ECONOMIC EVALUATION OF PROPHYLACTIC TREATMENT
WITH MISOPROSTOL IN OSTEARTHRITIC PATIENTS
TREATED WITH NSAIDs

The case of Belgium

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ABSTRACT

It has been demonstrated in clinical studies that Cytotec is effective in preventing gastric ulcers in osteoarthritic patients treated with non-steroidal anti-inflammatory drugs (NSAID's).

The primary purpose of this study is to analyse the cost-effectiveness of Cytotec. This is done by comparing the costs of using Cytotec with the costs associated with the standard form of treatment (i.e. without the use of prevention).

The crucial question thereby is whether costs of giving every osteoarthritic NSAID-taker a daily Cytotec dose, will cancel out the costs of treating more ulcer related diseases when Cytotec is not used. If Cytotec entails net costs, the question becomes how much society is willing to pay for those costs to save more people from ulcer or ulcer related diseases.

The methodology used is decision analysis. Clinical probability data for two groups (a Cytotec group and a placebo group) were combined with cost data of medical treatments and cytotec use.

The overall conclusion is that the preventive use of Cytotec in osteoarthritic patients with gastrointestinal problems entails net savings for society as a whole. However, the conclusion is rather sensitive to some important parameters as the presence of asymptomatic ulcers and the price of Cytotec.

Another result is that cost reductions can be realised by the Health Insurance Scheme but not by the patients themselves who will have to pay more for their Cytotec treatment.
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1. INTRODUCTION

In clinical trials, Misoprostol (Cytotec\textsuperscript{R}) has been demonstrated to be more effective than placebo in preventing gastric ulcers in osteoarthritic patients; it is understood that these ulcers are induced by the use of non-steroidal anti-inflammatory drugs (NSAIDs)\textsuperscript{1}. The basic clinical trial data are presented in section 2. The primary purpose of the present article is to compare the costs of using Misoprostol in a preventive way with the costs of the present standard form of treatment. First, use will be made of the clinical trial data and Belgian epidemiological data. The methodology adopted is that of clinical decision analysis\textsuperscript{2}. This is a technique whereby one models decision and chance events associated with alternative forms of treatment of a particular morbidity. The construction of the model is explained in section 3. Secondly, the costs associated with the various forms of treatment are discussed in section 4.

The application of decision analysis will then point out whether Misoprostol will either lead to additional costs or to cost savings vis-à-vis placebo. We will also present results concerning the effectiveness, in terms of lives saved, of Misoprostol. The results, introduced in section 5, will enable one to compare costs and efficiency of the proposed new treatment. Cost savings as well as greater efficiency would of course be the most favorable outcome: the
therapy saves resources and is simultaneously more effective by saving extra lives. However, it is more tedious to assess the combined result of extra costs and lives saved. Indeed, it leaves decision-makers to determine whether the lives saved are worth the extra costs. In section 6, sensitivity analyses will be performed to scrutinize the impact on results of alternative assumptions regarding epidemiology and costs. We conclude in section 7.

2. BASIC CLINICAL TRIAL DATA

2.1 Introduction

Basic clinical trial data are derived from GRAHAM et al. (1988). Their study was multi-center and double-blind and consisted of two clinical trials with identical protocols. The length of the trials was three months. The trials only included osteoarthritic patients (421) on NSAID therapy. The latter patients did not have gastric ulcer by endoscopy upon entry in the study; yet, they all suffered from abdominal pain. Patients were randomly assigned to three groups: 140, 143 and 138 patients were to receive 200 mcg Misoprostol QID, 100 mcg Misoprostol QID and placebo QID, respectively. All patients continued their established NSAID treatment.

The main objective of the trials was to monitor the prophylactic failure of Misoprostol. The latter was defined
as the presence of gastric ulcer(s) larger or equal to 0.3 cm in diameter, observed at one of the three monthly follow-up endoscopies organized within the trials. The combined clinical trial data show that there were statistically significantly fewer patients with endoscopically proven ulcers in each of the Misoprostol groups than in the placebo group \( (p \leq 0.001) \). However, in one trial the difference between the 100 mcg Misoprostol group and the placebo group was not statistically significant. Henceforth, we will therefore restrict ourselves to the data related to the 200 mcg Misoprostol group.

2.2 Clinical trial results of the 200 mcg Misoprostol group

2.2.1 Population characteristics

The age of the total patient population varied from 22 to 90 years. The average age of the Misoprostol and placebo group was 58.6 and 59.5 years, respectively; the standard deviations were 10.8 and 11.1 years, respectively. The age, as well as other social and demographic characteristics (smoking, alcohol use; weight, height, sex, race etc.) were comparable between the Misoprostol and placebo groups. The two treatment groups also did not differ in the baseline medical and epidemiological characteristics (history of osteoarthritis, NSAID use and ulcer disease). Note further that for all patients, the history of osteoarthritis and the
use of NSAIDs prior to admission into the trial was just over eight years and just over one year, respectively.

