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Section Health Technology Assessment

Health Technology Assessment (HTA)

HTA Report

Title	Treatment of non-erosive gastroesophageal reflux disease patients with proton pump inhibitor therapy.
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Technology	Proton-Pump Inhibitors
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Executive Summary

BACKGROUND: Proton-pump inhibitors (PPIs) represent, at the moment, the cornerstone for the treatment of gastroesophageal reflux disease (GERD) patients with symptoms such as heartburn or acid regurgitation. Due to the high safety profile and efficacy of the technology, the current reimbursement policy in Switzerland might favour the administration of PPIs in non-erosive GERD (NERD) patients in a continuous fashion, presumably leading to over-prescription of PPIs.

OBJECTIVE: This health technology assessment (HTA) focuses on the long-term continuous versus on-demand PPI therapy, in adult NERD and endoscopically uninvestigated GERD patients. The HTA is conducted in clinical effectiveness (including efficacy, effectiveness, and safety), cost-effectiveness, legal, social, ethical, and organisational domains. The operationalisation of the on-demand PPI therapy reimbursement is assumed to be realised with reimbursement restriction levels, defined as the maximum number of PPI pills to be reimbursed per year (100, 200 and 365 pills per year).

METHODS: Systematic literature searches were performed in PubMed (MEDLINE), Embase.com, and other complementary databases to identify relevant published evidence for all HTA domains between the years 2000 and 2019. For the clinical and cost-effectiveness domains, data was extracted from the included studies in predefined evidence tables and summary tables were made for different study types (i.e. comparison/non-comparison studies for the clinical-effectiveness and trial/model-based economic evaluations for the cost-effectiveness). For the other domains, the evidence was described narratively. The literature search on the cost-effectiveness of long-term continuous versus on-demand PPI therapy in Switzerland did not provide sufficient evidence. Therefore, for the cost-effectiveness and budget impact analysis of on-demand PPI therapy, a de novo Markov cost-effectiveness model and budget-impact model were developed, characterising the natural history of the disease in a patient's lifetime under the Swiss clinical practice. The cost-effectiveness and budget-impact models simulated the cost implications of implementing on-demand PPI therapy

reimbursement restriction with a given maximum quota for the number of PPI pills per year from a healthcare insurer perspective. Additionally, the out-of-pocket PPI medication cost estimates, resulting from different reimbursement restriction policies were also presented. The uncertainty around these estimates were explored in different sensitivity and scenario analyses.

RESULTS / Conclusions: Long-term PPI therapy is effective in managing the symptoms of NERD and uninvestigated GERD patients. Based on efficacy and effectiveness outcomes, the overall satisfaction of the patients with both therapy modalities (continuous and on-demand PPI therapy) and the health-related quality of life were in general high and differences between continuous and on-demand PPI therapy were quite small, resulting in a lacking clinically relevant difference between these two therapy modalities. Furthermore, no major safety issues were reported in the included studies. With the evidence found in the clinical-effectiveness review, for most outcomes of interest it was not possible to draw a conclusion in favour of continuous or on-demand PPI therapy, amongst others caused by lacking between-group statistical comparisons and heterogeneity in studies and study outcomes, resulting in mixed results. The efficacy evidence showed that long-term on-demand therapy results in lower PPI pill consumption per day compared with continuous therapy. The observed difference for the outcome heartburn symptom relief was in favour of continuous therapy and may largely be attributed to the specifications of the therapy modality (with on-demand therapy a dose of PPI is taken when clinical symptoms occur, which may explain the higher symptom load).

The results of the cost-effectiveness model showed, that on-demand PPI therapy is cost-effective under different reimbursement policies (no pill restriction, restriction to 100 pills, 200 pills [base case] and 365 pills per year) compared to continuous PPI therapy, for uninvestigated GERD and NERD populations. From the model outcomes it can be deducted that there is no significant difference expected in terms of QALYs, between on-demand and continuous PPI therapy. On the other hand, the on-demand PPI therapy is expected to lead to a cost saving of 1’276, 896 and 588 CHF per patient for the health insurer, respectively, over the course of a patient’s life time when the restriction levels of 100, 200 and 365 pills per year are applied. Since the QALY difference between two arms is extremely small, the cost savings due to the on-demand PPI therapy lead to tremendously high ICER values for continuous therapy. Under these reimbursement restriction levels (100, 200 and 365 pills per year), the additional lifetime out-of-pocket payment for PPI medications will be 760, 380 and 72 CHF per patient.

From the one-way sensitivity analysis results, one can observe that PPI usage and the per pill PPI price seem to be among the most influential parameters on the incremental costs. The probabilistic

sensitivity analysis results reveal that the cost-effectiveness is subject to substantial parametric uncertainty, however, the impact of this uncertainty on the decision is rather limited. The continuous PPI therapy is never cost-effective for plausible willingness to pay threshold levels (up to 100,000 CHF per QALY gained).

The 5-year estimated budget saving of changing from continuous PPI therapy to on-demand PPI therapy is estimated to be between 50 and 127 million CHF for the uninvestigated GERD and NERD patients in Switzerland. This budget impact depends on the nature of the policy implementation (sudden or gradual implementation) as well as the reimbursement restriction threshold (200 or 365 pills per year) and the scope of the reimbursement restriction (i.e. if patients who fail on-demand PPI therapy but are stable under continuous PPI therapy before endoscopy are included or not).

The present study did not find relevant issues or limitations pertaining the implementation of a restriction on PPIs reimbursement system in the legal, social, ethical, or organisational domains.

Zusammenfassung

EINLEITUNG: Protonenpumpeninhibitoren (PPI) sind derzeit die Standardbehandlung bei gastroösophagealer Refluxkrankheit (GERD), die durch Sodbrennen und Regurgitation gekennzeichnet ist. Aufgrund der Wirksamkeit und des guten Sicherheitsprofils wird die kontinuierliche PPI-Therapie von Patienten mit nicht-erosiver Refluxkrankheit (NERD) von der aktuellen Rückerstattungspolitik in der Schweiz möglicherweise gefördert, was eine übermässige Verschreibung von PPI zur Folge haben könnte.

ZIELSETZUNG: Schwerpunkt des vorliegenden Health Technology Assessments (HTA) ist ein Vergleich zwischen einer Dauerbehandlung mit kontinuierlicher PPI-Einnahme und einer PPI-Einnahme nach Bedarf (on-demand) bei erwachsenen Patienten mit NERD und mit nicht endoskopisch untersuchter GERD. Das HTA berücksichtigt die klinische Wirksamkeit (einschliesslich die Wirksamkeit unter idealen Bedingungen und unter Alltagsbedingungen und die Sicherheit), die Kosteneffizienz sowie die rechtlichen, organisatorischen und ethischen Aspekte. Es wird angenommen, dass die Umsetzung der Rückerstattungseinschränkungen bei einer PPI-Bedarfstherapie über die maximale Anzahl rückerstatteter PPI-Tabletten pro Jahr (100, 200 bzw. 365 Tabletten pro Jahr) erfolgt.

METHODE: Es wurde eine systematische Literaturrecherche in PubMed (MEDLINE), Embase.com und anderen ergänzenden Datenbanken durchgeführt, um für die einzelnen Bereiche des HTAs relevante Informationen zusammenzutragen, die im Zeitraum von 2000 bis 2019 publiziert wurden. Für die Bereiche klinische Wirksamkeit und Kosteneffizienz wurden die Daten der berücksichtigten Stu-

dien in vorgegebenen Tabellen erfasst und es wurden Übersichtstabellen für unterschiedliche Studientypen (vergleichende/nicht-vergleichende Studien zur klinischen Wirksamkeit bzw. versuchsbasierte/modellbasierte ökonomische Evaluationen zur Kosteneffizienz) erstellt. Für die anderen Bereiche wurden die gesammelten Daten narrativ beschrieben. Die Literatursuche zur Kosteneffizienz einer Bedarfstherapie gegenüber einer kontinuierlichen Therapie mit PPI in der Schweiz ergab nicht genügend Daten. Aus diesem Grund wurde zur Analyse der Kosteneffizienz und der Budgetauswirkungen (Budget Impact) der PPI-Bedarfstherapie *de novo* ein entsprechendes Markow-Modell erstellt, das die natürliche Entwicklung der Krankheit im Leben eines Patienten unter den Bedingungen der klinischen Praxis in der Schweiz beschreibt. Die Modelle zur Kosteneffizienz und zu den Budgetauswirkungen simulierten die finanziellen Auswirkungen von Einschränkungen der Rückerstattung bei einer PPI-Bedarfstherapie mittels einer vorgegebenen Maximalmenge von rückerstatteten PPI-Tabletten pro Jahr aus der Sicht der Krankenkasse. Ausserdem wurden die selbst getragenen Kosten der PPI-Behandlung bei verschiedenen Ansätzen von Rückerstattungseinschränkungen geschätzt. Die Unsicherheiten dieser Schätzungen wurden mit verschiedenen Empfindlichkeits- und Szenarioanalysen untersucht.

ERGEBNISSE / SCHLUSSFOLGERUNGEN: Die Langzeit PPI-Therapie ist zur Behandlung der Symptome von Patienten mit NERD und nicht untersuchter GERD wirksam. Gemessen an den Outcomes zur Wirksamkeit unter idealen Bedingungen und unter Alltagsbedingungen war die Zufriedenheit der Patienten bei beiden Therapiearten (kontinuierliche Therapie und Bedarfstherapie) und die gesundheitsbezogene Lebensqualität im Allgemeinen hoch, und die Unterschiede zwischen der kontinuierlichen und der bedarfsgerechten PPI-Therapie waren ziemlich gering und klinisch nicht relevant. Ausserdem wurden in den berücksichtigten Studien keine wichtigen Sicherheitsprobleme festgestellt. Aufgrund der gefundenen Daten zur Prüfung der klinischen Wirksamkeit konnte für die meisten untersuchten Outcomes nicht entschieden werden, ob eine kontinuierliche oder eine bedarfsorientierte PPI-Behandlung vorzuziehen ist, unter anderem auch wegen eines fehlenden statistischen Vergleichs zwischen den Gruppen und wegen der Heterogenität der Studien und der Studien-Outcomes, was zu uneinheitlichen Ergebnissen führte. Die Daten zur Wirksamkeit zeigten, dass eine langfristige Bedarfstherapie im Vergleich zu einer kontinuierlichen Therapie mit einer tieferen Zahl eingenommener PPI-Tabletten pro Tag verbunden ist. Der beobachtete Unterschied beim Outcome bezüglich Linderung des Symptoms Sodbrennen fiel zugunsten der kontinuierlichen Therapie aus, dies könnte aber zu einem grossen Teil auf die Eigenheiten der Therapiebedingungen zurückzuführen sein (bei der bedarfsgerechten Therapie wird eine PPI-Dosis erst eingenommen, wenn ein klinisches Symptom auftritt, wodurch sich die stärkeren Symptome erklären lassen).

Die Ergebnisse des Kosteneffizienz-Modells zeigten, dass die bedarfsgerechte PPI-Therapie unter

verschiedenen Rückerstattungsszenarien (keine Einschränkungen der Anzahl Tabletten, Einschränkung auf 100 Tabletten, 200 Tabletten [Grundszenario] und 365 Tabletten pro Jahr) bei Patientengruppen mit nicht-untersuchter GERD und mit NERD im Vergleich zur kontinuierlichen PPI-Therapie kostenwirksam ist. Aus den Outcomes der Modelle kann geschlossen werden, dass bezüglich QALY zwischen der bedarfsgerechten Therapie und der kontinuierlichen Therapie mit PPI kein signifikanter Unterschied zu erwarten ist. Andererseits sind bei der PPI-Bedarfstherapie Kosteneinsparungen für die Krankenkasse von 1'276, 896 bzw. 588 CHF pro Patient über dessen Lebensdauer bei Einschränkungen der Rückerstattung auf 100, 200 und 365 Tabletten pro Jahr zu erwarten. Da der Unterschied bezüglich QALY zwischen den beiden Studienpopulationen äusserst gering ist, führen die Kosteneinsparungen durch die PPI-Bedarfstherapie zu enorm hohen ICER-Werten für die kontinuierliche Therapie. Bei den untersuchten Rückerstattungseinschränkungen (100, 200 und 365 Tabletten pro Jahr) liegen die selbst getragenen Kosten für die PPI-Medikation bei 760, 380 und 72 CHF pro Patient über dessen Lebensdauer.

Aus den Ergebnissen der Einweg-Sensitivitätsanalyse lässt sich ableiten, dass die PPI-Anwendung und die Kosten pro Tablette zu den Parametern gehören, die den grössten Einfluss auf die inkrementellen Kosten haben. Die Ergebnisse der probabilistischen Sensitivitätsanalyse zeigen, dass die Kostenwirksamkeit zwar mit beträchtlichen parametrischen Unsicherheiten verbunden ist, dass der Einfluss dieser Unsicherheit auf die Entscheidung aber eher beschränkt ist. Die kontinuierliche PPI-Therapie ist nie kostenwirksam unter Berücksichtigung plausibler Schwellenwerte für die Zahlungsbereitschaft (bis zu 100'000 CHF pro gewonnenes QALY).

