, next to the introduction of generic omeprazole. First of all, there was the introduction of esomeprazole, a new drug in the class of PPIs. This introduction may cause more people to switch from omeprazole. Another possible reason may be the differences in pharmacokinetics of the capsules of generic omeprazole [14]. Patients have complained of lack of effect of the generic compounds compared to the branded product they first used. Further research on the reasons for the increase in switching from omeprazole to another PPI is necessary, to possibly prevent an increase of therapeutic substitution, after patent expiry, in other therapeutic groups.

9.1.2 Objectives achieved

In this part of the thesis 3 objectives were investigated:

a) To evaluate the clinical relevance of the differences between the currently available PPIs

b) To evaluate the pharmacoeconomic implications of switching between PPIs

c) To evaluate the impact of patent expiry of omeprazole on switching behaviour and costs

The first objective relates to the clinical impact of the differences in the PPIs currently used. In clinical practice the differences mentioned above seem to be of limited importance, as most studies, including our own review indicate comparable efficacy in clinical trials between the different PPIs. However, for particular patients these small differences may have great impact.

Secondly, the economic impact of switching from omeprazole to pantoprazole is investigated. A potential saving of €40.8 million was found when switching 90% of the patients on omeprazole to pantoprazole. However, with
changing prices in branded PPIs and the introduction of generic products this figure will constantly change.

Thirdly, it was found that after patent expiry more patients switch from omeprazole to another PPI. This switching has a negative effect on the potential savings on PPIs with the introduction of generic omeprazole.

9.2.1 *Helicobacter pylori* eradication

The second part of this thesis comprises the economic aspects surrounding *Helicobacter pylori* eradication. The aspects of *Helicobacter pylori* eradication versus acid suppression in peptic ulcer disease were investigated. Also, the use of acid suppressive therapy following *Helicobacter pylori* eradication, an important factor in cost-effectiveness analysis, was studied. *Helicobacter pylori* eradication strategy is also involved in the initial approach of patients consulting their general practitioner with dyspeptic complaints. Here a so called *Helicobacter pylori* test-and-treat approach is compared to a prompt endoscopy approach.

In chapter 5 a literature review revealed that *Helicobacter pylori* eradication was more cost-effective than maintenance therapy with histamine-2-receptor antagonists (H₂RAs). Nowadays, maintenance therapy with acid suppressive drugs will probably comprise of PPIs and not H₂Ras, because of their superior effectiveness [15,16]. This will positively influence the effectiveness of maintenance therapy and thus decrease the difference with eradication therapy in terms of effectiveness, it will however increase costs.

The studies examined chapter 5 were modelling studies. In modelling studies the results depend on the assumptions made concerning the various input parameters. One of the assumptions made was that no gastrointestinal drugs were used after successful *Helicobacter pylori* eradication. One of the studies in this review disputed this assumption and incorporated gastrointestinal drug use after
*Helicobacter pylori* eradication. In their model they used clinical trial data in which gastrointestinal drug use after eradication was seen [17]. There are several explanations for continued gastrointestinal drug use after eradication. Firstly *Helicobacter pylori* infection is not always responsible for the peptic ulcer disease [18]. In this case eradication of *Helicobacter pylori* might even increase complaints as *Helicobacter pylori* produces urease which decreases the acidity of the stomach. Secondly *Helicobacter pylori* eradication might fail, and peptic ulcer disease is not resolved. However, eradication percentages found are high [19] and even if eradication fails it is possible to use a second line treatment (e.g., including a bismuth containing compound) [20]. Furthermore, it is possible that other gastrointestinal diseases are present and eradication of *Helicobacter pylori* will resolve the peptic ulcer disease, but not the other disease. There has been much debate concerning the role of *Helicobacter pylori* in gastroesophageal disease. Some studies state that *Helicobacter pylori* has no influence on gastroesophageal disease, whereas other state that eradication of *Helicobacter pylori* will increase the risk on gastroesophageal reflux disease. No definite answer on this debate can be made [21-24].

