

RESEARCH PROPOSAL FOR MASTER OF MEDICINE

(OBSTETRICS AND GYNAECOLOGY)

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

UNIVERSITI MALAYA

**TITLE**

A comparative study of Gaviscon and Omeprazole for Gastroesophageal reflux in pregnancy: a prospective randomised controlled trial

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**1.0 TITLE**

A comparative study of Gaviscon and Omeprazole for Gastroesophageal reflux in pregnancy: a prospective randomised controlled trial.

**2.0 INTRODUCTION**

The American College of Gastroenterology (ACG) defines Gastroesophageal reflux disease (GERD) as “symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond, into the oral cavity (including larynx) or respiratory tract.([1](#_ENREF_1)) Prevalence of GERD in general population in Malaysia is 9.3%, however in pregnancy the prevalence is higher at about 30-80% throughout the pregnancy. Prevalence of GERD increases each gestations; 26.2% in first trimester, 36.1% in second trimester and 51.2% in third trimester.([2](#_ENREF_2))

Pregnancy is known to predispose to GERD and the commonly known cause of GERD in pregnancy is reduced lower oesophageal pressure (LES) tone due to hormonal changes in pregnancy, mainly increased levels of progesterone.([3](#_ENREF_3)) LES progressively decreases as the pregnancy advances, returning to normal values soon after delivery, hence the GERD symptoms worsens as the gestation progresses.([4](#_ENREF_4))

Montreal consensus from 2006 described GERD as a condition that develops when reflux of stomach causing troublesome symptoms (heartburn and regurgitation) and recommends diagnosis of GERD be made based on those symptoms. ([5](#_ENREF_5)) Initial endoscopy is generally unnecessary when alarm symptoms are absent.([6](#_ENREF_6)) Symptom based diagnosis of GERD can be made with a Gastroesophageal Reflux Disease Questionnaire, where scores ≥ 8 on GerdQ are defined as having GERD.([6](#_ENREF_6)) GerdQ is a validated diagnostic tool, which contains 6 items that enables quick diagnosis to made at the outpatient setting. ([7](#_ENREF_7)) To avoid misperception of GERD symptoms due to language differences by Malaysian population, this questionnaire has been validated in Malaysian language and has a sensitivity of 90% and specificity of 77%.([8](#_ENREF_8)) A survey done on 142 pregnant women at Antenatal clinic of University Malaya Medical Centre shows that 45 women (31.7%) have GERD. Out of this, 31 of them (21.8%) are keen to seek treatment for their symptoms.

Lifestyle modification can be advocated for management of GERD in pregnancy, however despite these measures, GERD symptoms still persist for many pregnant women.([9](#_ENREF_9)) Cochrane analysis of nine randomised controlled trials (RCTs) demonstrated that pregnant women who received pharmaceutical treatment reported complete heartburn relief more often than women receiving no treatment or placebo.([10](#_ENREF_10))

Medical treatment used for GERD in pregnancy includes antacids that line the stomach and esophageal and acid reducing agents such as Histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs).([11](#_ENREF_11)) First line of treatment are usually alginates or antacids because of their non-systemic effect.([12](#_ENREF_12)) Majority of GERD symptoms occur after meals, even though this is the least acidic period as the food buffers acidic nature of the intragastric contents. The discrepancy of the gastric pH leads to formation of ‘acid pocket’, the area of unbuffered, highly acidic gastric secretion that accumulates at the proximal part of the stomach.([13](#_ENREF_13)) Alginate based reflux suppressants such as Gaviscon forms a raft close to the gastro‐oesophageal junction and is able to preferentially reflux in place of gastric contents and the raft structure appeared to be retained within the stomach for up to 4 hours.([12](#_ENREF_12)) Timing of ingestion affects the gastric emptying duration of alginate-based formulations. When taken under fasting conditions, Gaviscon was reported to have a half-life of 20minutes, and when taken together with the meal the half-life was 30mins. However, when taken 30 minutes after meal, Gaviscon emptied after the meal, with a half-life of 180 minutes.([14](#_ENREF_14)) Williams et al. reported a large multicentre evaluation of liquid Gaviscon. A total of 596 patients were recruited and instructed to take 20 mL of liquid Gaviscon after meals and prior to bed for 2 weeks, and Gaviscon was noted to reduce the severity and frequency of symptoms in 82% of patients, and found to be effective in 327 out of 435 patients (75%).([15](#_ENREF_15)) A prospective, open label study conducted in UK and South Africa, found that Gaviscon liquid, 10- 20mls as required is safe for use in pregnancy.([12](#_ENREF_12))