Die geschätzten Budgeteinsparungen über 5 Jahre bei einem Wechsel von der kontinuierlichen Therapie auf die Bedarfstherapie mit PPI liegen in der Schweiz bei 50 bis 127 Millionen CHF für Patienten mit nicht untersuchter GERD und NERD. Der Budget Impact hängt davon ab, wie die Rückerstattungseinschränkungen umgesetzt werden (sofort oder schrittweise), von ihrem Geltungsbereich (d.h. ob Patienten, bei denen die PPI-Bedarfstherapie versagt, die aber unter einer kontinuierlichen Therapie vor der Endoskopie stabil sind, eingeschlossen werden oder nicht) und welcher Maximalwert für die Rückerstattung gilt (200 oder 365 Tabletten pro Jahr).

In der vorliegenden Studie wurden in Bezug auf die rechtlichen, sozialen, ethischen und organisatorischen Aspekte keine relevanten Probleme oder Limitationen für die Umsetzung von Rückerstattungseinschränkungen bei PPI-Behandlungen gefunden.

Résumé

CONTEXTE : Les inhibiteurs de la pompe à protons (IPP) représentent, à l'heure actuelle, la pierre angulaire du traitement du reflux gastro-œsophagien pathologique (GERD, *gastroesophageal reflux*

disease) chez les patients présentant des symptômes tels que des brûlures d'estomac ou une régurgitation acide. En raison du profil d'innocuité élevé et de l'efficacité de la technologie, la politique de remboursement actuelle en Suisse pourrait favoriser l'administration continue d'IPP chez les patients atteints de GERD non érosif (NERD, *non-erosive GERD*), ce qui entraînerait probablement une surprescription d'IPP.

OBJECTIF : La présente évaluation des technologies de la santé (ETS) compare le traitement continu à long terme par les IPP au traitement à la demande chez les patients adultes atteints de NERD et de GERD non exploré par endoscopie. L'ETS porte sur l'efficacité clinique (y compris l'innocuité et l'efficacité en conditions réelles et idéales), le rapport coût-efficacité et les domaines juridique, social, éthique et organisationnel. L'opérationnalisation du remboursement des traitements par les IPP à la demande est supposée se faire avec des niveaux de restriction de remboursement, définis comme le nombre maximum de comprimés d'IPP à rembourser par an (100, 200 et 365 comprimés par an).

MÉTHODES : Des recherches documentaires systématiques ont été effectuées dans PubMed (MEDLINE), Embase.com et d'autres bases de données complémentaires afin d'identifier les données probantes publiées pertinentes pour tous les domaines de l'ETS entre les années 2000 et 2019. Pour les domaines de l'efficacité clinique et du rapport coût-efficacité, les données ont été extraites des études incluses dans des tableaux de données probantes prédéfinis, et des tableaux récapitulatifs ont été établis pour différents types d'études (études comparatives/non comparatives pour l'efficacité clinique, évaluations économiques fondées sur des essais/modèles pour le rapport coût-efficacité). Pour les autres domaines, les données probantes ont été décrites de façon narrative. La recherche documentaire sur le rapport coût-efficacité du traitement par les IPP continu à long terme par rapport au traitement à la demande en Suisse n'a pas fourni de données probantes suffisantes. Par conséquent, pour l'analyse du rapport coût-efficacité et de l'impact budgétaire du traitement par les IPP à la demande, un modèle coût-efficacité de Markov *de novo* et un modèle d'impact budgétaire ont été développés, caractérisant l'histoire naturelle de la maladie au cours de la vie d'un patient dans la pratique clinique suisse. Les modèles coût-efficacité et d'impact budgétaire simulaient les répercussions financières de la mise en œuvre d'une restriction du remboursement des traitements par les IPP à la demande avec un quota maximal donné pour le nombre de comprimés d'IPP par année du point de vue de l'assureur de soins de santé. De plus, les estimations du coût à la charge des patients pour les médicaments IPP, résultant de différentes politiques de restriction du remboursement, ont également été présentées. L'incertitude entourant ces estimations a été explorée dans différentes analyses de sensibilité et de scénarios.

RÉSULTATS/CONCLUSIONS : Le traitement par les IPP à long terme est efficace dans la prise en

charge des symptômes du NERD et du GERD non exploré. D'après les résultats concernant l'efficacité (en conditions idéales et réelles), la satisfaction globale des patients à l'égard des deux modalités thérapeutiques (traitement par les IPP continu et à la demande) et la qualité de vie liée à la santé étaient généralement élevées, et les différences entre le traitement continu et à la demande étaient assez faibles : il n'y a donc pas de différence cliniquement pertinente entre ces deux modalités thérapeutiques. De plus, aucun problème d'innocuité majeur n'a été signalé dans les études incluses. Les données probantes identifiées dans l'examen de l'efficacité clinique n'ont pas permis de tirer une conclusion en faveur d'un traitement par les IPP continu ou à la demande pour la plupart des résultats recherchés. Les conclusions mitigées de cet examen s'expliquent notamment par l'absence de comparaisons statistiques entre groupes ainsi que par l'hétérogénéité des études et des résultats de celles-ci. Les données probantes sur l'efficacité dans des conditions idéales ont montré qu'un traitement à la demande à long terme entraîne une diminution de la consommation de comprimés d'IPP par jour par rapport à un traitement continu. La différence observée dans le soulagement des symptômes de brûlures d'estomac était en faveur d'un traitement continu et peut être attribuée en grande partie aux spécifications de cette modalité thérapeutique (dans le cas d'un traitement à la demande, une dose d'IPP est prise lorsque des symptômes cliniques apparaissent, ce qui peut expliquer la charge de symptômes plus élevée).

Les résultats de la modélisation du rapport coût-efficacité ont montré que le traitement par les IPP à la demande offre un bon rapport coût-efficacité avec différentes politiques de remboursement (aucune restriction quant à la prise de comprimés et restriction à 100 comprimés, 200 comprimés (cas de base) et 365 comprimés par année) par rapport au traitement par les IPP continu, dans les populations non examinées souffrant de GERD non exploré et de NERD. On peut également déduire de cette modélisation qu'il n'y a pas de différence significative à attendre en termes de QALY (années de vie pondérées par la qualité) entre le traitement par les IPP à la demande et continu. Par contre, le traitement à la demande devrait permettre à l'assureur de soins de santé d'économiser respectivement 1 276, 896 et 588 francs par patient pendant toute la durée de vie de ce dernier, si les niveaux de restriction de 100, 200 ou 365 comprimés par an sont appliqués. Étant donné que la différence de QALY entre deux bras d'essai est extrêmement faible, les économies réalisées grâce au traitement par les IPP à la demande entraînent des valeurs ICER (rapport coût-efficacité différentiel) extrêmement élevées pour le traitement continu. Avec ces niveaux de restriction du remboursement (100, 200 et 365 comprimés par an), la somme supplémentaire à la charge des patients, sur toute leur vie, sera de 760, 380 et 72 francs par patient.

D'après les résultats de l'analyse de sensibilité à une voie, on peut observer que l'utilisation des IPP

et leur prix par comprimé semblent figurer parmi les paramètres influençant le plus les coûts différentiels. Les résultats de l'analyse de sensibilité probabiliste révèlent que le rapport coût-efficacité est sujet à une incertitude paramétrique importante, mais que l'impact de cette incertitude sur la décision est plutôt limité. Le traitement par les IPP continu n'offre jamais un bon rapport coût-efficacité au regard de valeurs-seuils plausibles de la propension à payer (jusqu'à 100 000 francs par QALY gagné).

L'économie budgétaire estimée sur 5 ans du passage d'un traitement par les IPP continu à un traitement par les IPP à la demande est comprise entre 50 et 127 millions de francs pour les patients atteints de GERD non exploré et de NERD en Suisse. Cet impact budgétaire dépend de la façon dont la politique est mise en œuvre (application progressive ou non) ainsi que du seuil de restriction du remboursement (200 ou 365 comprimés par année) et de la portée de cette restriction (c.-à-d. si les patients qui ne répondent pas à un traitement par les IPP à la demande mais qui sont stables sous traitement continu par les IPP avant endoscopie sont inclus ou non).

La présente étude n'a pas relevé de problèmes ou de limites pertinentes concernant la mise en œuvre d'une restriction dans le mécanisme de remboursement des IPP dans les domaines juridique, social, éthique et organisationnel

List of contents

Abbreviations and acronyms

AE	Adverse event
BNF	British National Formulary
C	Continuous therapy
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost-effectiveness
CEAC	Cost-effectiveness acceptability curve
CHF	Swiss Franc
e.g.	Exempli gratia (for example)
ERD	Erosive reflux disease
EUnetHTA	European Network for Health Technology Assessment
FOPH	Federal Office of Public Health
GERD	Gastroesophageal reflux disease
GOS	Global overall symptom scale
GP	General practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GSAS	GERD symptoms assessment scale
GSRS	Gastrointestinal symptom rating scale
HAS	Haute Autorité de Santé (French National Authority for Health)
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
H_2RAs	Histamine-receptor antagonists
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
i.e.	Id est (that is)
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
iMTA	Institute for Medical Technology Assessment
ITT	Intention-to-treat analysis
LTFU	Lost to follow-up
LY	Life years
m	Months
MCS	Mental Component Summary

MEMS	Medical event monitoring system
MESH	Medical Subject Headings
NA	Not applicable
NERD	Non-erosive reflux disease
NHS	National Health Service
NHS/EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NR	Not reported
OD	On-demand therapy
OTC	Over the counter
OTE	Overall treatment evaluation questionnaire
OWSA	One-way sensitivity analysis
PAGIQOL	Patient assessment of upper gastrointestinal disorders - Quality of life questionnaire
PBAC	Pharmaceutical Benefits Advisory Committee
PCS	Physical Component Summary
PGWB	Psychological General Well-Being
PICO	Patients - Intervention – Comparator - Outcome
PP	Per-protocol analysis
PPI	Proton-pump inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSSRU	Personal Social Services Research Unit
QALYs	Quality-adjusted life years
QoL	Quality of life
QOLRAD	Quality of life in reflux and dyspepsia instrument
RCT	Randomised controlled trial
SAE	Severe adverse event
SD	Standard deviation
SF-36	Short Form-36
SIR	Standardised incidence ratio
UK	United Kingdom
USA	United States of America
w	Weeks
ZiN	Zorginstituut Nederland (National Health Care Institute)

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Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology are described. The analytical process is comparative, systematic, transparent and involves multiple stakeholders. The domains covered in a HTA report include clinical effectiveness and safety, costs, cost-effectiveness and budget impact, legal, social, ethical and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1 Policy question and context

All proton-pump inhibitors (PPIs) licensed in Switzerland are covered by the mandatory health insurance without any limitations for the treatment of patients with gastroesophageal reflux disease (GERD). That means, medical doctors are allowed to issue a long-term continuous PPI prescription for patients with reflux disease regardless of whether they have an erosive (ERD) or a non-erosive reflux disease (NERD), although it has been shown that NERD patients may be managed with on-demand PPI long-term therapy.

Because of the PPIs' good efficacy, effectiveness, and safety profile, the failure to re-evaluate the need for continuation of therapy, and the insufficient use of on-demand PPI therapy in ambulatory care settings, PPIs are presumably over-prescribed.

Therefore, the applicant (santésuisse) suggests limiting the prescription of PPIs for patients with NERD or uninvestigated GERD to 200 pills per year because it has been shown in the literature that NERD or univestigated GERD patients take in average approximately between 120 to 200 pills per year.[1] This prescription limitation does not apply for the erosive reflux disease patients, and they should still be able to receive their unrestricted, fully reimbursed continuous long-term PPI therapy.

This HTA aims to perform a focussed assessment of the efficacy, effectiveness, safety, costs, cost-effectiveness and budget-impact of PPI long-term continuous and long-term on-demand therapy for NERD and endoscopically uninvestigated GERD patients. Long-term is defined as PPI therapy taken during a period longer than 6 months.

2 Research question

What is the efficacy, effectiveness, safety, cost-effectiveness and budget-impact of continuous long-term PPI treatment (i.e. longer than 6 months) versus on-demand long-term PPI treatment (i.e. longer than 6 months) in adult NERD patients and uninvestigated GERD patients?