2.2.2 Compliance and ulcer incidence

Only a subset of the patients, that enrolled in the trial, completed the three-month study. Of the 278 patients enrolled in the placebo and Misoprostol groups, 195 completed the study (96 and 99 in the placebo and Misoprostol group, respectively). The latter group of 195 includes both patients that were free of gastric ulcer at the end of the trial and the patients who developed gastric ulcer(s). A number of patients (30) deviated from the protocol or because they were lost to follow-up. Other patients followed the protocol but experienced adverse reactions that lead them to withdraw from the trial (26 and 27 in the placebo and Misoprostol groups, respectively). Note that the adverse events with the highest incidence are diarrhea, dyspepsia, flatulence, abdominal pain and nausea.

In our study, valid data are considered to be the 195 patients that completed the 3-month study plus the 53 patients that stayed in the trial until their withdrawal. Note that endoscopically proven gastric ulcers occurred in 30 and 2 patients of the placebo and Misoprostol group, respectively. In Table 1, we present the probabilities related to compliance and ulcer incidence used in the
decision analysis.

Table 1
Probabilities of Compliance and Ulcer Incidence

<table>
<thead>
<tr>
<th>Probability</th>
<th>Misoprostol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance (1)</td>
<td>0.79 (99/126)</td>
<td>0.79 (96/122)</td>
</tr>
<tr>
<td>Gastric ulcer (2)</td>
<td>0.02 (2/99)</td>
<td>0.31 (30/96)</td>
</tr>
</tbody>
</table>

Notes: (1) The denominator in the figures between brackets refers to the number of valid cases; the numerator is the number of patients who comply.
(2) The denominator in the figures between brackets refers to the group of patients who complete the study; the numerator is the number of patients with ulcer.

3. THE DECISION TREE

3.1 Introducing the probability of complicated ulcer

The clinical trials focused on the incidence of uncomplicated gastric ulcer only. Strict modeling of the clinical trial in a decision tree would therefore exclude complications such as bleeding and perforation. However, we did decide to model the incidence of complicated ulcers in order to mirror reality as close as possible.

We used data from an epidemiological survey organized in 1984 by the Institute of Hygiene and Epidemiology (IHE)³ of the Belgian Ministry of Public Health. Gastric ulcer disease was
among the diseases monitored by the survey. The survey was held among some 100 GPs who constituted a representative sample of Belgian GPs. The information was collected during a period of 52 weeks.

One can safely assume that the vast majority of complicated ulcer patients are hospitalized. Hence, data on bleeding, perforation and other complicated ulcers can in principle be inferred from hospitalization data. The data reveal that 18.9 percent of gastric ulcer patients are hospitalized. The reasons for hospitalization are the following: perforation (1.2%), bleeding (12.6%), other complications (2.3%) and non-complicated ulcer (2.8%).

3.2 Ambulatory or hospital treatment of ulcer patients

First, according to expert opinion we received from university-based gastroenterologists, hospitalization always occurs in the event of complicated cases such as perforation and of serious bleeding. By using the data from the IHE-survey, it is thus implied that the reported cases of bleeding and other complications warranted hospitalization. Secondly, according to the same gastroenterologists, the treatment of a non-complicated case ought to be ambulatory. In principle, the latter rule is said to be respected at Belgian university hospitals. However, it is admitted that in practice, especially in other general hospitals,
hospitalization may occur. To account for this phenomenon, it is decided to analyze two decision models: one related to 'university' hospitals\(^6\), the other to 'general' hospitals\(^7\).

The probability of hospitalization of non-complicated cases in UH will thus be put at zero. The probability of hospitalization in GH of non-complicated cases is 3.3 percent\(^8\).

3.3 Surgical treatment in the case of hospitalization

Following expert opinion, all cases of perforation and approximately 10 percent of cases of bleeding necessitate surgery. We will also suppose here that 10 percent of 'other' complicated cases need surgery as well. Based on the data on the causes for hospitalization, we derive that approximately 16.7 percent of all complicated cases are subjected to surgery\(^9\). The latter probability will also be used as an estimate of the probability of surgery in non-complicated patients. It is granted that the latter is presumably an 'upper bound' estimate. Sensitivity analysis will be necessary to study how sensitive results are to changes in this probability.

3.4 The no-change and non-compliance category

Patients that do not develop a gastric ulcer constitute the
no-change category. These patients may continue to receive medication (e.g. antacids) in order to reduce remaining abdominal pain, however.