In chapter 6, pharmacy- and GP-data were used to investigate the use of gastrointestinal drugs after *Helicobacter pylori* eradication in daily practice. It was found that after *Helicobacter pylori* eradication there were still patients who used gastrointestinal drugs. Overal the use of gastrointestinal drugs decreased after *Helicobacter pylori* eradication, the patients who stil used gastrointestinal drugs were, however, more expensive users and predominantly used PPIs. When prescription data were used, as is with pharmacy records, it can be argued that eradication therapy was prescribed to patients without peptic ulcer disease and that these patients would therefore not always benefit from *Helicobacter pylori*. Therefore, further research was done using GP data and it was found that the indication for which *Helicobacter pylori* eradication therapy was prescribed did not influence the outcome. Also, the possiblility excists that no *Helicobacter pylori*
was present. For both studies no data were available on testing of *Helicobacter pylori* infection, which probably explains why some patients did not benefit from *Helicobacter pylori* eradication.

The role of *Helicobacter pylori* eradication in patients presenting with dyspeptic symptoms in primary care is also debated. The GP can choose between (1) symptom guided empirical treatment, (2) prompt referral for endoscopy and (3) test for *Helicobacter pylori* infection and treat positive patients (test-and-treat) for patients with dyspeptic symptoms. In chapter 7 the test-and-treat approach was compared to the ‘golden standard’ of prompt endoscopy. It was found that, in terms of quality adjusted life years, no significant differences were present between the prompt endoscopy approach and the *Helicobacter pylori* test-and-treat strategy; however, the *Helicobacter pylori* test-and-treat approach was less costly. This indicates that a *Helicobacter pylori* test-and-treat approach is more cost-effective than prompt endoscopy as an initial approach in patients presenting with dyspeptic complaints in general practice. This positive result for *Helicobacter pylori* eradication is dependent on the prevalence of *Helicobacter pylori* infection. With diminishing prevalence of *Helicobacter pylori* [25] the percentage of positive patients will decrease, and the number needed to test will increase. In the Netherlands however, immigrants from areas with high prevalence of *Helicobacter pylori* infection will probably benefit to an even greater extent from a *Helicobacter pylori* test-and-treat approach [26]. Endoscopy has the advantage of visualizing the oesophagus, stomach and upper duodenum and allows possible malignancies to be identified. Unfortunately, when the *Helicobacter pylori* test-and-treat approach is used, the opportunity to exclude malignancies through visual inspection is delayed.

The discussion remains whether or not a *Helicobacter pylori* test-and-treat strategy will be more cost-effective compared to empirical treatment with acid inhibitors. The number of endoscopies prevented was the most important reason for the cost advantage for the *Helicobacter pylori* test-and-treat approach. The
number of endoscopies prevented by empirical treatment with acid inhibitors is likely to be comparable. In patients where *Helicobacter pylori* is responsible for this dyspeptic complaints, acid inhibitors will reduce or ameliorate the symptoms, but in long-term the cause is not addressed. The advantage of acid suppressive therapy over *Helicobacter pylori* eradication is the diminished risk of antibiotic resistance, which is associated with a reduction in eradication rates. It has been shown that an increase in resistance impacts the cure rate of PPI-amoxicillin-clarithromycin and PPI-amoxicillin-metronidazol eradication regimes [27]. However, because *Helicobacter pylori* has been shown to be partly responsible for peptic ulcers and gastric cancers [28,29], a *Helicobacter pylori* eradication will have an additional positive health effect which was not incorporated in the short term analysis.