3 Medical background

GERD describes a spectrum of different reflux diseases, including NERD, ERD and complicated forms such as ulcer, columnar metaplasia, stricture, and Barrett's oesophagus.[2] In the Western world, GERD affects 10% to 20% of the people. The prevalence of GERD in Switzerland is similar to other industrialised countries and has been estimated to be approximately 18%.[3] More men than women are diagnosed with ERD and more women than men are diagnosed with NERD.[4] NERD is the most frequent diagnosed GERD (50% to70%).[2]

In the majority of patients GERD is not the result of a single underlying pathology, but arises from the interaction of several anatomical and physiological factors.[5] Common initial symptoms of the disease are a burning sensation in the chest (heartburn) and acid regurgitation.[6] GERD is characterised by reflux of gastric contents into the oesophagus (minimal 1 to 2 times per week), which may lead to oesophageal injury and, in long term, to oesophageal adenocarcinoma.[2, 6, 7] In 10% of the ERD patients, pre-cancerous Barrett's oesophagus is found.[8]

GERD is typically diagnosed by the evaluation of clinical symptoms and the response to acid suppression (i.e. the 'test and treat' regimen). Additional diagnostic procedures include upper endoscopy and oesophageal pH monitoring.[9] With conventional endoscopy, GERD can be further classified as NERD with the presence of symptoms without oesophageal mucosal erosions/breaks on endoscopic examination or ERD with erosions present at endoscopy.[4] The 'test and treat' regimen without an endoscopy has both advantages and disadvantages. It allows clinicians to treat the patient immediately, helps to alleviate symptoms, increase patients' satisfaction and quality of life, and reduces the overall economic burden of the cost of endoscopies. Caution is needed however, because there will be a very small number of patients with possible serious disease, which is masked through the treatment of symptoms alone.[10]

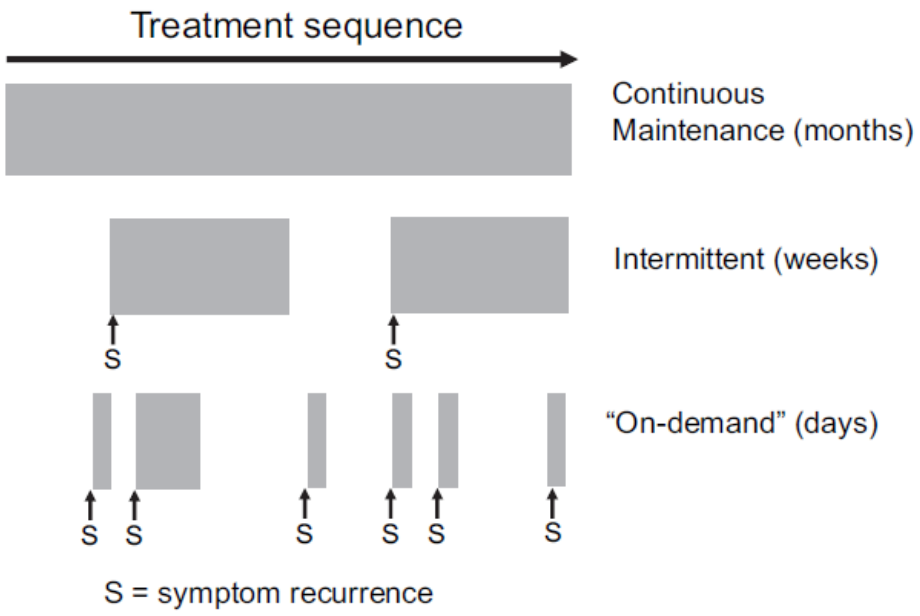
The main goal of GERD therapy is the control of symptoms, the healing of oesophagitis (if present), and the prevention of complications (i.e. stricture, Barrett's oesophagus, and oesophageal adenocarcinoma).[2] Symptomatic (or endoscopic) relapse is very frequent and it has been estimated that 80% of patients have oesophagitis relapse after 6 to 12 months of therapy; most patients therefore need long-term anti-secretory therapy.[2] First-line therapy consists of lifestyle modifications and medical treatment. For a subset of patients,

surgical interventions are needed. Several classes of medications exist, including antacids, histamine-receptor antagonists (H_2RAs), or PPIs.[9]

A turning point in the medical treatment of GERD was the introduction of the first PPI (omeprazole) in 1989. The superior efficacy of PPIs in GERD depends on their ability to elevate gastric pH substantially. PPIs are now one of the most commonly prescribed class of medications in the primary care setting and a major advance in the treatment of GERD.[5]

The management options in terms of use of PPIs are either daily therapy (i.e. continuous therapy), intermittent courses of (continuous) therapy, or symptom-driven on-demand therapy.[5] Intermittent therapy is a strategy whereby a patient is given repetitive daily treatment with a fixed treatment duration to relieve symptoms, typically with a duration of 2 to 4 weeks. Treatment is started when GERD symptoms recur and is stopped when the patient becomes asymptomatic once again.[11] With on-demand therapy, a dose of PPI is taken only when symptoms occur.[11] In Figure 1, the different PPI treatment schemes are visualised.

Figure 1: PPI treatment schemes [12]



Considerable clinical experience with PPIs endorses their efficacy and safety with long-term use. However, authors like Pace et al. (2008), public health authorities, third-party payers, and a proportion of patients expressed concerns about the cost and/or inconvenience of long-term continuous treatment with PPIs.[13] This has led to the evaluation of different long-term management strategies. These include various 'step-down'

approaches, including a switch to a cheaper agent (e.g. an H_2RA), or to non-continuous PPI therapy (e.g. alternate days, intermittently, or on-demand).[13]

4 Technology

4.1 Technology description

PPIs are a group of drugs whose aim is to reduce the stomach acid production enduringly and distinctively. PPIs mechanism of action is to irreversibly block the activated hydrogen/potassium adenosine triphosphatase enzyme system (proton pumps in the gastric parietal cells), which secretes hydrochloric acid into the gastric lumen. PPIs are given orally and are absorbed from the small intestine and carried by the blood stream to the gastric parietal cells. PPIs do not act immediately, first, they accumulate in the luminal space of the secretory canaliculus of the parietal cells. Then they are activated by the acid environment through a protonation reaction. The activated species of PPIs bind covalently the hydrogen/potassium pump and inhibit it permanently. For optimal efficacy, the PPI pills have to be taken orally before meals (30 to 60 minutes prior to the first meal).[14]

The therapy is prescribed to GERD patients with symptoms such as heartburn or acid regurgitation. This first-line empiric treatment is typically given for 4 to 8 weeks. If symptoms do not disappear after this treatment, further diagnostic tests (endoscopy and/or pH monitoring) can be performed.[9]

Discontinuation of the initial PPI therapy often results in a relapse of symptoms, therefore continuous PPI long-term therapy at the minimal efficacious dose is typically prescribed for GERD patients.[9] Continuous PPI long-term therapy (longer than 6 months) is also prescribed for uninvestigated GERD and NERD population. Nevertheless, it has been shown that approximately 30% to 80% of all GERD patients take PPIs intermittently or on-demand instead of continuously, as initially prescribed.[15-17] NERD patients may be managed with on-demand PPI long-term treatment[2, 9, 17, 18] and it has been reported that these patients take on average one PPI pill in every 3 to 4 days, which corresponds to more than 120 tablets per year.[19, 20] Daily dose can vary, depending on the specific PPI, in a range from around 20 mg once a day (Rabeprazole) to 40 mg once a day (Esomeprazole) or 30 mg once to twice a day (Lansoprazole).[21]

PPIs are reported to be associated with few side effects.[22] PPI intolerance has been observed in 1% to 3% of the population (mostly with symptoms of headache, abdominal pain, diarrhoea, flatulence, dyspepsia, and in some rare cases, rash and allergy).[16]

Given their efficacy, effectiveness, and the positive safety profile, PPIs are possibly over-prescribed.[22] The over-utilisation of PPIs in ambulatory care settings is often a result of failure to re-evaluate the need for

continuation of therapy or insufficient use of on-demand or step-down therapy.[20] Lee et al.[23] reported that 26% to 71% of the GERD patients could be managed without continuous PPI long-term medication. Their statement was based on the evidence generated from the systematic review of randomised and non-randomised clinical trials. However, it should be noted that these conclusions are based on patients' reporting of their symptoms and their level of willingness to continue on less intensive therapy rather than on formal assessments of quality of life (QoL).

4.2 Alternative technologies

Alternative first-line GERD treatments include antacids and H_2RAs. Over-the-counter (OTC) antacids are very common during the first manifestations of the disease. Differently from PPIs, they do not prevent acid production, but rather buffer the protons in the lumen of the stomach neutralising part of the acidity.[21] Patients tend to visit a medical doctor only when symptoms increase or persist. OTC antacids have shown to be effective in only approximately 25% of patients with GERD. Similarly, H_2RAs are available over the counter or by prescription. H_2RAs mostly exert their anti-acid effect by binding H_2 histamine receptors on gastric parietal cells. H_2 receptors, when stimulated, determine the migration of the hydrogen/potassium pump from the cytoplasmic tubular membranes to the surface of the canaliculi of the parietal cells. By antagonizing this mechanism, H_2RAs prevent the extrusion of hydrogen protons in the gastric lumen and therefore reduce acidity.[24] Patients with persistent symptoms after continuous H_2RA treatment are often switched to PPI therapy.[25]

4.3 Regulatory status / provider

PPIs find application in many medical specialities, as heartburn and GERD-like symptoms are common in many medical conditions across multidisciplinary settings, such as gastroenterology, otolaryngology, internal medicine, surgery, and general practice as well. PPIs are prescribed not only in GERD patients, but also to treat dyspepsia and, concomitantly with antibiotics, infections by Helicobacter pylori. In addition to gastroenterological diseases, PPIs are prescribed in the context of long-term therapy with non-steroidal anti-inflammatory drugs (NSAIDS) and acetylsalicylic acid (ASA). For example in patients with chronic inflammatory diseases or to prevent cardiovascular events in specific risk categories of patients PPIs are used, with the intent of protecting the gastric mucosa from ASA and to reduce the incidence of peptic ulcer.[26]

Some PPIs (especially Esomeprazole) are available OTC in many countries, the others require a prescription by a medical doctor. Both, general practitioners (GPs) or specialists can prescribe PPIs.[27]

The PPIs approved in Switzerland for treatment of reflux oesophagitis are dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. The specific indications are described in Table 1.[28] All PPIs licensed in Switzerland are covered by the mandatory health insurance without any volume restrictions. In Switzerland, prescription of PPIs results in considerable costs (CHF 151 million in 2018[29]), which has to be – apart from the standard deductibles for patients - fully covered by the health insurance.

In Germany, PPIs that need a prescription are reimbursed by the statutory health insurance (Gesetzliche Krankenversicherung). OTC PPIs, such as esomeprazole, are reimbursed for children and adolescents up to the age of 18 years and for adults in case of chronic conditions (not specified).[30]

In the Netherlands, all patients who start using PPIs have to pay for the first prescription of 14 days themselves. For patients who use PPIs for a period shorter than 6 months, this also holds for subsequent PPI prescriptions. Patients who have to use PPIs chronically (>6 months) only have to pay the first prescription, subsequent prescriptions are reimbursed.[31]

In France, in 2013, reimbursements for PPIs accounted for approximately 530 million euros. The French National Authority for Health (Haute Autorité de Santé) and the French Agency for the Safety of Health Products (Agence Française de Sécurité Sanitaire des Produits de Santé) outline the guidelines and the proper indications, dosage, and duration of the treatment with PPIs to curb costs. PPIs under medical prescription are partially reimbursed, OTC PPIs, such as pantoprazole, are not reimbursed.[32]

In Italy, PPIs are reimbursed by the National Health System depending on the underlying medical condition. For a period of 4 to 6 weeks when prescribed for the treatment of GERD (AIFA nota 48) or indefinitely when prescribed for chronic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) in patients under anti-aggregating therapy with low-dose ASA (AIFA nota 1).[33]

Table 1 Regulatory status of PPIs in Switzerland

Dexlansoprazole	Dexlansoprazole is indicated for the treatment of adults and adolescents aged 12 to 17 years: • For the healing of erosive esophagitis. • For long-term therapy of healed erosive esophagitis and relief of gastric burning.
Esomeprazole	Esomeprazole is indicated for: • The treatment of reflux oesophagitis. • Long-term relapse prophylaxis of reflux oesophagitis. • Symptomatic treatment of gastroesophageal reflux (heartburn, acid regurgitation) without erosive/ulcerated reflux oesophagitis.