Proton pump inhibitors (PPI) are often used and found to be effective in treatment of GERD due to its profound and consistent acid suppression property.([16](#_ENREF_16)) PPI acts by irreversibly inactivating the active form of the proton pump (H+ -K+ -ATPase), suppressing acid secretion up to 36 hours and it takes up to 3 days for inhibition of acid secretion to reach a steady state.([17](#_ENREF_17)) OSCAR trial reported that optimal timing for Omeprazole ingestion was 30mins prior to the first meal of the day and should be taken for at least 3-5days to achieve 66% of steady state inhibition of maximal acid secretion.([18](#_ENREF_18)) A meta-analysis done to investigate the effect of 14-day treatment with PPI compared to H2 receptor antagonist (H2RA) for nonerosive gastroesophageal reflux disease found that PPI has a superior rate of symptomatic relief compared to H2RA. The overall rate of efficacy of PPI at relieving NERD symptoms compared to placebo was 51.4%.([19](#_ENREF_19)) Omeprazole have been classified by US Food and Drugs Administration as pregnancy category C, however a meta-analysis based on 1530 women exposed to PPIs in early pregnancy, showed that there was no significant increase in the risk of birth defects associated with exposure to PPIs. The commonly used PPI in this meta-analysis was Omeprazole, 592 out of 1969 cases, and the occurrence of birth defect reported was 2.9% compared to the control group, 2.6%, which is the lowest rate of birth defect compared to other PPIs reported in this study.([20](#_ENREF_20))

GERD in pregnancy is commonly treated with antacid and PPI, however there has not been a direct comparison made between the two treatment among pregnant women. Hence this study is done to demonstrate the efficacy of Gaviscon verses Omeprazole in treating GERD in pregnancy.

**3.0 OBJECTIVE**

1) To assess the symptoms and treatment response of Gaviscon and Omeprazole in GERD in pregnancy.

2) To assess the severity of GERD symptoms and effects to the quality of life.

**4.0 RESEARCH HYPOTHESIS**

Omeprazole and Gaviscon is equally effective in reducing the symptom frequency and severity of GERD in pregnancy.

**5.0 ENDPOINT**

 **5.1 PRIMARY OUTCOMES**

To identify sufficient relief of GERD two weeks after starting the treatment using GerdQ on day 7 and day 14. Sufficient relief is defined as score ≤ 1 for question no 1, 2, 5 and 6 on GerdQ. Complete relief is defined as score of 0 on Gerd questionnaire.

**5.2 SECONDARY OUTCOMES**

1) To determine the severity of GERD symptoms and quality of life after starting the treatment

2) The time onset of the first 24hour GERD symptom free period after initial dosing.

3) Use of any rescue treatment over the course of two weeks.

**5.3** Risk and Benefit to Study Participants

This study does not present any direct risk or major harm to the participants. Treatment given in this study will help resolve or reduce the symptoms of GERD symptoms in pregnancy.

**6.0 METHODOLOGY**

**6.1 STUDY DESIGN**

This is a prospective, open label, randomised controlled clinical trial carried out at antenatal clinic at a University hospital from 12 September 2020 until 1 December 2020. This study was conducted in accordance with Malaysian Guidelines for Good Clinical Practice (GCP) as required by the Ministry of Health Malaysia and the World Medical Association Declaration of Helsinki between May 2016 and November 2017.

**6.2 STUDY POPULATION**

Pregnant women with GERD from 14weeks until 38weeks at antenatal clinic, University Malaya Medical Centre.

**6.3 SAMPLING**

Participant must fulfil the inclusion and exclusion criteria.

