Summary and General conclusions
In this thesis the pharmacoeconomics aspects of upper gastrointestinal problems were investigated. The comparability of proton pump inhibitors (PPIs) was discussed as well as switching patterns after the ending of the patent protection of omeprazole, the first drug marketed in this class. In addition, the pharmacoeconomics of the eradication of *Helicobacter pylori* were investigated. For example, the cost-effectiveness of *Helicobacter pylori* eradication was compared to maintenance therapy with an acid inhibitor. Also, the pharmacoeconomics of a so called *Helicobacter pylori* test-and-treat approach in dyspeptic patients were compared to a prompt endoscopy approach. Thirdly the cost-effectiveness of a potential *Helicobacter pylori* vaccine was addressed. This last part also investigated the impact of using different discount rates for health.

**Proton pump inhibitors**

The use of health resources for upper gastrointestinal drugs is high. The use of gastrointestinal drugs accounted for approximately 7% of the outpatient drug expenditures, totally €295.4 million in 2004. The main driver for these drug expenditures were the PPIs, which accounted for €263.4 million (89%).

Controlling the drug expenditures from gastrointestinal drugs therefore starts with controlling the expenditures relating to the use of the PPIs. As is shown in this thesis in chapter 2, it is very likely that the different PPIs do not have clinically important differences on population level. The question remains whether the currently described defined daily dose (DDD) for the different PPIs is the correct DDD. As is shown in chapter 3, for omeprazole it was not uncommon that patients’ prescribed daily dose (PDD) was higher than de DDD for omeprazole. For pantoprazole this was not the case. For an estimation of potential cost savings by using the least expensive PPI it is prudent to investigate what the actual used daily
Summary and General conclusions

dose is for each PPI. This, because the eventual cost savings of a switch in PPI use, depends on the dose used of the different PPIs.

The clinical interchangeability of PPIs currently available in the Netherlands is discussed in chapter 2. In this chapter it is shown that, although pharmacokinetic differences between the PPIs exist, in clinical practice these differences are of limited importance for the general population. In most studies, no differences in overall efficacy exist between the different PPIs. Although for the majority of the patients there is no reason to prefer one PPI over the other, there are differences between PPIs which may be of importance for specific patients. Although generic omeprazol products did show bio-equivalence in their registration studies, it is important to clarify the clinical impact of the difference in pharmaco-kinetics of generic omeprazole formulations.

*Helicobacter pylori* eradication

*Helicobacter pylori* is associated with the development and recurrence of peptic ulcer disease as well as the development of gastric cancer. This part of the thesis investigated *Helicobacter pylori* eradication versus maintenance therapy with a histamine-2-receptorantagonist (H2RA) in controlling peptic ulcer disease. In most studies it was shown that *Helicobacter pylori* eradication is the most cost-effective approach in controlling peptic ulcer disease. However, in one of the studies used in this review, maintenance therapy was shown to be the more cost-effective approach over a 5 year period. The studies comparing *Helicobacter pylori* eradication to H2RA maintenance therapy used models to predict cost-effectiveness. In most models used, it was assumed that after successful *Helicobacter pylori* eradication no further gastrointestinal drugs were used. In unsuccessful eradication it was assumed that gastrointestinal drug use was comparable to the drug use in the maintenance therapy group. To investigate this assumption one prescription database with pharmacy records and one prescription
database with general practitioner (GP) records was investigated. In the first
database more patients could be identified, but no indication for *Helicobacter pylori*
eradication was recorded. The second database was smaller, but the
indication was known. In these two studies it was shown that after *Helicobacter pylori*
eradication the majority of the patients stop using gastrointestinal drugs.
However, some patients continue to use gastrointestinal drugs. The majority of
these patients used PPIs after eradication. Also it was demonstrated that patients
who continue to use gastrointestinal drugs after *Helicobacter pylori* eradication had
higher average drug costs as compared to before eradication. These findings
indicate that the pharmacoeconomic evaluations used in the review probably over-
estimated the favourable cost-effectiveness profile of *Helicobacter pylori*
eradication. However, it is clear that in proven peptic ulcer disease and a positive
*Helicobacter pylori* test, *Helicobacter pylori* eradication is necessary, particular as
*Helicobacter pylori* is a factor that has been shown to be important in gastric
cancer.

In the Western world the prevalence of dyspeptic complaints is high, and is one of
the most seen complaints by GPs. GPs have different treatment options or
approaches when a patient presents with dyspeptic complaints. In this thesis the
health economic comparison of two of these approaches was discussed. The two
strategies investigated were a *Helicobacter pylori* test-and-treat strategy and a
prompt endoscopy strategy. For both approaches, the difference in effectiveness
measured in terms of quality adjusted life years is small. As zero effectiveness is
incorporated in the 95% confidence interval, it is demonstrated that the difference
for clinical practice is not present. However, the difference in cost is significant, as
all bootstrap replicates show less costs for the *Helicobacter pylori* test-and-treat
approach.