	• Eradication of Helicobacter pylori in combination with appropriate antibiotics. • Healing of Helicobacter pylori-associated duodenal ulcer. • Recurrence prophylaxis of Helicobacter pylori-associated peptic ulcer disease. • Healing of gastric ulcers caused by NSAIDs (including COX-2 selective NSAIDs). • Prevention of gastric ulcer and duodenal ulcer in high-risk patients taking NSAIDs (including COX-2 selective NSAIDs). • The treatment of pathological hypersecretion including Zollinger-Ellison syndrome and idiopathic hypersecretion. • The prevention of re-bleeding in bleeding gastric ulcer or duodenal ulcer after treatment with esomeprazole intravenous
Lansoprazole	Lansoprazole is indicated for: • The treatment of duodenal ulcer/gastric ulcer including NSAID-induced duodenal ulcer/gastric ulcer in patients in need of continued NSAID therapy. • Prophylaxis of NSAID-induced gastric ulcer and duodenal ulcer in patients in need of continued NSAID therapy who are at increased risk of developing NSAID-induced ulcer. Controlled studies to demonstrate efficacy and safety lasted only 12 weeks. • Eradication of Helicobacter pylori in gastric ulcer, duodenal ulcer, and Helicobacter pylori-associated gastritis with concomitant administration of 2 antibiotics for 7 days, where one of the two should be clarithromycin. • The treatment of reflux oesophagitis (including prophylaxis and long-term therapy). • The treatment of symptomatic gastroesophageal reflux without erosive ulcerous reflux oesophagitis. • The treatment of Zollinger-Ellison syndrome. • Short-term symptomatic treatment of upper abdominal discomfort (such as acid regurgitation, heartburn, epigastric pain). • Children from 12 months of age: treatment of reflux oesophagitis.
Omeprazole	Omeprazole is indicated for: • The treatment of duodenal ulcer, gastric ulcer, reflux oesophagitis, and Zollinger-Ellison syndrome. The diagnosis should be endoscopically

	proven, if possible. • Long-term therapy and prophylaxis in patients with reflux oesophagitis, relapse prevention of duodenal ulcer in therapy-resistant Helicobacter pylori. • Relapse prophylaxis of gastric ulcer. • Eradication of Helicobacter pylori in peptic ulcer with simultaneous administration of two antibiotics. • The treatment of NSAIDs induced peptic ulcers or gastroduodenal erosions. • The treatment of symptomatic gastroesophageal reflux (dyspepsia, heartburn, acid regurgitation). • For relapse prophylaxis in healed reflux oesophagitis. • The therapy of functional acid-related dyspepsia. • For children aged up to 12 years: treatment of reflux oesophagitis.
Pantoprazole	Pantoprazole is indicated for: • The amelioration of the discomfort and cure of mild forms of reflux disease (grade 1 according to Savary-Miller). It is also indicated for the long-term treatment and relapse prevention of a healed inflammation in the area of the lower oesophagus. • The cure and amelioration of the discomfort of mild and moderate forms of oesophagitis, duodenal ulcers, and gastric ulcers. It is also indicated for the treatment of Helicobacter pylori infection in combination with two antibiotics in duodenal ulcer and gastric ulcer. It is also used to prevent NSAID induced gastric and duodenal ulcers in patients at increased risk of developing such lesions and who cannot avoid NSAID treatment. • The treatment of mild and moderate forms of reflux oesophagitis (grade 2-3 according to Savary-Miller). • For the treatment of the Zollinger-Ellison syndrome and other diseases that are associated with a pathological overproduction of gastric acid.
Rabeprazole	Rabeprazole is indicated for: • The treatment of symptomatic erosive or ulcerative reflux oesophagitis. • Long-term therapy and relapse prevention in patients with reflux oesophagitis. • Symptomatic treatment of gastroesophageal reflux (heartburn, acid regurgitation) without erosive/ulcerative reflux oesophagitis.

	• The treatment for florid duodenal ulcer and gastric ulcer.
	• In combination with suitable antibiotics:
	  ○ H. pylori eradication in patients with H. pylori-associated duodenal or ventricular ulcers or chronic gastritis.
	  ○ The healing and prevention of relapse of H. pylori-associated duodenal or ventricular ulcers.

5 PICO

P:	1. Adult patients with endoscopically proven NERD, who are symptom-free after 4-8 weeks of initial acute PPI therapy 2. Adult patients with endoscopically uninvestigated GERD, who are symptom-free after 4-8 weeks of initial acute PPI therapy
I:	Continuous (daily) PPI long-term therapy (i.e. longer than 6 months) with the minimal efficacious dose
C:	On-demand PPI long-term therapy (i.e. longer than 6 months) on 30-50% of the days per year with the minimal efficacious dose

O (clinical):	1. PPI pill consumption per day or number of therapy days per year 2. Number of endoscopic investigations per year 3. Patient-reported therapy satisfaction 4. Compliance and adherence to PPI long-term therapy 5. Health-related quality of life (HRQoL) 6. Symptom relief: - Heartburn - Regurgitation - Perception of flow of gastric content into oesophagus 7. Safety: - Short-term (<6 months) and long-term (longer than 6 months) adverse events, (e.g. incidence of progression to erosive gastroesophageal reflux disease or pre-cancerous Barrett's oesophagus) 8. All other outcomes reported in RCTs comparing continuous with on-demand PPI long-term therapy
O (costs):	1. Resource use due to GERD and PPI side effects 2. Health-care costs (total and incremental) a. Medication costs within 6 months, 2 years, 5 years, …, lifetime (PPIs) b. Costs of endoscopic investigations c. Costs of adverse events/side effects d. Cost related to progression to erosive gastroesophageal reflux disease e. Costs related to hospitalisations f. Other resource use costs (e.g. formal caregiver costs such as nurses, general practitioners, etc.) 3. Quality adjusted cost comparison after 6 months, 2 years, 5 years, …, lifetime 4. Non-health related care costs (to be used only in supplementary analyses) * a. Productivity costs b. Travel costs c. Informal caregiver costs 5. Incremental cost-effectiveness ratio (ICER), incremental/total costs, Quality-adjusted-life-years (QALYs) and life years (LYs) after 6 months, 2 years, 5 years, …, lifetime

* Non-health related care costs will not be used in the model but will be collected in the data extraction sheet just to provide insight in interpreting the cost-effectiveness results of the published studies. Furthermore, these might be incorporated in supplementary analyses.

It should be noted that the PICO box above is presented for the framing purposes, and the key questions listed in the next section reflect the actual scope of the HTA, covering the other domains such as legal, social, ethical and organisational.

6 HTA key questions

For the evaluation of the technology, the following key questions covering central HTA domains, as designated by the EUnetHTA Core Model[34] (clinical effectiveness, safety, costs, cost-effectiveness, budget impact, legal, social, ethical, and organisational aspects), are addressed:

1. Is continuous PPI therapy effective/efficacious compared to on-demand PPI therapy?
    a. How does continuous PPI long-term therapy compared to on-demand PPI long-term therapy affect symptoms and findings of the disease or health condition (superior, inferior, or equivalent)?
    b. Do continuous PPI long-term therapy and on-demand PPI long-term therapy affect progression (or recurrence) of the disease or health condition differently?
    c. What is the effect of continuous PPI long-term therapy compared to on-demand PPI long-term therapy on generic/disease-specific health-related quality of life?
    d. Were patients more satisfied with continuous PPI long-term therapy or with on-demand PPI long-term therapy?
2. Is continuous PPI therapy safe compared to on-demand PPI therapy?
    a. Is the continuous PPI long-term therapy safe?
    b. Is the on-demand PPI long-term therapy safe?
    c. Are the harms related to dosage or frequency of applying continuous PPI long-term therapy?
    d. Are the harms related to dosage or frequency of applying on-demand PPI long-term therapy?
    e. Do continuous PPI long-term therapy and on-demand PPI long-term therapy modify the need for hospitalisation?
3. What are the costs of continuous and on-demand PPI therapy?
    a. What types of resources (and in what amounts) are used when delivering continuous PPI long-term therapy and on-demand PPI long-term therapy (resource-use identification)?
4. What is the budget impact of continuous PPI long-term therapy compared to on-demand PPI long-term therapy?
5. How cost-effective is the continuous PPI long-term therapy compared to on-demand PPI long-term therapy?

a. What are the estimated differences in costs and outcomes between continuous PPI long-term therapy and on-demand PPI long-term therapy?
b. What are the uncertainties surrounding the costs and economic evaluation(s) of continuous PPI long-term therapy and of on-demand PPI long-term therapy?

6. Are there legal, social, or ethical issues related to continuous and on-demand PPI therapy?

a. Are there specific legal issues associated with a potential change in reimbursement of the continuous PPI long-term therapy?

b. What are the morally relevant consequences (benefits and harms) of a potential change in reimbursement of continuous PPI long-term therapy?

7. Are there organisational issues related to continuous and on-demand PPI therapy?

a. What organisational issues are attached to continuous PPI long-term therapy and to on-demand PPI long-term therapy?

6.1 Additional question(s)

Not applicable.

7 Effectiveness, efficacy and safety

7.1 Methodology effectiveness, efficacy and safety

Since a limited number of studies was found comparing continuous with on-demand long-term PPI therapy (with either identical or different PPI and dosage), non-comparison studies were also selected to provide additional input. This resulted in the categorisation of the following two different types of studies:

- Comparison studies which compare continuous with on-demand long-term PPI therapy;
- Non-comparison studies (i.e. single-arm studies or studies comparing continuous PPI therapy or on-demand PPI therapy with other treatments). These studies include one arm with continuous PPI therapy or one arm with on-demand PPI therapy but not both arms, hence direct comparison between continuous PPI therapy and on-demand PPI therapy is not possible.

7.1.1 Databases and search strategy

PubMed (MEDLINE) and Embase.com databases were searched for peer-reviewed scientific literature. Since there is large overlap in studies included in other literature databases (such as Cochrane Library) for the efficacy, effectiveness, and safety search it was decided to search in these two main databases. The searches were built using the PICO-framework (see Section 4). Given the various outcomes of interest, it was decided to keep the search broad; only search strings on 'Patient' and 'Intervention' were included. One search was conducted to capture both comparison and non-comparison studies. The applied search filters were publication period (2000-2019) and the language of the publications (English, Dutch, French, and German). Furthermore, animal studies, case reports, and non-pertinent publication types (e.g. editorials, letter, and comments) were excluded with additional search strings. The details of the search strategies are included in Appendix 15.1. The search was run on 26 March 2019. The database output, including all indexed fields per record (e.g. title, authors, abstract), was exported to Endnote version X7.8, where the hits were de-duplicated.

Selection procedure

From the articles retrieved from PubMed (MEDLINE) and Embase.com the relevant references were selected by a three-step selection procedure, based on:

1. Screening of title and abstract: this step yielded the articles that were assessed in full-text. The major topics of the articles were assessed on relevancy for the objectives by the title and abstract. In this step, articles that seemed to contain relevant data for the objectives were selected for full-text screen-

ing, while articles that did not seem to contain relevant data were not selected for full-text assessment. Note that the titles and abstracts were screened also based on their relevancy to other HTA domains, as well (i.e. cost-effectiveness, legal, social, ethical, and organisational).

2. Screening of full article: the articles selected during the first phase were assessed in full-text. PDF-files of the original articles were downloaded and stored. Articles were included if the reported information was relevant, based on the inclusion and exclusion criteria.
3. In a third selection step further scrutiny of the article during the data-extraction phase might lead to exclusion. For example, when articles make use of the same dataset and present identical outcome measures, the most recent or the most complete article was included.

Relevant meta-analyses and systematic reviews were selected during the screening of title and abstract phase. During the full-text screening phase, reference lists of these meta-analyses and systematic reviews were checked for possibly missed individual articles. Data-extraction was only performed for individual articles, not for the reviews.

One of the researchers registered the process of selection and inclusion and exclusion of articles in an Endnote library. The exclusion criteria applied in the selection procedure are reported in the PRISMA flow chart (Figure 2).

Inclusion and exclusion criteria

The list of inclusion and exclusion criteria applied during the selection process is presented in Table 2. Note that the population as presented in the PICO table in Section 5 is extended, in order to increase the number of hits by including the studies analysing a mixed adult population with endoscopically proven NERD and low grade GERD.

Table 2: Inclusion and exclusion criteria for the efficacy, effectiveness, and safety review

	Inclusion		Exclusion
	Review step I	Review step II	
Period publication	• 2000-2019		
Language of publication	• English • Dutch • French • German		• All other languages
Country of study	• All countries		

Study design/type	• RCTs	• Non-randomised controlled studies (i.e. non-randomised controlled trials, cohort studies, case-control studies) • Prospective observational studies • Database studies • Cross-sectional studies	• Meta-analysis/systematic review* • Narrative review • Case reports • Non-pertinent publication types (e.g. expert opinion, letter to editor, editorial, comment)
Study quality			• No exclusion based on study quality
Study population	• Patients ≥18 years with endoscopically proven NERD • Patients ≥18 years with endoscopically uninvestigated GERD • Mixed population of patients ≥18 years with endoscopically proven NERD and low grade† GERD		• Patients <18 years • Healthy population • Population with other diagnosis than NERD/GERD, e.g. erosive reflux esophagitis • Population with NERD/GERD and erosive reflux esophagitis, without stratification of the results • Too specific study population (e.g. patients eligible for surgery)
Study intervention	• Continuous (daily) PPI long-term therapy (i.e. longer than 6 months)	• Continuous (daily) PPI long-term therapy (i.e. longer than 6 months) • On-demand PPI long-term therapy (i.e. longer than 6 months)	• All other interventions (e.g. intermittent PPI therapy) • PPI short-term therapy (i.e. <6 months)
Study comparison	• On-demand PPI long-term therapy (i.e. longer than 6 months)	• Not applicable	• PPI short-term therapy (i.e. <6 months)
Study outcomes	• See PICO table	• See PICO table	

Keys: RCTs = randomised controlled trials, NERD = non-erosive reflux disease, GERD = gastroesophageal reflux disease, PPI = proton pump inhibitor, PICO = Patients - Intervention – Comparator - Outcome
*Relevant meta-analyses and systematic reviews were selected during the screening of title and abstract phase. During the full-text phase, reference lists of these reviews were checked for possibly missed relevant individual articles; † According to the Savary-Miller classification. Grade I: Single or isolated erosive lesion(s), oval or linear, but affecting only one longitudinal fold; Grade II: Multiple erosive lesions, non-circumferential, affecting more than one longitudinal fold, with or without confluence; or according to the Los Angeles classification. Grade A: One or more mucosal breaks < 5 mm in maximal length; Grade B: One or more mucosal breaks > 5mm, but without continuity across mucosal folds

Quality assurance approach

The following quality control measures were applied:

- Two independent researchers from Pallas screened the first 30% of titles and abstracts from the peer-reviewed literature in duplicate. They compared and discussed the results before the remaining references were assessed by one researcher. During screening there was less than 5% discrepancy between the two researchers.
- Two independent researchers from Pallas assessed the relevancy and critically appraised the first 10% of the full-text articles from the peer-reviewed literature in duplicate. One researcher conducted the remaining full-text selection in close collaboration with a second reviewer; any doubts were discussed in detail. During screening there was less than 5% discrepancy between the two researchers.