Patients who do not comply with Misoprostol treatment are assumed to experience the same development of their disease as patients in the placebo-group. That is to say that we will apply the ulcer incidence rate of 31% to this particular group. Likewise, those that do not comply with placebo are considered to be no different, in terms of ulcer incidence, from patients who do comply with placebo treatment.

3.5 Presentation of the decision tree

We are now equipped to construct the basic decision tree for our baseline analysis. In Figure 1, we present the decision tree related to a general hospital. Note that the decision tree related to a university hospital has no hospital branch for uncomplicated ulcers.
4. COST DATA

Each of the end branches in Figure 1 is associated with an outcome in terms of resource costs. In this article, we focus on the medical costs only. The main distinction is between costs for ambulatory treatment (of the 'no change' category of patients and of ulcer patients) and for hospital treatment (either surgery or medical treatment).

Note that, as far as financing of medical costs is concerned, the (compulsory) Belgian Health Insurance Scheme (HIS) has devised a system of copayments. The latter differ according to whether one belongs to the category of the 'active' (all active persons and their dependents) or the 'widows, orphans, pensioners, invalids and their dependents' (WOPI); below a certain minimum income level, the WOPI pay a lower out-of-pocket cost than the active.10 In section 5, the cost-effectiveness results will be unscrambled in order to study the cost implications for the three above mentioned payors, viz. the HIS, the active and the WOPI. In the following subsections we inform the reader about the composition of costs for ambulatory treatment and hospitalization (excluding Misoprostol costs) and the costs due to preventive administration of Misoprostol.
4.1 Ambulatory treatment

The total costs of ambulatory ulcer treatment consist of the costs of GP consultations, endoscopies and drugs.\textsuperscript{11}

It is first assumed that treatment of patients starts with one GP consultation. We use the average cost of a GP consultation; note that fees are different according to whether the GP received a supplementary training or not.

Further data on costs of ambulatory treatment of the no-change category result from an interview with an expert in primary health care. All patients in this category receive a second GP consultation\textsuperscript{12}. Furthermore, 8 percent and 4 percent have a third and fourth consultation, respectively. Half of the patients receive a Maalox prescription (5 packages) whereas 9 percent of the patients have an endoscopy. The total average cost per patient is 1072 BEF. (without misoprostol costs).

Costs of ambulatory ulcer treatment are based on an average of ambulatory treatment prescribed by a GP and of hospital-based ambulatory treatment prescribed by a hospital physician. The former involves three GP consultations, an endoscopy, treatment with Ranitidine (Zantac\textsuperscript{R}); half of the patients receive a Maalox prescription (one package). The latter treatment includes 3 consultations with a GP and 3
consultations with a specialist, 2 endoscopies (with biopsies), one ECG and RX of the thorax, a series of lab-tests and three months of Ranitidine and Maalox. The total costs of both variants amount to 10964 and 23659 BEF respectively. It follows that the average cost of ambulatory ulcer treatment becomes 17312 BEF.

4.2 Hospitalization

Treatment at the hospital is always preceded in this analysis by one GP consultation. Hospital cost data are further acquired from the study by Closon et.al. [1988] and a related databank that was prepared especially for the present study. These authors classify hospital services of three Belgian university hospitals into Diagnosis Related Groups (DRGs). The database contains data of some 42510 patients. The latter were admitted to the hospital after April 1, 1985 and were discharged between July 1, 1985 and December 31, 1985.13

Hospital treatment of ulcer pathology can be either of surgical or medical nature. The two DRGs related to ulcer surgery are DRG 154 and 155. The former comprises 'stomach, esophageal and duodenal procedures' for patients above the age of 70 or for patients (of all ages) with complications and/or comorbidities. The latter contains identical procedures but for patients aged below 70 and without complications and/or comorbidities. Note that the procedures
include partial gastrectomy, pyloroplasty, suture, gastroenterostomy and vagotomy.

The three DRGs that comprise medical treatment of ulcers are 176, 177 and 178: they contain medical treatment for 'complicated peptic ulcer', 'uncomplicated peptic ulcer (age > 69 or with complications and/or comorbidities)' and 'uncomplicated peptic ulcer (age < 70 without complications and/or comorbidities)', respectively.

Medical treatment of gastrointestinal hemorrhage is associated with DRGs 174 (age > 69 and with complications and/or comorbidities) and DRG 175 (age < 69 and without complications and/or comorbidities).