6.3.1  INCLUSION CRITERIA

6.3.1.1 Pregnant women aged 18- 40 years

6.3.1.2 Gestational age 14 weeks to less than 38 weeks

6.3.1.3 Able to provide signed and dated informed consent

6.3.2  EXCLUSION CRITERIA

6.3.2.1 Pregnant women younger than 18 years or older than 40 years

6.3.2.2 Gestational age less than 14 weeks and more than 38 weeks

6.3.2.3 Presence of alarm symptoms (dysphagia, odynophagia, aspiration pneumonia, dysphonia, recurrent or persistent cough, gastrointestinal bleeding, frequent nausea/vomiting, persistent pain, iron deficiency anemia, and weight loss)

6.3.2.4 Presence of underlying gastrointestinal disease pre-pregnancy

6.3.2.5 Hypersensitivity to Gaviscon or Omeprazole or both

6.3.2.6 Participants who are already on Gaviscon or Omeprazole or both

6.3.2.7 Unable to provide signed and dated informed consent

**6.4 METHODS**

1) Pregnant women attending antenatal clinic UMMC are screened for inclusion and exclusion criteria.

2) Eligible participants are then diagnosed with GERD using GERD questionnaire in dual language. The questionnaire is distributed in antenatal clinic and collected immediately once completed. Participants with score ≥ 8 from GerdQ are eligible for this study.
3) Participants that agree to be enrolled into the study are asked to sign consent forms prior to enrolment into this study.

4) Participants will be interviewed by the investigator to obtain participant’s characteristics and **Case Report Form** is filled up by the investigator at baseline.

5) Participants are the interviewed for further baseline information based on GERD-HRQL questionnaire.

6) Randomisation of the treatment is performed by the staff nurse in charge with the opening of random sealed and opaque envelope. The envelopes are kept at an allocated place in antenatal clinic. Any opened/unsealed envelopes are discarded. Participants were randomly allocated at a 1:1 ratio to two treatment groups;

(A) Syrup Gaviscon 10mls, three times a day.

(B) Omeprazole, 20mg, once a day.

7) The study is going to be an open-label study as the two treatments differed in appearance and taste, thus study was not conducted double-blind.

(A) Gaviscon Liquid 10mls/three times a day, taken 30mins after meals.

(B) Omeprazole 20mg/once a day, taken 30mins prior the first meal of the day.

8) Participants are then advised to consume the treatment received for 14 days according to the proposed dosage and timing of consumption.

9) Participants with worsening of symptoms or hypersensitivity reaction towards the treatment received are then asked to present to hospital for reassessment and possibly change of medication.

10) GERD treatment response is assessed using the GerdQ, GERD-HRQL questionnaire and patient symptom diary.

11) Participants are required to answer GerdQ and GERD-HRQL questionnaire before starting the treatment, after 7 days and after 14 days of starting the treatment. Questionnaires were distributed via Google form. This method is found to be convenient for participants to respond promptly during the course of the study without having to be physically present at the hospital.

12) Participants are also required to fill up Patient symptom diary daily for 14 days after initiating the treatment. This diary is then submitted to the investigator at the end of the trial.

13) No other treatment given for the management of GERD, however if symptoms worsen or patient develops any signs of hypersensitivity towards the treatment, participants are encouraged to report back to the care providers. Care providers have full discretion in deciding care in participant’s best interest at all times if rescue treatment is needed or the adverse side effects are intolerable and whether the treatment needs to be discontinued.

14) Participants will be followed up every week via telephone interview to ensure compliance.

15) All the information collected are tabulated and analysed.

**6.5 Research tools:**

1) Gerd questionnaire (GERD-Q) is a valid tool used for diagnosis and management of GERD by health care professionals without the need of endoscopy. The questionnaire has 6 components; (1: heartburn, 2: regurgitation, 3: epigastric pain, 4: nausea, 5: sleep disturbance due to heartburn or regurgitation, and 6: use of over-the-counter (OTC) medication to manage heartburn or regurgitation). It is a self-administered questionnaire consisting of six questions Questions 1, 2, 5, and 6 are positive predictors of GERD, and questions 3 and 4 are negative predictors. Scores ranging from 0 to 3 indicate symptom frequency per week of positive predictors (score of 0= never, 1= day, 2= 2-3days and 3= 4-7days).

2) GERD-HRQL was used to assess symptomatic outcomes and therapeutic effects in patient with GERD. The questionnaire has 11 items, which focus on heartburn symptoms, dysphagia, medication effects and patient’s present health status. Each item is scored from 0 to 5, with a higher score indicating a better QOL.