In case of discrepancy or disagreements during the selection phase, a third researcher was consulted. They discussed the study discussed until consensus was reached.

- A first researcher compiled the data extraction and summary tables and those were reviewed by a second researcher of the project.

7.1.2 Other sources

Not applicable.

7.1.3 Assessment of quality of evidence

Limitations in the study design and implementation may bias the estimates of an intervention effect; the more serious the limitations the more likely it is that the quality of evidence will be downgraded. Based on the key risk of bias criteria used in the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach, the risk of bias of the RCTs comparing continuous versus on-demand PPI long-term therapy was assessed and reported in a risk of bias table.[35]

For RCTs, the following limitations are likely to result in biased results and were critically appraised:

- Randomisation
- Allocation concealment
- Blinding
- Loss to follow-up
- Intention to treat
- Other limitations (e.g. non-validated method to assess the outcome)

Single arms of RCTs made up the large part of the non-comparison studies. These were also critically appraised using the RCT GRADE approach, even though data was only extracted from one of these RCT arms and the (irrelevant) comparison was not taken into account. For the remaining observational non-comparison studies included in this review (i.e. with the study designs cross-sectional study, database study, and prospective observational study), no formal checklist exists. Relevant (general) quality aspects were assessed and reported, but no overall quality score was given for these remaining observational non-comparison studies.

7.1.4 Methodology data analyses efficacy, effectiveness and safety

We extracted data from the included studies in predefined evidence tables in Excel and further summarised these data in extensive summary tables in this report (see Appendix 15.3). Separate sets of tables were made for the four different study types, based on the comparison or non-comparison within a study. The term ‘comparison’ or ‘non-comparison’ in these study types refers to comparing on-demand versus continuous

therapy, and does not refer to the study design such as RCT: direct comparison within a study between on-demand versus continuous PPI therapy (with identical or different PPI or dosage) or no comparison within a study between on-demand and continuous PPI therapy (e.g. a single arm of on-demand PPI therapy in a RCT compared with an irrelevant intervention out of scope for this HTA; or continuous PPI therapy studied in a cross-sectional study). The four different study types are defined as: 1) on-demand versus continuous comparison studies on identical PPI and dosage; 2) on-demand versus continuous comparison studies on different PPI and dosage or same PPI and different dosage (referred to as different PPI and/or dosage for the remainder of the document); 3) non-comparison studies on continuous PPI therapy; 4) non-comparison studies on on-demand PPI therapy.

Pooling of the data and presentation of the data in GRADE tables was planned if more than one study on a given outcome was available and data from these studies were sufficiently homogeneous in terms of clinical, methodological, and statistical characteristics. The evidence found on the comparison of continuous versus on-demand PPI long-term therapy (i.e. in study type group 1 and 2; see above) in adult patients with NERD or GERD was insufficiently homogenous to apply this data synthesis approach. Therefore, the data was descriptively summarised in concise summary tables for the efficacy, effectiveness, and safety outcomes (see below). The data was stratified for the three populations of interest: endoscopically proven NERD, mixed population of endoscopically proven NERD and low grade GERD, and endoscopically uninvestigated GERD.

7.2 Results effectiveness, efficacy and safety

7.2.1 Evidence base pertaining to efficacy, effectiveness and safety

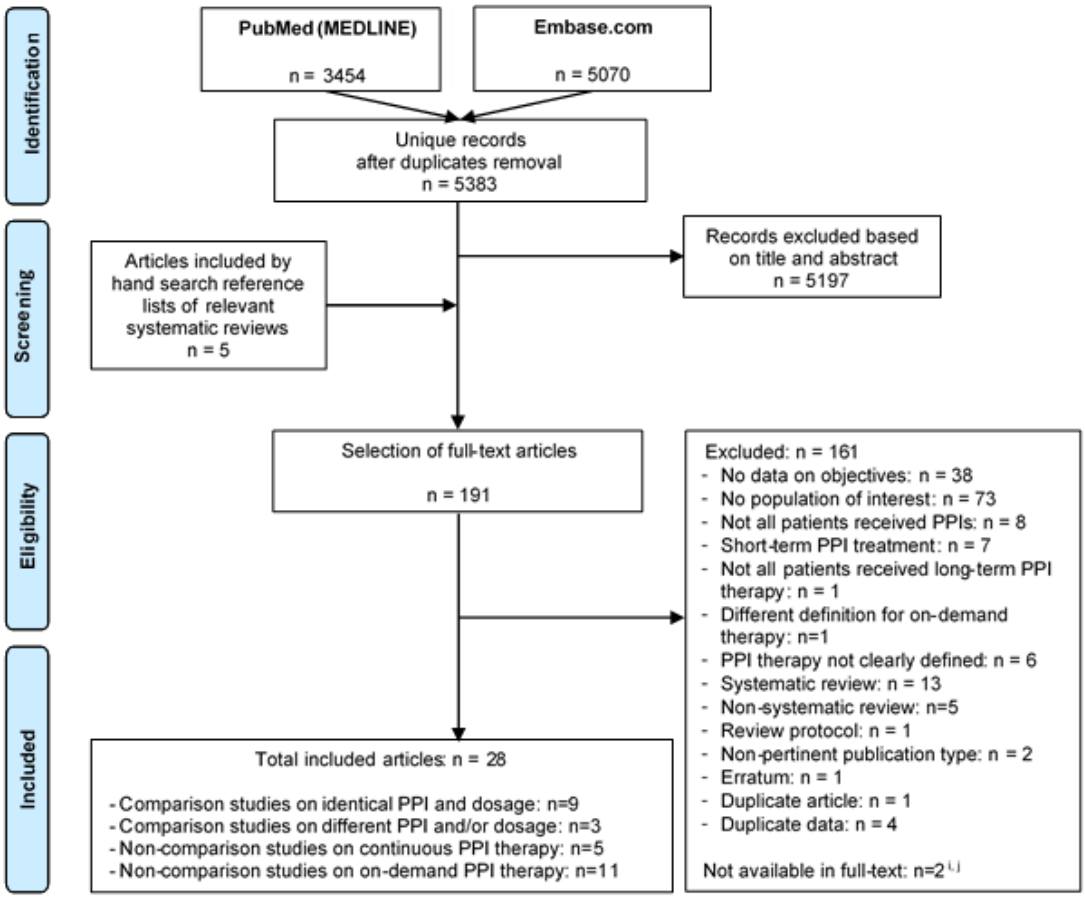
The evaluation of the overall effectiveness of the technology encompasses its efficacy, its effectiveness, and its safety.

- Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (i.e. internal validity).
- Effectiveness is the extent to which a specific health technology, when applied in real world circumstances in the target group, does what it is intended to do for a diagnostic or therapeutic purpose regarding the benefits compared with alternative technologies (i.e. external validity).
- Safety is a judgement of the harmful effects and their severity using the health technology. Relevant adverse events (as predefined during the project) are those that result in death, are life-threatening, require inpatient hospitalisation or cause prolongation of existing hospitalisation (i.e. severe adverse events) and those that occur repetitively and the most frequent (highest rate).

7.2.2 PRISMA flow diagram

In total, 5'383 unique records were identified in PubMed (MEDLINE) and Embase.com for the efficacy, effectiveness, and safety review (Figure 2). Of those, 5'197 records were excluded based on their title and/or abstract. Five articles were additionally included by the hand search of reference lists of relevant systematic reviews (i.e. reviews were excluded), resulting in 191 articles selected to be screened in full-text. Two articles were not available in full-text (see references below Figure 2). After applying the inclusion and exclusion criteria, 28 articles were included in the efficacy, effectiveness, and safety review. Twelve RCTs compared continuous versus on-demand PPI long-term therapy in adult patients with NERD or GERD. The other studies were non-comparison studies, which include one arm with continuous PPI therapy (five studies) or one arm with on-demand PPI therapy (11 studies). The two main reasons for exclusion were no population of interest (e.g. erosive esophagitis population) and no data on objectives (e.g. step-down PPI therapy or intermittent PPI therapy). A complete overview of the reasons for exclusion is enclosed in the PRISMA flow chart.

Figure 2: PRISMA flow diagram efficacy, effectiveness, and safety review



Keys: PPI = proton pump inhibitor

7.2.3 Study characteristics table

Separate tables with the study characteristics of the included studies were made for the four different study types: 1) continuous versus on-demand comparison studies on identical PPI and dosage; 2) continuous versus on-demand comparison studies on different PPI and/or dosage; 3) non-comparison studies on continuous PPI therapy; 4) non-comparison studies on on-demand PPI therapy. The studies in these tables were stratified for the three populations of interest. Additionally, risk of bias tables were made to provide an overview on the aspects which were critically appraised for the comparison studies and part of the non-comparison studies (i.e. single arms of RCTs).

Continuous versus on-demand comparison studies on identical PPI and dosage

Nine articles reporting data of eight studies directly comparing continuous and on-demand PPI therapy with identical PPI and dosage were included in the clinical review.[10, 36-43] Hansen et al. reported the outcomes of their study in two separate articles, one focusing on the efficacy and safety aspects [10] and the second article on health-related quality of life.[38] All studies were open-label RCTs, providing data on efficacy and safety outcomes. An overview of the study characteristics is included in Table 3. The studies were conducted in Canada, France, Italy, Japan, Norway, Switzerland, and two multi-country studies (in Austria, France, Germany, South Africa, Spain; and in Germany, France, Switzerland, and Hungary). Two studies investigated an endoscopically proven NERD population, three studies patients with endoscopically uninvestigated GERD, and three studies a mixed population of NERD and low grade GERD patients. Four different PPIs were studied to compare continuous versus on-demand PPI therapy (esomeprazole 20 mg, omeprazole 20 mg, pantoprazole 20 mg, rabeprazole 10 mg or 20 mg; all reflect the minimal efficacious dose)[44]; all with a treatment duration of six months. The total sample size ranged from 35 to 5265 patients. Nagahara et al., 2014 studied patients with NERD and reflux esophagitis, only part of the results was stratified for NERD patients, resulting in a small sample size of 35 patients.[37] Five studies had a low risk of bias, two a moderate, and one study a high risk of bias (see Table 4).

Not available in full-text (n=2):
[i] **Velanovich V.** Quality of life implications of medical and surgical treatment of gastroesophageal reflux disease. Practical Gastroenterology. 2000;24(7):26-32;
[j] **Walan A.** The long-term treatment of GERD with omeprazole. Therapeutic Research. 2001;22(5):1074-87.

Table 3: Study characteristics of comparison studies on identical PPI and dosage

Reference	Country	Study design, study period	Study population	Intervention	Comparator	Sample size	Age (mean±SD in years)	Risk of bias	Funding
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS									
Bayerdörffer, 2016[36]	Austria, France, Germany, South Africa, Spain	Open-label RCT August 2001-April 2002	Endoscopically proven NERD	Continuous esomeprazole 20 mg once daily (6 months)	On-demand esomeprazole 20 mg (6 months)	- Total: 598 - C: 297 - OD: 301	- C: 47.6±15.1 - OD: 48.2±13.6	Low	Astra-Zeneca
Nagahara, 2014[37]	Japan	Open-label RCT April 2009-April 2013	Endoscopically proven NERD	Continuous omeprazole 20 mg once daily (6 months)	On-demand omeprazole 20 mg (6 months)	Total: 35 - C: 18 - OD: 17	- NR (total group: 56.2±12.8)	High	Connections with Astra-Zeneca
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS									
Hansen, 2005[10], Hansen, 2006[38]	Norway	Open-label RCT Sep 2000-Nov 2001	Endoscopically uninvestigated GERD	Continuous esomeprazole 20 mg once daily (6 months)	On-demand esomeprazole 20 mg (6 months)	- Total: 1902 - C: 658 - OD: 634	- C: 50.5 (SD NR) - OD: 51.4 (SD NR)	Low	Authors from Astra-Zeneca
Morgan, 2007[39]	Canada	Open-label RCT July 2004-July 2005	Endoscopically uninvestigated GERD	Continuous rabeprazole 20 mg once daily (6 months)	On-demand rabeprazole 20 mg (6 months)	- Total: 268 - C: 137 - OD: 131	- C: 49±11.0 - OD: 47±11.0	Moderate	Janssen-Ortho
Szucs, 2009[40]	Switzerland	Open-label RCT NR	Endoscopically uninvestigated GERD	Continuous esomeprazole 20 mg once daily (6 months)	On-demand esomeprazole 20 mg (6 months)	- Total: 1904 - C: 913 - OD: 991	- C: 55±14.5 - OD: 54±14.9	Low	Astra-Zeneca
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS									
Bour, 2005[43]	France	Open-label RCT June 2000-May 2001	Mixed population of endoscopically proven NERD and Grade I-II* GERD	Continuous rabeprazole 10 mg once daily (6 months)	On-demand rabeprazole 10 mg (6 months)	- Total: 152 - C: 81 - OD: 71	- C: 49.8±13.1 - OD: 48.6±2.7	Moderate	Jansen-Cilag
Janssen, 2005[42]	Germany, France, Switzerland, Hungary	Open-label RCT NR	Mixed population of endoscopically proven NERD and Grade I* GERD	Continuous pantoprazole 20 mg once daily (24 weeks)	On-demand pantoprazole 20 mg (24 weeks)	- Total: 432 - C: 217 - OD: 215	- C: 51.8±13.5 - OD: 50.4±13.6	Low	NR
Pace, 2005[41]	Italy	Open-label RCT March 2001-Feb 2002	Mixed population of endoscopically proven NERD and Grade I* GERD	Continuous esomeprazole 20 mg once daily (6 months)	On-demand esomeprazole 20 mg (6 months)	- Total: 5265 - C: 2628 - OD: 2637	- C: 46.7±15.1 - OD: 47.3±14.8	Low	Astra-Zeneca

Keys: C = continuous therapy, GERD = gastroesophageal reflux disease, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, RCT = randomised controlled trial, SD = standard deviation. * According to the Savary-Miller classification. Grade I: Single or isolated erosive lesion(s), oval or linear, but affecting only one longitudinal fold; Grade II: Multiple erosive lesions, noncircumferential, affecting more than one longitudinal fold, with or without confluence.