The cost data from the databank comprise all costs incurred during the stay at the hospital. First, they include the typical 'medical' costs: lab-tests, pharmaceuticals, blood transfusions, medical materiel, physician fees for services in the field of radiology, surgery, anesthesia, reanimation etc. Secondly, costs related to 'nursing care' and 'hotel costs' (food, linen, administration etc.) are included as well. Note that, in Belgium, medical costs are financed on a fee-for-service basis. However, nursing and hotel costs are reimbursed by the HIS on a per diem basis. In the case of hospitalization, there is also a copayment for the stay in the hospital itself, for drugs and minor lab-tests: Patients
pay a daily fee per hospital-day, viz. 189 BEF and 76 BEF in the case of the 'active' and the WOPI, respectively; the daily copayment for pharmaceuticals is 25 BEF; only the active pay 25 percent of costs of minor lab-tests.

It is important to note that we only took account of the variable cost component in the per diem hospital cost. It is evident that fixed costs do not have to be considered, since they will not be modified by alternative forms of ulcer prevention or therapy. Note that in the Belgian context, the fixed part of the per diem cost includes depreciation of fixed assets, the cost of loans and the cost originated in the 'common' departments of the hospital (e.g. administration, hotel services etc.)\textsuperscript{14}. Based on data of 224 Belgian hospitals, Meunier and Donnay [1988] have estimated the average share of variable costs in per diem costs to be 56 percent. This particular figure was used to adjust per diem costs.

Five further remarks are in order. First, we have added post-hospital ambulatory care to hospital costs. Data were provided to us by a hospital physician specializing in gastroenterology. This particular type of care may include follow-up consultations with a GP and specialist, lab-tests, the administration of Maalox, the administration of Zantac and the application of an endoscopy. Secondly, the databank served also to estimate the costs in general hospitals. We
will suppose that the purely medical treatment of ulcer and its costs are similar in UH and GH. Per diem costs for GH are different, however; we have adopted an average total per diem cost of 3529 BEF. Thirdly, it is evident that the lengths of stay associated with the DRGs are related to a whole array of procedures. The databank mentions a length of stay of 25.6 and 15.2 days for DRG 154 and 155, respectively. However, we were able to obtain indications of the length of stay for ulcer surgery specifically from the French database 'Base de Données Nationales PMSI' [1988]: lengths of stay for ulcer surgery are reported to be 21 and 14.2 days, respectively. The latter data were integrated in our analysis. Fourthly, the cost data do not include any supplements paid by patients to hospital management and/or physicians; note that supplements can be charged if patients stay in a single-bed hospital room. Fifthly, the costs used in the decision analysis are weighted averages of costs associated with the different DRGs. The weights are based on the patient volumes presented in the databank of Closon et.al. [1988] and/or on the relative importance of complicated cases as derived from the IHE-data. The hospital treatment costs are presented in Table 2.

4.3 Prophylaxis with Misoprostol

The total costs associated with the preventive administration of Misoprostol during three months are 5856 BEF according to
the actual price regulation in Belgium. Patients who do not comply with this treatment are assumed to receive one-half course of Misoprostol only. In addition, it is assumed that the administration of Misoprostol to those patients who nevertheless contract ulcer disease, is restricted to six weeks.
4.4 Overview of costs

Table 2
Treatment costs for a 3 month period (in BEF)

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>University hospital</th>
<th>General hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventive Treatment with Misoprostol</td>
<td>5856</td>
<td>5856</td>
</tr>
<tr>
<td>Ambulatory treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no change category</td>
<td>1072</td>
<td>1072</td>
</tr>
<tr>
<td>uncomplicated ulcer</td>
<td>17312</td>
<td>17312</td>
</tr>
<tr>
<td>Hospital treatment of complicated ulcer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>surgical treatment (1)</td>
<td>198582</td>
<td>172173</td>
</tr>
<tr>
<td>medical treatment (2)</td>
<td>95234</td>
<td>82051</td>
</tr>
<tr>
<td>Treatment of uncomplicated ulcer (general hospitals only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>surgical treatment (3)</td>
<td></td>
<td>172173</td>
</tr>
<tr>
<td>medical treatment (4)</td>
<td></td>
<td>67510</td>
</tr>
</tbody>
</table>

Notes: (1) Weighted average of the costs of DRGs 154 and 155.  
(2) Weighted average of the costs of DRGs 174, 175 and 176.  
(3) Weighted average of the costs of DRGs 154 and 155.  
(4) Weighted average of the costs of DRGs 177 and 178.
5. RESULTS

5.1 Cost implications of use of Misoprostol

We can now link the probabilities in the decision trees with the various outcomes in terms of health care costs. We first investigate whether the preventive use of Misoprostol would result in net costs or net savings vis-à-vis placebo; the results are presented in Table 3. In Table 4, we look into the cost-sharing between patients and the HIS.