### 9.2.2 Objectives achieved

In this part of the thesis 3 objectives were investigated:

a) To estimate the cost-effectiveness of *Helicobacter pylori* eradication therapy compared to acid suppressive therapy in the management of peptic ulcer disease

b) To evaluate the effect on gastrointestinal drug costs and use of *Helicobacter pylori* eradication in patients with gastrointestinal problems

c) To estimate the cost-effectiveness of a *Helicobacter pylori* test-and-treat strategy as the initial management strategy of dyspeptic patients compared to a prompt endoscopy approach

*Helicobacter pylori* eradication was considered to be more cost-effective in the management of peptic ulcer disease compared to acid suppressive therapy. However, the comparisons made were with H$_2$RAs. Effectiveness obtained with the use of PPIs might be higher; however, higher costs are likely to be incurred.
In daily practice, *Helicobacter pylori* eradication leads to less drug use and their associated costs. Patients still using gastrointestinal drugs were primarily using PPIs. No difference was found in outcome, when patients were stratified for difference in gastrointestinal problems as documented by the GP.

In the management of dyspeptic patients, a *Helicobacter pylori* test-and-treat strategy is considered a cost-effective option as the initial management strategy, when compared with the prompt endoscopy approach. Further research is required on the cost-effectiveness of empiric acid suppressive therapy versus the *Helicobacter pylori* test-and-treat strategy.

### 9.3.1 *Helicobacter pylori* vaccination

In chapter 8 a cost-effectiveness analysis of a fictitious *Helicobacter pylori* vaccine was performed. The cost-effectiveness ratio found when using the currently prescribed discounting procedure, with a discount rate of 4% for health and costs, was below the currently advocated threshold in the Netherlands of €20,000 per life year gained [30]. When using a lower discount rate for health, the cost-effectiveness ratio of a potential *Helicobacter pylori* vaccine would become even more attractive.

Currently no *Helicobacter pylori* vaccine is available for human use. This introduces obvious weaknesses to the model which was used, there are no real life data on effectiveness and the costs of a vaccine are unknown. In the sensitivity analysis, the biggest influence found was the discount rate used for health.

This part also focuses on the impact of introducing a lower discount rate for health effects. Discounting is an important factor for the cost-effectiveness ratio found in preventive programs (e.g. screening and vaccination). The currently used discount rates, in which money and health are discounted equally [20], diminishes the change of acceptance of preventive programs compared to using a lower discount rate for health. The primary reason for this is that preventive programs
incur cost immediately (not discounted) and the beneficial effects occur in the future (and thus discounted). Lowering the discount rate will therefore benefit preventive programs.

For the determination of the discount rate for health, it is acceptable to use the same calculation method as used for money. This calculus incorporates the growth rate of money, the higher this growth rate, the higher the discount rate. Because the growth rate of money is generally higher than that of health, a lower discount rate for health is justified. The impact of a differential discount rate for money and health was demonstrated in chapter 8, showing a more favourable cost-effectiveness ratio when using the 1.5% discount rate for health instead of the currently used 4%.

A change in pharmacoeconomic guidelines with regard to discounting will greatly benefit preventive programs and will make decision making more fair towards our future generations.

9.3.2 Objectives achieved
In this part of the thesis 2 objectives were investigated:

a) To estimate the cost-effectiveness of a potential *Helicobacter pylori* vaccine

b) To evaluate the impact on cost-effectiveness, of this potential *Helicobacter pylori* vaccine, of using different discount rates for health effects

A potential *Helicobacter pylori* vaccine has a cost-effectiveness ratio which is below the currently used threshold of €20,000/LYG [20]. This is true when a 4% discount rate for health is used, as well when a 1.5% discount rate for health is used.

The most important factor in the cost-effectiveness of the potential *Helicobacter pylori* vaccine is the discount rate used for health effects. Lowering the discount rate, from 4% to 1.5%, leads to a lowering of the cost-effectiveness
range of the difference scenarios. With a 4% discount rate the range is approximately €6,600 to €23,000 and with a 1.5% discount rate this is approximately €2,600 to €4,300. It is clear that a lower discount rate for health effects leads to markedly lower cost-effectiveness ratios in the evaluation of a potential *Helicobacter pylori* vaccine.
References