Table 4: Risk of bias of the comparison studies on identical PPI and dosage

Reference	Randomisation	Allocation concealment	Blinding	Loss to follow-up	Intention to treat	Other limitations	RISK OF BIAS
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Bayerdörffer, 2016[36]							Low
Nagahara, 2014[37]							High
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS							
Hansen, 2005; 2006[10, 38]							Low
Morgan, 2007[39]							Moderate
Szucs, 2009[40]							Low
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS							
Bour, 2005[43]							Moderate
Janssen, 2005[42]							Low
Pace, 2005[41]							Low

Low risk of bias; Moderate or unclear risk of bias; High risk of bias

Continuous versus on-demand comparison studies on different PPI and/or dosage

Additionally, three studies comparing continuous and on-demand PPI therapy with different PPI and/or dosage were included.[18, 45, 46] Two studies were open-label RCTs and one RCT was single-blinded, providing data on efficacy and safety outcomes. An overview of the study characteristics is included in Table 5. The studies were conducted in Poland, Slovenia, and the UK. Two studies investigated an endoscopically proven NERD population, and one study reported stratified data for a population of NERD patients and a mixed population of NERD and low grade GERD patients. Three PPIs in different dosages were studied to compare continuous versus on-demand PPI therapy (lansoprazole 15 mg/30 mg, omeprazole 10 mg/20 mg, esomeprazole 20 mg; all reflect the minimal efficacious dose)[44]; with a treatment duration of 6 to 12 months. The total sample size ranged from 56 to 622 patients. All studies had a high risk of bias (see Table 6).

Table 5: Study characteristics of comparison studies on different PPI and/or dosage

Reference	Country	Study design, study period	Study population	Intervention	Comparator	Sample size	Age (mean±SD in years)	Risk of bias	Funding
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS									
Cibor, 2006[45]	Poland	Open-label RCT NR	Endoscopically proven NERD	Continuous **lansoprazole 15 mg** (11 months)	On-demand **lansoprazole 30 mg** (11 months)	- Total: 60 - C: 20 - OD: 20	- C: 48±11 - OD: 49±12	High	NR
Tepeŝ, 2009[46]	Slovenia	Open-label RCT NR	Endoscopically proven NERD	Continuous **omeprazole 10 mg** (12 months)	On-demand **omeprazole 20 mg** (12 months)	- Total: 56 - C: 25 - OD: 23	NR	High	NR

Tsai, 2004[18]	UK	Single-blind RCT NR (analysis in June 2002)	Endoscopically proven NERD	Continuous **lansoprazole 15 mg** (6 months)	On-demand **esomeprazole 20 mg** (6 months)	- Total: 622 - C: 311 - OD: 311	- C: 51±13.8 - OD: 51±13.8	High	Astra-Zeneca
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS									
Tepeŝ, 2009[46]	Slovenia	Open-label RCT NR	Mixed population of endoscopically proven NERD and LA Grade A-B* GERD	Continuous **omeprazole 10 mg** (12 months)	On-demand **omeprazole 20 mg** (12 months)	- Total: 196 - C: 102 - OD: 94	NR	High	NR

Keys: C = continuous therapy, GERD = gastroesophageal reflux disease, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, RCT = randomised controlled trial, SD = standard deviation, UK = United Kingdom. * According to the Los Angeles classification. Grade A: One or more mucosal breaks < 5 mm in maximal length; Grade B: One or more mucosal breaks > 5mm, but without continuity across mucosal folds.

Table 6: Risk of bias of the comparison studies on different PPI and dosage

Reference	Randomisation	Allocation concealment	Blinding	Loss to follow-up	Intention to treat	Other limitations	RISK OF BIAS
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Cibor, 2006[45]							High
Tepeŝ, 2009[46]							High
Tsai, 2004[18]							High
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS							
Tepeŝ, 2009[46]							High

Low risk of bias; Moderate or unclear risk of bias; High risk of bias

Non-comparison studies on continuous PPI therapy

Besides comparison studies also non-comparison studies were selected, to provide additional input for the efficacy, effectiveness, and safety outcomes. In total, five non-comparison studies on continuous PPI therapy in populations of endoscopically proven NERD patients or endoscopically uninvestigated GERD patients were included[47-51]: three single arms from RCTs, one cross-sectional study, and one database study. An overview of the study characteristics is included in Table 7. The three RCTs each had a high, moderate and low risk of bias, respectively (Table 8).

Table 7: Study characteristics of non-comparison* studies on continuous PPI therapy

Reference	Country	Study design, study period	Study population	Continuous PPI group I	Continuous PPI group II	Sample size	Age (mean±SD in years)	Risk of bias	Funding
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS									
Dabholkar, 2011[48]	USA	Open-label RCT (phase 3	Endoscopically	Continuous dexlansoprazole MR	NA	153	47.8±13.8	High	Takeda

		safety extension study) Jan 2006 - June 2008	proven NERD	60 mg once daily (12 months)					
Kusano, 2014[51]	Japan	Cross-sectional study 2011-2012	Endoscopically proven NERD	Continuous omeprazole 10-20 mg/day, lansoprazole 15-30 mg/day, or rabeprazole 10 mg/day (≥1 year)	NA	46	65.2±13.0	NA	Eisai, Astellas, AstraZeneca, Daiichi-Sankyo, Given Imaging (first author)
POPULATION OF ENDOSCOPICALLY UNINVESTIATED GERD PATIENTS									
Brusselaers, 2018[49]	Sweden	Database study July 2005 - Dec 2012	GERD patients (using ICD codes)	Continuous any PPI at defined daily dose (at least 6 months)	NA	201744	NR	NA	Karolinska Institute, Swedish Research Council, Swedish Cancer Society
Kaplan-Machlis, 2000[47]	USA	Open-label RCT NR	Symptomatic GERD	Continuous omeprazole sodium 20 mg once daily (24 weeks)	NA	130	45.3±13.4	Moderate	AstraZeneca
Talley, 2002[50]	Australia	Double-blind RCT	Symptomatic GERD	Continuous pantoprazole 20 mg once daily and placebo twice daily (12 months)	NA	154	53 (SD NR)	Low	Pharmacia, Janssen-Cilag, Novartis, AstraZeneca, Lederie

Keys: GERD = gastroesophageal reflux disease, ICD = International Classification of Diseases, NERD = non-erosive reflux disease, NA = not applicable, NR = not reported, RCT = randomised controlled trial, SD = standard deviation, USA = United States of America.
* Comparison possible within these studies, but no direct comparison between continuous and on-demand therapy.

Table 8: Risk of bias of the non-comparison* studies on continuous PPI therapy

Reference	Randomisation	Allocation concealment	Blinding	Loss to follow-up	Intention to treat	Other limitations	RISK OF BIAS
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Dabholkar, 2011[48]							High
Kusano, 2014[51]	NA	NA	NA	NA	NA	NA	- Relatively small sample size - It was not possible to completely exclude patients with functional heartburn and dyspepsia, although it seems unlikely that they were included
POPULATION OF ENDOSCOPICALLY UNINVESTIATED GERD PATIENTS							
Brusselaers, 2018[49]	NA	NA	NA	NA	NA	NA	- Lack of information on PPI exposure before study period and limited duration of follow-up, making assessment of duration of PPI treatment unreliable - Residual confounding, cannot be ruled out, and severity of gastroesophageal reflux is not recorded
Kaplan-Machlis, 2000[47]							Moderate
Talley, 2002[50]							Low

Low risk of bias; Moderate or unclear risk of bias; High risk of bias; NA: not applicable

* Comparison possible within these studies, but no direct comparison between continuous and on-demand therapy.

Non-comparison studies on on-demand PPI therapy

In total, 11 non-comparison studies on on-demand PPI therapy were included[19, 52-61], 9 single arms of RCTs and 2 prospective observational studies. An overview of the study characteristics is included in Table 9. Different PPIs and dosages were studied, all with a treatment duration of 6 months. One RCT had a low risk of bias, while the rest had a moderate risk of bias (Table 10).

Table 9: Study characteristics of non-comparison* studies on on-demand PPI therapy

Reference	Country	Study design, study period	Study population	On-demand PPI group I	On-demand PPI group II	Sample size	Age (mean±SD in years)	Risk of bias	Funding
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS									
Bytzer, 2004[19]	Greece, Italy, Netherlands, Spain, France, Portugal, Sweden, Denmark, Ireland, Belgium, UK, Russia, Poland, Lithuania	Double-blind RCT Aug 2001-Oct 2002	Endoscopically proven NERD	On-demand rabeprazole 10 mg max once daily (6 months)	NA	279	47±NR	Low	AstraZeneca, Janssen-Cilag, Eisai, Wyeth, Byk Gulden, Novartis, Nestec, Roche, Merck & Co, Johnson & Johnson
Juul-Hansen, 2009[54]	Norway	Open-label RCT 2003-2005	Endoscopically proven NERD	On-demand lansoprazole max 60 mg daily (15 mg capsules; 6 months)	NA	32	NR (median 47.5)	Moderate	Wyeth
Ponce, 2004[53]	Spain	Prospective observational study NR	Endoscopically proven NERD	On-demand rabeprazole 20 mg max once daily (6 months)	NA	17	39±11	NA	Instituto de Salud Carlos III (Spanish public health research institute)
Talley, 2001[55]	Denmark, Finland, Norway, Sweden	Double-blind RCT NR	Endoscopically proven NERD	On-demand esomeprazole 20 mg max once daily (6 months)	NA	170	49±NR	Moderate	AstraZeneca
Talley, 2002 [56]	UK, Ireland, Canada	Double-blind RCT November 1997-Jan 1999	Endoscopically proven NERD	On-demand esomeprazole 40 mg max once daily (6 months)	On-demand esomeprazole 20 mg max once daily (6 months)	- Total: 575 - Group I: 293 - Group II: 282	- Group I: 48.0±NR - Group II: 48.4 ±NR	Moderate	AstraZeneca
POPULATION OF UNINVESTIGATED GERD PATIENTS									
Bigard, 2005[57]	France	Double-blind RCT May 2002-June 2003	Endoscopically uninvestigated GERD	On-demand lansoprazole 15 mg max once daily (6 months)	NA	84	52.5±15.0	Moderate	Takeda
Meinecheschmidt, 2004[52]	Denmark	Open-label RCT NR	Endoscopically uninvestigated GERD	On-demand esomeprazole 20 mg max once daily (26 weeks)	NA	453	52±15	Moderate	AstraZeneca

Reference	Country	Study design, study period	Study population	On-demand PPI group I	On-demand PPI group II	Sample size	Age (mean±SD in years)	Risk of bias	Funding
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS									
Kaspari, 2005[58]	Germany, Lithuania	Double-blind RCT NR	Mixed population of endoscopically proven NERD or Grade I GERD (Savary-Miller†)	On-demand pantoprazole 20 mg max once daily (6 months)	NA	213	50.7±13.7	Moderate	ALTANA Pharma
Ponce, 2004[53]	Spain	Prospective observational study NR	Mixed population of endoscopically proven NERD or LA Grade A or B GERD†	On-demand rabeprazole 20 mg max once daily (6 months)	NA	55	41±13	NA	Instituto de Salud Carlos III (Spanish public health research institute)
Scholten (Digestion), 2005[59]	Austria, the Netherlands, Germany	Double-blind RCT Nov 2000-Sept 2001	Mixed population of endoscopically proven NERD or mild GERD (grade 0-1 Savary-Miller†)	On-demand pantoprazole 40 mg max once daily (24 weeks)	On-demand pantoprazole 20 mg max once daily (24 weeks)	- Total: 435 - Group I: 218 - Group II: 217	- Group I: 53.9±13.9 - Group II: 51.9±14.1	Moderate	ALTANA Pharma
Scholten (Clin Drug Invest), 2005[60]	Germany	Prospective observational study NR	Mixed population of endoscopically proven NERD or mild GERD (grade 0-1 Savary-Miller†)	On-demand pantoprazole 20 mg max once daily (24 weeks)	NA	234	53.9±15.2	Moderate	ALTANA Pharma
Scholten, 2007[61]	Germany	Double-blind RCT NR	Mixed population of endoscopically proven NERD or LA Grade A or B GERD†	On-demand pantoprazole 20 mg max once daily (6 months)	On-demand esomeprazole 20 mg max once daily (6 months)	- Total: 199 - Group I: 99 - Group II: 100	- Group I: 54.5±12.6 - Group II: 52.7±13.4	Moderate	ALTANA Pharma

Keys: GERD = gastroesophageal reflux disease, ICD = International Classification of Diseases, NERD = non-erosive reflux disease, NA = not applicable, NR = not reported, RCT = randomised controlled trial, SD = standard deviation, UK = United Kingdom

* Comparison possible within these studies, but no direct comparison between continuous and on-demand therapy; † According to the Savary-Miller classification. Grade I: Single or isolated erosive lesion(s), oval or linear, but affecting only one longitudinal fold; Grade II: Multiple erosive lesions, non-circumferential, affecting more than one longitudinal fold, with or without confluence.