Table 3
Expected Cost of Misoprostol vs. Placebo, in BEF

<table>
<thead>
<tr>
<th>Type of hospital</th>
<th>Expected cost of Misoprostol</th>
<th>Expected cost of placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>University hospital</td>
<td>9224</td>
<td>11223</td>
</tr>
<tr>
<td>General hospital</td>
<td>9129</td>
<td>11035</td>
</tr>
</tbody>
</table>
We derive from Table 3 that in the UH scenario, the use of Misoprostol would entail net savings per patient of 1989 BEF. In the GH scenario, net savings per patient of 1906 BEF would be obtained. Thus, the use of Misoprostol would result in savings for society: it entails (gross) savings resulting from a reduction in hospitalizations and ambulatory care, that outweigh the extra costs (over placebo) of the use of the drug. It is also interesting to note that there is a modest difference between the two scenarios. The latter is largely due to the fact that the cost of lab-tests, physician fees, drugs, and blood and medical materiel, constitute the major components of the total cost; these components were
supposed not to differ between UH and GH. It is evident then that the final results are only slightly sensitive to the differences in per diem cost between UH and GH.

In Table 4, the information on cost-sharing reveals that the HIS realizes cost savings. In the UH scenario, these range from 2589 BEF for the WOPI to 2786 BEF for the active; in the GH analysis, cost savings vary from 2439 BEF for the WOPI to 2626 BEF for the active. One also notices that patients are, in all cases, subjected to higher health care costs. The latter result is mainly due to the magnitude of the price of Misoprostol relative to the charges normally paid for standard ulcer-treatment.

5.2 Effects on the number of lives saved

The clinical trial showed that Misoprostol can prevent ulcers during a three-month period. Thus, Misoprostol has an influence on the mortality rates of ulcer patients. The data obtained from Closon et.al. [1988] also include the mortality rates associated with the various DRGs. Using these mortality rates, it is therefore possible to obtain a tentative estimate of the number of lives saved resulting from the preventive use of Misoprostol. Any estimate we obtain is indeed preliminary, since the mortality rates used also incorporate mortality of patients not necessarily suffering from gastric ulcer disease.
The mortality rates associated with DRGs 154 and 155 are 0.1004 and 0.0052, respectively; the weighted mortality rate is therefore 0.0531. There is no observed mortality in DRGs 176, 177 and 178. Among patients in DRGs 174 and 175, there is a mortality rate of 0.07 and 0 respectively; the weighted mortality rate is 0.0353.

The weighted mortality rates can now be connected to the decision tree. The outcomes in terms of expected mortality of the prevention and placebo strategies can then be compared. It is thus estimated that the number of lives saved due to the preventive use of Misoprostol ranges from 142 per 100000 (in the case of the UH scenario) to 147 per 100000 patients (in the case of the GH scenario).

We conclude from both scenarios that the prevention strategy is to be favored: one would save both medical care resources and human resources.
6. SENSITIVITY ANALYSES

So far, we adopted a number of reasonable assumptions regarding the values for probabilities and costs. The latter are subjected to some degree of uncertainty, however. Hence, it is recommendable to analyze the sensitivity of the decision model's results to alternative assumptions. We will analyze the effect of changes in the probabilities of hospitalization and surgery, and in the probabilities of treatment and the associated costs for elderly patients. Furthermore, we will take account of the probability of asymptomatic ulcers. Finally, we address the issue of clinical significance of ulcers; we will examine the implications of the assumptions that only ulcers, larger than 0.5 cm, are medically relevant. A summary of results is presented in Table 6.

6.1 Modifying probabilities

6.1.1 Probability of surgery

First, in view of the expert opinion that uncomplicated ulcer only needs ambulatory treatment, the probability of surgery of 0.167 may be overestimated. We therefore computed expected costs conditional upon a probability of surgery (for uncomplicated ulcer) of 0.02. Secondly, the probability of surgery of complicated ulcer may be judged to be too low. In
fact, in a study concerning bleeding of peptic ulcer in NSAID users, De Boer et al. [1988] report a surgical rate of 32 percent. When using these figures in the analysis, the level of costs exceed those of the baseline costs in Table 3. Yet, net savings increase vis-à-vis the baseline savings (2629 BEF for UH and 2318 BEF for GH respectively). The former conclusion of the baseline analysis that the Misoprostol strategy is favored over placebo, is maintained despite a rather drastic change in surgery probabilities.

6.1.2 Probability of hospitalization of uncomplicated ulcer

In this sensitivity analysis, we suppose that therapeutic strategies regarding uncomplicated ulcer in UH become valid in GH as well. We obtain the result that expected costs of Misoprostol in the GH scenario remain inferior to those associated with placebo. We obtain that net cost savings due to Misoprostol treatment amount to 1476 BEF.