3) Daily symptom diary for GERD is used to record daytime and bedtime heartburn episodes experienced and the symptoms severity is described with 4 graded scale. This diary is to be filled up by the patient starting day 1 of initiating the treatment until day 14. The number of doses of treatment taken is also stated in the diary. This diary allows the investigator to determine the onset of 24hour heartburn free period after initiating the treatment and to identify the number of heartburn free days in a week.

Omeprazole group

Gaviscon group

GerdQ score ≥ 8

**Day 0**

- Gerd-HRQL

**Day 14**

-GerdQ

- Gerd-HRQL

**Day 7**

-GerdQ

- Gerd-HRQL

Patient symptom diary

**6.6 Subject withdrawal Criteria**

Subjects are free to withdraw from participation in the study at any time upon request. There are no financial benefits for participating in this study.

**6.7 Data Handling & record keeping**

Patient’s identity will be kept confidential by using the initials of the names, name of the subjected will not be mentioned in any part of the study. This is explained in the informed consent that the patient will be asked to sign prior enrolling to this study.

**6.8 Methods for handling Missing data and outliers**

Incomplete questionnaire will be excluded from the study to ensure accuracy and completeness of the study.

**7. DATA HANDLING AND RECORD ARCHIVING**

**7.1 Confidentiality and security of source documents and study data**

All the information obtained in this study will be kept and handled in a confidential manner, in accordance with applicable laws and/or regulations. No information concerning the study or the data will be released to any unauthorized third party without prior written approval.

**7.2 Record archiving**

**Please stated duration of archival process**

The document will be retained for 7 years until August 2027, after the period of archiving, all study data will be destroyed by shredding.

**7.3 Conflict of Interest**

The investigator declares that there is no conflict of interest

**6.12 CONSORT Flowchart of study**

Eligibility

Women fulfilling the inclusion criteria (from antenatal clinic)

## Enrollment

Excluded

  Not meeting inclusion criteria

  Declined to participate

  Other reasons

Assessed for Inclusion criteria

GERD diagnosis based on GerdQ

Recruitment, patient information leaflet and consent

Patient demographic information, baseline GERD-HRQL

## Randomization

Allocated to Gaviscon group (n= 34)

Allocated to Omeprazole group (n= 34 )

## Questionnaires

Answer questionnaire on day 0, day 7 and day 14

* GerdQ
* GERD-HRQL
* Daily symptom diary

## Analyses

Answers obtained in the questionnaire, listed in Microsoft Excel and analysed with SPSS.

**6.6 ETHICAL CONSIDERATION**

This study includes vulnerable group which is pregnant population, in order to protect this group, identity of the subjects enrolled for the study are kept private and confidential. The investigator will ensure that the study will be carried out in accordance with Malaysian Guidelines for Good Clinical Practice (GCP) as required by the Ministry of Health Malaysia and the World Medical Association Declaration of Helsinki between May 2016 and November 2017. This protocol and the associated recruitment material must be reviewed and approved by Medical ethic committee before the study can commenced. Any amendments to the protocol or consent forms must also be approved before they are used.

**6.7 SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS**

The sample size of this study was determined to be a total of 68 evaluable subjects which be divided into two groups. It was based on two-sided 95% significance level and with the assumption that percentage of complete heartburn relief in Gaviscon group is 30% and percentage of complete heartburn relief in Omeprazole group is 64% based on previous published study to provide 80% power to demonstrate the non-inferiority of Gaviscon to Omeprazole in pregnant women with GERD. (21) The dropout rate was assumed to be 10%. Therefore, it was determined that approximately minimum of 75 patients should be enrolled to ensure the completion of total 68 evaluable subjects.

The Intention-To-Treat (ITT) population consist of all randomised subjects who administered at least one dose of study medication. The per-protocol (PP) population was a subject of ITT population and further satisfied the following criteria: completed 14 days of treatment and completed all the questionnaires and patient symptom diary for 14 days. Descriptive statistical analyses were performed on data collected on day 0, day 7 and day 14 for ITT and PP population. Efficacy analysis was performed on PP population as the objective was to determine whether Omeprazole is non-inferior to Gaviscon.

The percentage of patients with sufficient/complete relief were compared between treatments groups by a chi-squared test. Symptom severity and symptom frequency were compared between treatments by Mann–Whitney U test and within treatments Wilcoxon signed rank test was used. Changes of quality of life scores (higher QOL indicates better quality of life) from baseline were compared within treatment by paired t-test and between treatments by the two-sample t-test.