Table 10: Risk of bias of the non-comparison* studies on on-demand PPI therapy

Reference	Randomisation	Allocation concealment	Blinding	Loss to follow-up	Intention to treat	Other limitations	RISK OF BIAS
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Bytzer, 2004[19]							Low
Juul-Hansen, 2009[54]							Moderate
Ponce, 2004[53]	NA	NA	NA	NA	NA	NA	Relatively small sample size
Talley, 2001[55]							Moderate
Talley, 2002[56]							Moderate
Bigard, 2005[57]							Moderate
Meineche-Schmidt, 2004[52]							Moderate
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS							
Kaspari, 2005[58]							Moderate
Ponce, 2004[53]	NA	NA	NA	NA	NA	NA	Relatively small sample size
Scholten (Digestion), 2005[59]							Moderate
Scholten (Clin Drug Invest), 2005[60]	NA	NA	NA	NA	NA	NA	Pilot study
Scholten, 2007[61]							Moderate

Low risk of bias; Moderate or unclear risk of bias; High risk of bias; NA: not applicable

* Comparison possible within these studies, but no direct comparison between continuous and on-demand therapy

Below, all findings on the efficacy, effectiveness, and safety outcomes are summarised in concise summary tables and short accompanying text. For more extensive data see summary tables (Appendix 15.3).

7.2.4 Findings efficacy

Multiple efficacy outcomes were reported in RCTs investigating PPI therapy under study conditions: treatment use (pills per day), endoscopic investigations, treatment satisfaction (general patient satisfaction at end of follow-up, satisfaction with treatment of heartburn, satisfaction with way taking treatment), PPI intake or compliance during study, health-related quality of life, and symptom relief (heartburn at end of follow-up, heartburn-free days, weeks with ≤2 days/week heartburn, heartburn control at end of follow-up, regurgitation at end of follow-up).

Efficacy – Treatment use: pills/day

Six comparison studies reported on the PPI pill use per day (Table 11).[18, 36, 40, 42, 43, 45] The pill use ranged from 0.91 to 1.03 per day for continuous PPI therapy and from 0.3 to 0.55 per day for on-demand therapy. Only two studies conducted a statistical analysis to compare these differences, which was in favour of on-demand therapy. In addition, six non-comparison studies on on-demand therapy[50, 55, 57-59, 61] were included. The pill use per day reported in the single treatment arms of these non-comparison studies were in line with the ranges found in the comparison studies.

Efficacy - Endoscopic investigations

One open-label RCT conducted in Switzerland reported on the percentage of patients received an endoscopic investigation during treatment (Table 12).[40] During 6 months, in the continuous and the on-demand therapy arm 3.1% and 2.8% of the endoscopically uninvestigated GERD patients respectively had an endoscopy during treatment. No statistical comparison was done between these groups, however the difference in percentages is small.

Efficacy – Treatment satisfaction: general patient satisfaction

Four comparison studies published data on general patient satisfaction, measured with various scales (Table 13).[10, 36, 43, 45] Relatively high general patient satisfaction levels were found at the end of continuous as well as on-demand PPI therapy. Two RCTs showed statistically significant differences in favour of continuous PPI therapy, while two other RCTs did not find a significant difference. Additionally, one non-comparison study on on-demand PPI therapy reported satisfaction data, which was in line with the comparison study results.[52]

Efficacy – Treatment satisfaction: satisfied with treatment of heartburn

Patient satisfaction with the treatment of heartburn was reported in five comparison studies, of which two RCTs[39, 41] found a significant difference in favour of continuous PPI therapy and three RCTs[18, 36, 40] did not find a significant difference (Table 14).

Efficacy – Treatment satisfaction: satisfied with way taking treatment

One comparison study was included which reported on how patients were satisfied with the way they were taking their treatment (Table 15). Among the NERD population, the difference in terms of patients' satisfaction between the continuous and the on-demand arm was not statistically significant, 82.8% versus 81.7% respectively.[36]

Efficacy – PPI intake or compliance during study

Without comparing the study results statistically, one comparison study reported a PPI intake on 97% of the days in the continuous therapy group and on 45% of the days in the on-demand group (Table 16).[39] The percentage of days PPI intake in two non-comparison studies[48, 50] was in line with this reported rate for continuous therapy, however a non-comparison study on on-demand therapy[57] published a much lower percentage.

Efficacy – Health-related quality of life

In total six comparison studies reported data on the HRQoL (Table 17).[36, 38, 39, 41, 43, 46] The HRQoL was measured with different instruments (for details see tables in Appendix 15.3). A larger part of the study results showed statistically significant differences in favour of continuous therapy, though it is important to keep in mind that the differences were quite small and the HRQoL levels for the on-demand therapy group remained at relatively high levels during PPI treatment. Furthermore, part of the studies explicitly reported that not all domains of the HRQoL instruments are clinically relevant for NERD and GERD patients on PPI therapy. Additionally, two non-comparison studies reported data on the HRQoL.[19, 48]

Efficacy – Symptom relief: heartburn

Two comparison studies reported the percentage of heartburn at the end of follow-up (Table 18)[10, 40] The percentage of patients without heartburn was significantly higher in the continuous PPI therapy group (72% and 86%) in comparison with on-demand therapy (45% and 80%). The percentage of heartburn reported in the single treatment arms of three non-comparison studies was not in line with the ranges found in the comparison studies.[47, 55, 60]

Efficacy – Symptom relief: heartburn – heartburn-free days

One comparison study reported significantly more heartburn-free days with 6 months of continuous PPI therapy (90.3%) compared with on-demand therapy (64.8%) in endoscopically uninvestigated GERD patients (Table 19).[39]

Efficacy – Symptom relief: heartburn – weeks with ≤2 days/week heartburn

Endoscopically uninvestigated GERD patients in the continuous PPI therapy group reported a significantly larger proportion of weeks with two days or less of heartburn per week (with maximum symptom severity rated mild) than patients in the on-demand group, 84% versus 41% respectively (Table 20).[39]

Efficacy – Symptom relief: heartburn – heartburn control

One non-comparison study[50] on continuous PPI therapy in endoscopically uninvestigated GERD patients and one non-comparison study[19] on on-demand PPI therapy in diagnosed NERD patients found a similar percentage of 86% of the patients who had sufficient control of heartburn symptoms at the end of follow-up (Table 21).

Efficacy – Symptom relief: regurgitation

After 6 months of PPI therapy in endoscopically uninvestigated GERD patients, 78% and 89% of the patients on continuous therapy versus 62% and 86% of the patients on on-demand therapy had no symptoms of regurgitation. [10, 40] One study[40] did not find a statistically significant difference between the two therapy modalities and the other study[10] did not compare these study results (Table 22).

Table 11: Treatment use - mean (SD) pills/day

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Out-come	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	[36]: C: 0.91 (0.16) OD: 0.41 (0.25)	NR	Low (n=1)[36]	?	[45]: C: NR OD: 0.3 (0.3) [18]: C: 0.8 (NR) OD: 0.3 (NR)	NR (both studies)	High (n=2)[18, 45]	?	-	-	[50]: 0.29 (NR), 0.33 (NR)† [55]: 0.34	Moderate (n=2)[50, 55]
Endoscopically proven NERD and low grade GERD	[42]: C: 0.93 (0.17) OD: 0.51 (0.31) [43]: C: 0.96 (0.64-1.03*) OD: 0.31 (0.00-0.95*)	S (both studies)	Low (n=1)[42] Moderate (n=1)[43]	OD	-	-	-	?	-	-	[58]: 0.34 (NR) [59]: 0.40 (NR), 0.41 (NR)‡ [61]: 0.31 (NR), 0.36 (NR)§	Moderate (n=3)[58, 59, 61]
Endoscopically uninvestigated GERD	[40]: C: 1.03 (NR) OD: 0.55 (NR)	NR	Low (n=1)[40]	?	-	-	-	?	-	-	[57]: 0.30	Moderate (n=1)[57]

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, S: statistically significant difference between continuous and on-demand therapy (p<0.05), SD: standard deviation, ?: no data/statistical comparison

* Min-max; † Mean (SD) pills/day in the esomeprazole 40 mg group and the esomeprazole 20 mg group, respectively; ‡ Mean (SD) pills/day in the pantoprazole 40 mg group and the pantoprazole 20 mg group, respectively; § Mean (SD) pills/day in the pantoprazole 20 mg group and the esomeprazole 20 mg group, respectively.

Table 12: Percentage of patients with endoscopic investigations during treatment

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically uninvestigated GERD	[40]: Total: - C: 3.1% - OD: 2.8% Without biopsy: - C: 0.8% - OD: 0.9% With biopsy: - C: 2.3% - OD: 1.9%	NR	Low (n=1)[40]	?	-	-	-	?	-	-	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, ?: no data/statistical comparison

Table 13: Treatment satisfaction - general patient satisfaction at end of follow-up

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Out-come	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	[36]: Satisfied: - C: 84.8% - OD: 78.7%	NS	Low (n=1)[36]	None	[45]: Completely satisfied[c]: - C: 95% - OD: 90%	NS	High (n=1)[45]	None	-	-		-
Endoscopically proven NERD and low grade GERD	[43]: VAS score: - C: 90 mm - OD: 83 mm	S	Moderate (n=1)[43]	C	-	-	-	?	-	-		-
Endoscopically uninvestigated GERD	[10] Very satis-fied: - C: 82.2% - OD: 75.4%	S	Low (n=1)[10]	C	-	-	-	?	-	-	[52]: Satisfied: 96% Very satis-fied: 80%	Moderate (n=1)[52]

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, NS: no statistically significant difference between continuous and on-demand therapy (p≥0.05), OD: on-demand therapy, S: statistically significant difference between continuous and on-demand therapy (p<0.05), VAS: visual analogue score (0-100, the higher the more satisfied), ?: no data/statistical comparison

Table 14: Treatment satisfaction - percentage satisfied with treatment of heartburn

Population	Continuous vs. on-demand comparison studies Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Out-come	Risk of bias (nr studies)
Endoscopically proven NERD	[36]: C: 86.2% OD: 82.1%	NS	Low (n=1) [36]	None	[18]: C: 89.1% OD: 91.6%	NS	High (n=1)[18]	None	-	-	-	-
Endoscopically proven NERD and low grade GERD	[41]: C: 64.5% OD: 59.7%	S	Low (n=1)[41]	C	-	-	-	?	-	-	-	-
Endoscopically uninvestigated GERD	[39]: C: 92% OD: 79% [40]: C: 93% OD: 94%	[39]: S [40]: NR	Low (n=1)[40] Moderate (n=1)[39]	?	-	-	-	?	-	-	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, NS: no statistically significant difference between continuous and on-demand therapy (p≥0.05), OD: on-demand therapy, S: statistically significant difference between continuous and on-demand therapy (p<0.05), ?: no data/statistical comparison

Table 15: Treatment satisfaction - percentage satisfied with way taking treatment

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	[36]: C: 82.8% OD: 81.7%	NS	Low (n=1)[36]	None	-	-	-	?	-	-	-	-
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	-	-		-
Endoscopically unin-vestigated GERD	-	-	-	?	-	-	-	?	-	-	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, NS: no statistically significant difference between continuous and on-demand therapy (p≥0.05), OD: on-demand therapy, ?: no data/statistical comparison

Table 16: Treatment use - percentage days PPI intake or compliance during study

Population	Continuous vs. on-demand comparison studies Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Out-come	Significant difference	Risk of bias (nr studies)		Out-come	Risk of bias (nr studies)	Out-come	Risk of bias (nr studies)
Endoscopically proven NERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	[48]: 97%	High (n=1)[48]	-	-
Endoscopically un-investigated GERD	[39]: C: 97% OD: 45%	NR	Moderate (n=1)[39]	?	-	-	-	?	[50]: 90%	Low (n=1)[50]	[57]: 26%	Moderate (n=1)[57]

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, ?: no data/statistical comparison