6.2 Expected costs of treatment of elderly patients

6.2.1 Gastrointestinal disease in elderly NSAID-users

Osteoarthritis and the associated use of NSAIDs is particularly prevalent in older age groups. The literature suggests that the NSAID-users among the elderly are especially prone to gastrointestinal side effects such as
ulcers, bleeding and perforation. We refer to De Boer and Van Berge Henegouwen [1988], and to De Boer, Van Berge Henegouwen and Kluitman [1988]; we also mention Boyd and Wormsley [1985] and Bianchi Porro, Pace and Caruso [1987] in the international literature.

Belgian data also suggest a high incidence of gastrointestinal problems in older patients. Indeed, the share of the age groups of 55-64 and ≥65 years in the total of NSAID prescriptions is 19.2 and 32.2 percent, respectively\(^{16}\). Finally, it is important to note that 53.7 percent of NSAIDs in Belgium are taken as a result of arthritis and rheumatism.

6.2.2 Modified probabilities

We will first assume that the ulcer incidences from the clinical trial (0.02 and 0.31 for the Misoprostol and placebo groups, respectively) can also be applied to older age groups. The values for the other probabilities are derived from the IHE-data on patients over 60 years of age: the probability of bleeding, perforation and other complicated cases is 26.2 percent, the probability of uncomplicated cases 73.8 (=100-26.2), the probability of hospitalization of uncomplicated cases is 5.6 percent\(^{17}\), whereas the probability of surgery is 17.2 percent\(^{18}\).
6.2.3 Modified Costs

The mean age of elderly patients in the IHE sample is 75 years. Hence, the costs associated with the group of the elderly can safely be approximated by those of the DRGs connected to patients over 69 years old, viz. DRG 154 (for surgery), 174 (for medical treatment of bleeding and other complicated cases) and 177 (for medical treatment of uncomplicated ulcer).

6.2.4 Results

The results of the adjusted decision analysis are presented in Table 5.

Table 5
Expected Costs (patients >60 years), in BEF

<table>
<thead>
<tr>
<th>Type of hospital</th>
<th>Misoprostol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>University hospital</td>
<td>10792</td>
<td>17410</td>
</tr>
<tr>
<td>General hospital</td>
<td>10700</td>
<td>17058</td>
</tr>
</tbody>
</table>

The figures show that Misoprostol treatment remains more cost-effective than placebo, in both the UH and GH scenarios. The costs of treatment in the placebo group clearly outweigh costs due to administration of Misoprostol. In fact, net

26
savings are between three and four times as large as those of the baseline scenario. This result is due to the fact that the treatment of gastrointestinal problems in the elderly is much more costly than those for other age groups. It thus follows that prevention of ulcers and subsequent costs entails more important savings.

We can also estimate the number of lives saved of elderly patients due to Misoprostol treatment. We use the mortality rates associated with DRGs 154, 174 and 177, viz. 0.1004, 0.07 and 0, respectively. The result is that between 278 (UH) and 288 (GH) lives per 100000 are saved.
6.3 Asymptomatic ulcers

6.3.1 Introduction

Remember that the ulcers in the clinical trial were confirmed by endoscopy. However, the clinical reality is different: all ulcers are not be detected due to the presence of asymptomatic ulcers. According to the experts' opinion, approximately half of patients have a silent ulcer\textsuperscript{19}. Thus, patient demand for health check-ups as a result of complaints is also likely to be halved. In order to approach clinical reality, we will study the effects of a reduction of the baseline incidence of ulcers by 50 percent. Two analyses will be carried out, viz. for patients of all age groups and for the group of the elderly.

6.3.2 Patients of all age groups

In the Misoprostol strategy, the probability to get uncomplicated ulcer and bleeding and/or perforation would become 0.0084 and 0.0016, respectively; in the placebo strategy, these probabilities would become 0.13 and 0.025, respectively.

The level of costs is lower than in the baseline analysis (see Table 2). However, what is more striking is that one obtains net costs of Misoprostol vis-à-vis placebo. These are
1598 BEF and 1668 BEF in the case of the UH and GH, respectively. The relative magnitude of the costs of preventive treatment (vis-à-vis the cost of standard treatment) is primarily responsible for this cost differential. Concerning the number of lives saved due to the use of Misoprostol by patients with symptomatic ulcer, we use the method explained above in section 5.2. In the UH and GH scenarios, the number of lives saved amount to 71 per 100000 patients and 74 per 100000 patients, respectively.