Both approaches have their own advantage not shown in this study. Prompt
endoscopy has the advantage of a direct image of the stomach and oesophagus and
would therefore help in the early discovery of serious illness of the stomach and oesophagus, such as Barrett’s disease and gastric carcinomas. In the current investigation there was no indication that this would be a real advantage in clinical practice as no maligncies were found in the prompt endoscopy group. The *Helicobacter pylori* test-and-treat approach has the advantage of eradication of *Helicobacter pylori*, which plays an important role in the etiology of peptic ulcer disease and gastric cancers. Hence, by eradicating *Helicobacter pylori*, the risk of developing those diseases will be diminished. This Study shows that the *Helicobacter pylori* test-and-treat approach should be favoured over the prompt endoscopy method.

**Helicobacter pylori vaccination**

*Helicobacter pylori* plays a role in the etiology of peptic ulcer disease and gastric cancer. Development of a preventive vaccine against *Helicobacter pylori* would be a significant step forward in preventing peptic ulcers and gastric cancers. In chapter 8, the cost-effectiveness of such a vaccine was estimated. The base-case estimates for the 4% discount rate (current pharmacoeconomic guideline) and the 1.5% discount rate (as is currently discussed) for health were €14,300 per life year gained and €2,600 per life year gained, respectively. If a vaccine against *Helicobacter pylori* is developed it is likely to be cost-effective according to the current Dutch economic guidelines. If the discount rate of 1.5% is used, which is currently under debate, the cost-effectiveness ratio becomes more attractive.

In estimating the cost-effectiveness of a vaccine against *Helicobacter pylori* there are several limitations. Firstly and most importantly, there is no vaccine available and therefore factors such as the vaccine costs and effectiveness are derived from expert opinion. Secondly, it is known that *Helicobacter pylori* is involved in the etiology of gastric cancer and peptic ulcer disease and the impact of
*Helicobacter pylori* eradication in infants on these conditions has not been investigated.

Discounting is an important factor in evaluating the cost-effectiveness of preventive programmes such as vaccines. Discounting is a technique in which the future benefits and costs are valued less than current benefits and costs. The main drivers of discounting are economic growth and uncertainty. This uncertainty (uncertainty about existence and/or new treatment options) is described by people’s time preference. In the current pharmacoeconomic guidelines (1999) it was advocated to use a discount rate of 4% for money and 4% for health. This 4% was derived from the real rate of return in monetary investments. It is obvious that this 4% is developed for money and not for health. Currently there is a discussion on the appropriateness of using the same discount rate for health as for money. The appendix of chapter 8 shows why an equal discount rate for money and health is not appropriate and reasons are given why the discount rate for health should be changed from 4% to 1.5% in the Netherlands. In chapter 8 the impact of lowering the discount rate is shown. It is clear that with the lower discount rate the cost-effectiveness ratio of *Helicobacter pylori* vaccine is greatly improved. This improvement in cost-effectiveness ratios for preventive programmes might impact the acceptance of (new) preventive programmes in the community.
Main observations from this thesis

This thesis shows that, although small differences exist, clinical differences in effectiveness between proton pump inhibitors are of limited importance. This observation would make it possible to choose a proton pump inhibitor solely on the basis of the costs of daily doses used. However, the clinical effectiveness of generic omeprazole may be lower, as after patent expiry more people switch from omeprazole to another proton pump inhibitor. Whether the increase in switches is due to a difference in clinical effectiveness or due to some other reason needs to be clarified.

In the treatment of peptic ulcer disease it is more cost-effective than H₂RA maintenance therapy. However, it must be said that *Helicobacter pylori* eradication does not totally halt the use of gastrointestinal drugs. After *Helicobacter pylori* eradication some patients continue using gastrointestinal drugs and especially proton pump inhibitors. This observation is true for all indications identified in chapter 6.

A *Helicobacter pylori* test-and-treat approach in patients presenting with first signs of dyspepsia at the GP is less costly and has comparable effectiveness compared to a prompt endoscopy approach. As *Helicobacter pylori* eradication is also favourable in terms of preventing peptic ulcers and gastric cancers, this strategy may eventually also be more effective in terms of life years gained.

In controlling *Helicobacter pylori* infection and the serious illness it causes, development of a *Helicobacter pylori* vaccine is still considered a valuable asset. With the current available information such a vaccine is considered cost-effective. When using a lower discount rate for health as is currently discussed, the cost-effectiveness ratio for a preventive vaccine greatly improves.