Treatment were also compared using patient symptom diary. If the distribution to a 24-h heartburn-free period was non-normal, non-parametric Wilcoxon test was used. The percentage of symptom-free days and nights were compared using Mann-Whitney U test.

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**Appendix 1: Gantt chart**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Activities** | **Apr 2020** | **May 2020** | **June 2020**  | **Jul 2020** | **Aug 2020** | **Sep 2020** | **Oct 2020** |  **Nov 2020** | **Dec 2020** |
| **1.** | **Identify research area** |  |  |  |  |  |  |  |  |  |
| **2** | **Formulate research question** |  |  |  |  |  |  |  |  |  |
| **3** | **Formulate research strategy, research design and select methods** |  |  |  |  |  |  |  |  |  |
| **4** | **Literature review** |  |  |  |  |  |  |  |  |  |
| **5** | **Write research proposal** |  |  |  |  |  |  |  |  |  |
| **6** | **Medical ethics committee approval** |  |  |  |  |  |  |  |  |  |
| **7** | **Data Collection** |  |  |  |  |  |  |  |  |  |
| **5** | **Data Analysis** |  |  |  |  |  |  |  |  |  |
| **6** | **Write first draft** |  |  |  |  |  |  |  |  |  |
| **7** | **Second draft** |  |  |  |  |  |  |  |  |  |
| **8** | **Final draft**  |  |  |  |  |  |  |  |  |  |
| **9** | **Thesis defense** |  |  |  |  |  |  |  |  |  |

**Appendix 2**

**ELIGIBILITY SCREENING AND RECRUITMENT FORM**

STUDY TITILE: A comparative study of Gaviscon and Omeprazole for Gastroesophageal reflux in pregnancy: a prospective randomised controlled trial

Date: \_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_\_

EDD: \_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_\_(\_\_\_\_\_POA/POG)

Inclusion criteria

 Pregnant women aged 18- 40years

 Gestational weeks 14 to less than 38 weeks

 Able to provide signed and dated informed consent

Exclusion criteria

 Pregnant patients younger than 18 years or older than 40 years

 Gestational age less than 14weeks and more than 38weeks

 Presence of alarming GERD symptoms (dysphagia, odonophagia, aspiration pneumonia, dysphonia, recurrent or persistent cough, gastrointestinal bleeding, frequent nausea/vomiting, persistent pain, iron deficiency anemia, and weight loss)

 Presence of underlying gastrointestinal disease pre-pregnancy

 Hypersensitivity to Gaviscon or Omeprazole or both

 Unable to provide signed and dated informed consent

 Not Eligible Eligible but declined Eligible and consented

**Randomised to:**

Patient’s sticker

**Appendix 3**

**Case Report Form**

Patient’s sticker

Version 1

Date:

1) Date of recruitment :

(dd/mm/yy)

2) Estimated due date :

(dd/mm/yy)

3) Parity :

Age:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_DOB: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Ethinicity: Malay/ Chinese/ Indian/ Others

BMI:\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Education level:\_\_\_\_\_\_\_\_\_\_\_\_

Marital status: Single/ Married/ Cohabiting/ Widow

Occupation:\_\_\_\_\_\_\_\_\_\_\_\_

Underlying medical illness:

Previous history of GERD:

Pre-pregnancy

Previous pregnancy

Previous use of medications for GERD

Current drug history: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Appendix 4**

**Outcome form**

**Version 1: 12/7/2020**

1)GERD questionnaire (English)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| No  | Take only the last 7 days into account | Never(0) | 1 day(1) | 2-3 days(2) | 4-7 days(3) |
| 1 | How often did you have a burning feeling behind your breastbone (heartburn)? |  |  |  |  |
| 2 | How often did you feel the unpleasant sensation of stomach contents (food or liquid) move upwards into your throat or mouth (regurgitation)? |  |  |  |  |
| 3 | How often did you have pain in the center of the upper stomach region? |  |  |  |  |
| 4 | How often did you have nausea? |  |  |  |  |
| 5 | How often did you have difficulty getting a good night’s sleep because of your heartburn and/or regurgitation? |  |  |  |  |
| 6 | How often did you take additional medications for your heartburn and/or regurgitation (such as Tums, Pepcid, Prilosec, etc.)? |  |  |  |  |