If the present sensitivity analysis mirrors reality more than the baseline analysis, the question is whether Misoprostol is to be recommended over placebo. Here, we enter into the tedious question of evaluating the lives saved by Misoprostol. The values of lives saved would have to be compared with the expected costs of those lives. The latter issue is outside the scope of the present study, however.

6.3.3 Elderly patients

In the Misoprostol strategy, the probability of uncomplicated ulcer and complicated ulcer would become 0.0074 and 0.0026, respectively. In the placebo strategy, these probabilities would be 0.1145 and 0.0405, respectively.

One continues to obtain net savings for the Misoprostol
strategy, be it that they decrease vis-à-vis the baseline results. Net savings per patient vary from 556 BEF to 689 BEF in the GH and UH scenarios, respectively. Note that the estimated number of lives saved amounts to 139 per 100000 (UH) and 144 per 100000 (GH).

6.4 Ulcers larger than 0.5 cm

Though it is difficult to state in general when an ulcer is medically significant, one can hypothesize that ulcers with size ≥ 0.5 cm. are more clinically meaningful than ulcers with size ≥ 0.3 cm. In this scenario then, the probabilities for ulcer development become 0.01 (1/99) and 0.177 (17/96) for the misoprostol and the placebo group, respectively. For the other probabilities, the same values were used as in the baseline analysis. We now obtain that the use of Misoprostol would entail net costs per patient of 1076 BEF in the UH scenario. In the GH scenario, net costs per patient of 1132 BEF would be obtained. However, when we use the probability and cost values for elderly patients, Misoprostol continues to be cost-reducing vis à vis placebo.
6.5 Summary of sensitivity analyses

Table 6
Cost-effectiveness results (BEF)

<table>
<thead>
<tr>
<th></th>
<th>Cytotec</th>
<th>Placebo</th>
<th>Net costs (+)</th>
<th>Net savings (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>. UH</td>
<td>9224</td>
<td>11223</td>
<td>- 1999</td>
<td></td>
</tr>
<tr>
<td>. GH</td>
<td>9129</td>
<td>11035</td>
<td>- 1906</td>
<td></td>
</tr>
<tr>
<td><strong>Sensitivity analyses</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lower surgery probability for uncomplicated ulcer + higher surgery probability for complicated ulcers.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>. UH</td>
<td>9384</td>
<td>12013</td>
<td>- 2629</td>
<td></td>
</tr>
<tr>
<td>. GH</td>
<td>9274</td>
<td>11592</td>
<td>- 2318</td>
<td></td>
</tr>
<tr>
<td>No hospitalisation for uncompl. ulcer in a GH</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>. GH</td>
<td>8978</td>
<td>10454</td>
<td>- 1476</td>
<td></td>
</tr>
<tr>
<td><strong>Old age patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>. UH</td>
<td>10792</td>
<td>17410</td>
<td>- 6618</td>
<td></td>
</tr>
<tr>
<td>. GH</td>
<td>10700</td>
<td>17058</td>
<td>- 6358</td>
<td></td>
</tr>
<tr>
<td>50% asymptomatic ulcers (with baseline data)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>. UH</td>
<td>7924</td>
<td>6326</td>
<td>1598</td>
<td></td>
</tr>
<tr>
<td>. GH</td>
<td>7900</td>
<td>6232</td>
<td>1668</td>
<td></td>
</tr>
<tr>
<td>50% asymptomatic ulcers (with data for old aged)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>. UH</td>
<td>8731</td>
<td>9419</td>
<td>- 688</td>
<td></td>
</tr>
<tr>
<td>. GH</td>
<td>8684</td>
<td>9239</td>
<td>- 555</td>
<td></td>
</tr>
<tr>
<td>Ulcer rates for ulcers bigger than 0.5 cm. (with baseline data)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>. UH</td>
<td>8092</td>
<td>7016</td>
<td>1076</td>
<td></td>
</tr>
<tr>
<td>. GH</td>
<td>8042</td>
<td>6910</td>
<td>1132</td>
<td></td>
</tr>
<tr>
<td>Ulcer rates for ulcers bigger than 0.5 cm. (with data for old aged)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>. UH</td>
<td>9874</td>
<td>10574</td>
<td>- 1600</td>
<td></td>
</tr>
<tr>
<td>. GH</td>
<td>8920</td>
<td>10636</td>
<td>- 1716</td>
<td></td>
</tr>
</tbody>
</table>
7. CONCLUSION

Modeling the clinical trial and incorporating Belgian epidemiological and cost data results in the 'baseline' finding that the preventive use of Misoprostol in osteoarthritic patients with gastrointestinal problems entails net savings for society as a whole: the Health Insurance Scheme thereby realizes health care cost reductions, whereas patients pay more than in the placebo or standard treatment strategy.