2) GERD questionnaire (Bahasa Malaysia)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| No | Soalan ( berdasarkan tempoh 7 hari yang lepas ) | Tiada(0) | 1 hari(1) | 2-3 hari(2) | 4-7 hari(3) |
| 1 | Berapa kerap anda berasa seperti panas dan / atau pedih di kawasan ulu hati? |   |  |  |  |
| 2 | Berapa kerap anda berasa seperti cecair atau makanan bergerak ke arah atas menuju ke tekak atau mulut? |  |  |  |  |
| 3 | Berapa kerap anda mengalami kesakitan di kawasan ulu hati? |  |  |  |  |
| 4 | Berapa kerap anda berasa loya atau perasaan hendak muntah? |   |  |  |  |
| 5 | Berapa kerap anda mengalami kesukaran tidur lena disebabkan pedih ulu hati dan/atau rasa hendak muntah? |  |  |  |  |
| 6 | Berapa kerap anda mengambil ubat-ubatan tambahan ( seperti Gaviscon, Zantac, Omesec) untuk mengatasi masalah pedih ulu hati atau rasa hendak muntah? |  |  |  |  |

Interpretation of the GerdQ are

* Total score of 0-2points: likelihood of GERD 0%
* Total score of 3-7 points: likelihood of GERD 50%
* Total score of 8- 10 points: likelihood of GERD 79%
* Total score of 11- 18 points: likelihood of GERD 89%

**Appendix 5: GERD-Health Related Quality of Life Questionnaire(GERD-HRQL)**

Scale:

0 =No symptom

1 =Symptoms noticeable but not bothersome

2 =Symptoms noticeable and bothersome but not everyday

3 =Symptoms bothersome everyday

4 =Symptoms affect daily activity

5 =Symptoms are incapacitating to do daily activities

*Please check the box to the right of each question which best describes your experience over the past 2 weeks*

1) How bad is the heartburn? □0 □1 □2 □3 □4 □5

2. Heartburn when lying down? □0 □1 □2 □3 □4 □5

3. Heartburn when standing up? □0 □1 □2 □3 □4 □5

4. Heartburn after meals? □0 □1 □2 □3 □4 □5

5. Does heartburn change your diet? □0 □1 □2 □3 □4 □5

6. Does heartburn wake you from sleep? □0 □1 □2 □3 □4 □5

7. Do you have difficulty swallowing? □0 □1 □2 □3 □4 □5

8. Do you have pain with swallowing? □0 □1 □2 □3 □4 □5

9. If you take medication does this affect your daily life? □0 □1 □2 □3 □4 □5

10. How bad is the regurgitation? □0 □1 □2 □3 □4 □5

11. Regurgitation when lying down? □0 □1 □2 □3 □4 □5

12. Regurgitation when standing up? □0 □1 □2 □3 □4 □5

13. Regurgitation after meals? □0 □1 □2 □3 □4 □5

14. Does regurgitation change your diet? □0 □1 □2 □3 □4 □5

15. Does regurgitation wake you from sleep? □0 □1 □2 □3 □4 □5

16. How satisfied are you with your present condition? □ Satisfied □ Neutral □ Dissatisfied

**Appendix 6:** **Patient symptom diary**

The diary is to be filled out in the morning and at bedtime each day.

Start filling in the diary at bedtime the evening of day 1 of treatment and continue until daytime on day 14.

Bedtime:

At bedtime please:

1) Fill in the severity of the most intense heartburn episodes during the past 24hours.

2) Record the number of doses of medication taken in the past 24hours.

Morning:

In the morning please:

1) Record if you had any burning feeling during the night.

Definition of 4-graded symptom scale

None: no symptoms

Mild: awareness of sign or symptom, but easily tolerated

Moderate: discomfort or pain, which disturbs daily activities

Severe: discomfort or pain, which makes it impossible to do some daily activities**:**

|  |  |  |
| --- | --- | --- |
| **Date** | **Please answer in the morning** | **Please answer prior to bedtime** |
| Did you have any burning feeling during the night | The most intense burning feeling during the daytime (place an ‘X’ in one box) | Number of doses of medications taken the last 24hours |
|  |  **Yes No** |  **None Mild Moderate Severe** |  |
|  |  |  |  |
|  |  |  |  |

**Sample size calculation**