One may not completely agree with the baseline ulcer probabilities, however. First, due to the presence of silent ulcers, one is likely to detect less ulcers than predicted by the trial. Secondly, not all ulcers with size $\geq 0.3$ cm. are necessarily clinically meaningful. Two sensitivity analyses were then performed: in one analysis, baseline ulcer incidences are reduced by 50 percent, whereas in the other ulcer probabilities were related to ulcers $\geq 0.5$ cm. The net savings per patient (all age groups) are clearly sensitive to these modified ulcer incidences. Indeed, the preventive strategy becomes more expensive than the standard treatment in both analyses. However, a striking result is that for elderly patients, one continues to realize net cost savings.

An additional number of caveats need to be signaled. First, the DRGs considered comprise treatments other than of gastric
ulcer disease. Secondly, the sensitivity analysis related to the elderly uses the ulcer incidence (of all age groups) from the clinical trial; incidence of gastric ulcer may differ according to age, however. Third, the probabilities of complicated ulcer, hospitalization and surgery are assumed to be identical in the Misoprostol and placebo groups. Fourth, the decision model has no branch for other gastrointestinal diseases such as gastritis. Yet, its incidence may be important and its treatment may turn out to be as costly as the medical treatment of ulcer. Fifthly, as yet it is not clear what would be the relapse rate of gastric ulcer among users of Misoprostol. It is evident that, over longer periods of time, the relapse rate will affect the overall cost-effectiveness of Misoprostol.

Still, despite these caveats and remaining uncertainties, our study clearly shows that the clinical decision analysis undertaken is a workable and powerful instrument for assessing the economic value of Misoprostol. Further refined information concerning costs and epidemiology of ulcer disease can easily be incorporated into the analysis. Decision-makers can only benefit from the use of this particular methodology.
REFERENCES

1. See Kochman, Bartkus, Deysach and Nissen [1988] and Graham et.al.[1988].

2. See Weinstein and Fineberg [1980] for an excellent account of the methodology of clinical decision analysis.

3. See Van Casteren et.al.[1986].

4. These include stenosis, malignant tumor, diarrhea, large size ulcers, several ulcers, vomiting.

5. Gastric ulcer incidence is reported to be 29.3 per 10000 (See Van Casteren et.al. [1986,p.16]. It follows that 37 per 100000, 3 per 100000 and 8 per 100000 are hospitalized for hemorrhage, perforation and uncomplicated ulcer, respectively. The hospitalization rates for hemorrhage and perforation tally rather well with those published for the U.S. by Kurata and Corboy [1988].

6. Henceforth, 'university hospital(s)' may be abbreviated to UH.

7. Henceforth, 'general hospital(s)' may be abbreviated to GH.

8. This percentage is derived as follows: $3.3 \approx 2.8 / [100 - 16.1]$, whereby 16.1 refers to the percentage of hospitalized patients for complicated ulcer disease.

9. $16.7 \approx [1.2 + 0.1x 14.9] / 16.1$.

10. There is also the category of the self-employed, for whom insurance against small risks (such as medicines, consultations etc.) is not compulsory. However, in this study they are considered to be part of the 'active'.

11. All costs of ambulatory care are in prices of June 1988 (according to the official nomenclature of the Health Insurance Scheme).

12. This consultation is in addition to the GP consultations all patients have.

13. All DRG costs mentioned here are in 1985 prices. Between the end of 1985 and June 1988 there has been a very small increase in the per diem price and an increase of 3% in physician fees. There was however a decrease in the prices for lab tests with almost 10%. Holding the number of physician contacts and lab tests constant, these changes in prices neutralize each other. Thus these 1985 costs are almost perfectly comparable to June 1988 prices, which are
used for calculating all non-hospital costs.

14. For an overview of recent Belgian hospital legislation, see Hermesse [1986] and De Cooman and Marchand [1987].

15. This is the per diem cost before adjustment for variable costs. This figure is mentioned by Meunier and Donnay [1988, p.130].

16. See Duchêne [1988].

17. Note that 30.3 percent of ulcer patients (>60 years) are hospitalized, of which 4.1 percent are 'uncomplicated' cases. Hence, it follows that the probability of being hospitalized as an uncomplicated ulcer patient is 5.6 ($\approx 4.1/[100-26.2]$).

18. Note that 26.2 percent of ulcer patients are hospitalized for complications (2.1 percent for perforation and 24.1 for bleeding and 'other' complications). Accepting that perforation is always treated surgically and that 10 percent of bleeding and other complications need surgery, we obtain the result that 17.2 percent ($\approx [2.1 + 0.10 \times 24.1]/26.2$) of all complicated cases receive surgical treatment.

19. See also Boyd and Wormsley [1985, p.1015].
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