Table 17: Health-related quality of life

Population	Continuous vs. on-demand comparison studies Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	[36]: C greater improvement in all QoL domains	S	Low (n=1)[36]	C	-	-	-	?	[48]: Statistically significant improvement from baseline to each time point in each subscale and the total score	High (n=1)[48]	[19]: Mean score at normal population level during treatment	Low (n=1)[19]
Endoscopically proven NERD and low grade GERD	[41]: C greater improvement in all QoL domains [43]: C greater improvement in total QoL, daily life, sleep and food/diet, no difference in relationships, well-being, mental state, fears	[41]: S [43]: partly S	Low (n=1)[41] Moderate (n=1)[43]	C	[46]: No difference at study end	NS	High (n=1)[46]	None	-	-	-	-
Endoscopically uninvestigated GERD	[38]: C greater improvement in all QoL domains, no difference in physical activity [39]: C greater improvement in total QoL and all domains, no difference in relationships	Mostly S (both studies)	Low (n=1)[38] Moderate (n=1)[39]	C	-	-	-	?	-	-	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, NS: no statistically significant difference between continuous and on-demand therapy (p≥0.05), OD: on-demand therapy, S: statistically significant difference between continuous and on-demand therapy (p<0.05), ?: no data/statistical comparison

Table 18: Symptom relief: heartburn - percentage heartburn at end of follow-up

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	-	-	-	?	-	-	-	?	-	-	[55]: Moderate-severe heartburn: 13%	Moderate (n=1) [55]
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	-	-	[60]: Moderate-severe heartburn: 4.3%	NA (n=1)[60]
Endoscopically uninvestigated GERD	No heartburn: [10]: C: 72.2% OD: 45.1% [40]: C: 86% OD: 80%	S (both studies)	Low (n=2) [10, 40]	C	-	-	-	?	[47]: No heartburn: ~32% (in Figure)	Moderate (n=1) [47]	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, S: statistically significant difference between continuous and on-demand therapy (p<0.05), ?: no data/statistical comparison

Table 19: Symptom relief: heartburn – percentage heartburn-free days

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Out-come	Risk of bias (nr studies)
Endoscopically proven NERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically uninvestigated GERD	[39]: C: 90.3% OD: 64.8%	S	Moderate (n=1)[39]	C	-	-	-	?	-	-	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, S: statistically significant difference between continuous and on-demand therapy (p<0.05), ?: no data/statistical comparison

Table 20: Symptom relief: heartburn – percentage weeks with ≤2 days/week heartburn

Population	Continuous vs. on-demand comparison studies Identical PPI and dosage			CONCLU-SION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand compari-son studies. Different PPI and/or dos-age			CONCLU-SION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Out-come	Risk of bias (nr studies)	Out-come	Risk of bias (nr studies)
Endoscopically proven NERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically unin-vestigated GERD	Maximum mild se-verity: [39]: C: 84% OD: 41%	S	Moderate (n=1)[39]	C	-	-	-	?	-	-	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, S: statistically significant difference between continuous and on-demand therapy (p<0.05),?: no data/statistical comparison

Table 21: Symptom relief: heartburn – percentage heartburn control at end of follow-up

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	-	-	-	?	-	-	-	?	-	-	[19]: Sufficient control: 86.4% Complete control for full 24 hours: - After 1-2 days of treatment: 30% - After ≤4 days of treatment: 59%	Low (n=1)[19]
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically uninvestigated GERD	-	-	-	?	-	-	-	?	[50]: Complete control: 77% Sufficient control: 86%	Low (n=1)[50]	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, ?: no data/statistical comparison

Table 22: Symptom relief: regurgitation – percentage regurgitation at end of follow-up

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Out-come	Risk of bias (nr studies)	Out-come	Risk of bias (nr studies)
Endoscopically proven NERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically unin-vestigated GERD	No regurgitation: [10]: C: 78% OD: 62% [40]: C: 89% OD: 86%	[10]: NR [40]: NS	Low (n=2) [10, 40]	?	-	-	-	?	-	-	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, NS: no statistically significant difference between continuous and on-demand therapy (p≥0.05), OD: on-demand therapy, ?: no data/statistical comparison

7.2.5 Findings effectiveness

In this review no continuous versus on-demand PPI therapy comparison studies were found with clinical effectiveness data, because all studies were designed as RCTs which investigated the therapy under specific study conditions (these efficacy results are reported in Section 7.2.4). One non-comparison study was included with real-world data on continuous PPI therapy: a Japanese cross-sectional study evaluated the symptoms of patients with endoscopically proven NERD after at least one year of continuous PPI therapy with omeprazole, lansoprazole or rabeprazole.[51] Furthermore, two non-comparison prospective observational studies on on-demand PPI therapy were included. One study evaluated the effectiveness of on-demand therapy with rabeprazole for 6 months in patients with mild GERD in Spain[53] and a German study investigated 6 months of on-demand pantoprazole treatment in patients with grade 0 and 1 Savary-Miller GERD.[60] These studies reported data on five different effectiveness outcomes: treatment use (pills/day), treatment satisfaction (general patient satisfaction at end of follow-up, willingness to change therapy), and symptom relief (heartburn duration at end of follow-up, regurgitation at end of follow-up).

Effectiveness – Treatment use: pills/day

The mean amount of PPIs used ranged from 0.27 to 0.44 pills per day during 6 months of on-demand PPI therapy (Table 23).[53, 60]

Effectiveness – Treatment satisfaction: general patient satisfaction

In a non-comparison study, among NERD patients after at least one year of continuous PPI therapy, 50% of patients were totally satisfied (out of five answer options ranging from totally dissatisfied to totally satisfied). The percentage of patients either totally or partially satisfied (the upper two of the five answer options) was 80%.[51] In the non-comparison study on on-demand PPI therapy, the median patient satisfaction visual analogue score ranged from 90 to 97 on a scale of 0 to 100 (Table 24).[53]

Effectiveness – Treatment satisfaction: willingness to change therapy

After at least one year of continuous PPI therapy, 13% of the NERD patients were willing to switch to another PPI and 13% of the patients were willing to increase the PPI dosage (Table 25).[51]

Effectiveness – Symptom relief: heartburn

At the end of 6 months on-demand PPI therapy, 6.2% of the endoscopically proven NERD patients and 12.8% of the mixed patient group of endoscopically proven NERD and low grade GERD patients presented symptoms of heartburn on at least two days per week (Table 26).[53]

Effectiveness – Symptom relief: regurgitation

During 6 months of on-demand PPI therapy the observed symptomatic relapse rate was 2.3% for acid regurgitation in the mixed population of endoscopically proven NERD and low grade GERD patients (Table 27).[60]

Table 23: Treatment use – mean (SD) pills/day

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Out-come	Significant difference	Risk of bias (nr studies)		Out-come	Significant difference	Risk of bias (nr studies)		Out-come	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	-	-	-	?	-	-	-	?	-	-	[53]: 0.27 (0.18)	NA (n=1)[53]
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	-	-	[53]: 0.30 (0.19) [60]: 0.44 (NR)	NA (n=2) [53] [60]
Endoscopically unin-vestigated GERD	-	-	-	?	-	-	-	?	-	-	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, ?: no data/statistical comparison

Table 24: Treatment satisfaction - *general patient satisfaction*

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Out-come	Significant difference	Risk of bias (nr studies)		Out-come	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	-	-	-	?	-	-	-	?	[51]: Satisfied: 80.4% Totally satisfied: 50.0%	NA (n=1)[51]	[53]: Median VAS score: 97	NA (n=1)[53]
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	-	-	[53]: Median VAS score: 90	NA (n=1)[53]
Endoscopically uninvestigated GERD	-	-	-	?	-	-	-	?	-	-	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, VAS = visual analogue score (0-100, the higher the more satisfied), ?: no data/statistical comparison

Table 25: Treatment satisfaction - willingness to change therapy

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	-	-	-	?	-	-	-	?	[51]: Willing change therapy: - Yes: 13.0% - Maybe: 8.7% - Increase PPI dosage: 13.0% - Satisfied with current PPI: 65.2%	NA (n=1)[51]	-	-
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically uninvestigated GERD	-	-	-	?	-	-	-	?	-	-	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, ?: no data/statistical comparison

Table 26: Symptom relief: heartburn - percentage weeks with ≥2 days/week heartburn

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLU-SION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLU-SION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Out-come	Significant difference	Risk of bias (nr studies)		Out-come	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	-	-	-	?	-	-	-	?	-	-	[53]: ≥2 days/ week: 6.2%	NA (n=1)[53]
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	-	-	[53]: ≥2 days/ week: 12.8%	NA (n=1)[53]
Endoscopically unin-vestigated GERD	-	-	-	?	-	-	-	?	-	-	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, ?: no data/statistical comparison

Table 27: Symptom relief: regurgitation - percentage regurgitation at end of follow-up

Population	Continuous vs. on-demand comparison studies Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Out-come	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Out-come	Risk of bias (nr studies)
Endoscopically proven NERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	-	-	[60]: 2.3%	NA (n=1)[60]
Endoscopically unin-vestigated GERD	-	-	-	?	-	-	-	?	-	-	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, ?: no data/statistical comparison

7.2.6 Findings safety

Data on four different safety outcomes was found in the included studies. Two concerned short-term safety outcomes (adverse events, severe adverse events; <6 months) and two concerned long-term safety outcomes (cancer and death; longer than 6 months). Examples of short-term adverse events were abdominal pain, arthralgia, back pain, constipation, diarrhoea, fatigue, headache, nausea, and skin rash. Short-term severe adverse events were defined in studies as life-threatening events or events resulting in hospitalisation, such as aggravated angina pectoris, pulmonary embolism, or hernia.

Short-term safety – Adverse events

Five comparison studies reported on the occurrence of adverse events during PPI therapy (Table 28).[10, 18, 36, 42, 46] In four studies, this percentage ranged from 13.7% to 46.0% for continuous PPI therapy and from 0% to 47.8% for on-demand therapy; one study did not find a significant difference between the two treatment modalities and three studies did not compare the PPI therapies.[10, 36, 42] A fifth study, comparing continuous versus on-demand therapy, found that the occurrence of adverse events was similar in the two groups. Nevertheless, the paper did not report the percentages of adverse events in a disaggregated way, but only reported a 71% incidence of adverse events among patients in the maintenance phase.[18] In addition, two non-comparison studies on continuous PPI therapy[48, 50] and eight non-comparison studies on on-demand therapy[19, 50, 57-60, 62] were included. The adverse events percentages reported in the single treatment arms of these non-comparison studies were in line with the ranges found in the comparison studies.

Short-term safety – Severe adverse events

Four comparison studies reported on the occurrence of severe adverse events during PPI therapy (Table 29).[18, 36, 42, 46] This percentage ranged from 0% to 5.9% for continuous PPI therapy and from 0% to 2.9% for on-demand therapy. None of the studies statistically compared the differences between the two treatment modalities. In addition, two non-comparison studies on continuous PPI therapy[48, 50] and five non-comparison studies on on-demand therapy[50, 57, 60-62] were included. The severe adverse events proportions reported in the single treatment arms of these non-comparison studies were in line with the ranges found in the comparison studies.

Long-term safety – Cancer

One database study was included which linked data from different patient populations on continuous PPI therapy (i.e. defined as a cumulative defined daily dose of at least 6 months during the study period)

to the outcome oesophageal adenocarcinoma derived from four nationwide Swedish registers (Table 30).[49] In GERD patients (defined using ICD codes) the standardised incidence ratio for adenocarcinoma was 6.87 (95% CI 6.13-7.67) and for squamous cell carcinoma 3.35 (95% CI 2.76-4.03).

Long-term safety – Death

One of the included studies reported on the outcome death. In the USA a phase 3 safety extension RCT was conducted in patients with endoscopically proven NERD on continuous therapy of 60 mg dexlansoprazole (Table 31).[48] In total, 2 of the 153 (1.3%) NERD patients died after completing or prematurely discontinuing the study. None of these deaths were treatment-related: one patient died from acute promyelocytic leukaemia and the other from acute respiratory failure.

Table 28: Short-term safety - adverse events

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	[36]: C: 35.4% OD: 36.2%	NR	Low (n=1)[36]	?	[18]: Similar proportion (overall 71%, NR per group)	NS	High (n=1)[18]	None	[48]: 71.2%	High (n=1)[48]	[19]: 40.5% [55]: 42.9% [56]: 73.7%, 67.0%*	Low (n=1) [19] Moderate (n=2) [55, 56]
Endoscopically proven NERD and low grade GERD	[42]: C: 37.3% OD: 29.9%	NS	Low (n=1)[42]	None	[46]: C: 13.7% OD: 0%	NR	High (n=1)[46]	?	-	-	[58]: 35.7% [59]: 30%, 31%† [60]: 33.8% [61]: 21.0%, 23.0%‡	Moderate (n=3)[58, 59, 61] NA (n=1) [60]
Endoscopically uninvestigated GERD	[10]: C: 46.0% OD: 47.8% [40]: No clinically relevant difference (not further specified)	NR (both studies)	Low (n=2)[10, 40]	?	-	-	-	?	[50]: 56%	Low (n=1)[50]	[57]: 54.8%	Moderate (n=1)[57]

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, NS: no statistically significant difference between continuous and on-demand therapy (p≥0.05), OD: on-demand therapy, ?: no data/statistical comparison

* % short-term adverse events in the esomeprazole 40 mg group and the esomeprazole 20 mg group, respectively; † % short-term adverse events in the pantoprazole 40 mg group and the pantoprazole 20 mg group, respectively; ‡ % short-term adverse events in the pantoprazole 20 mg group and the esomeprazole 20 mg group, respectively.

Table 29: Short-term safety - severe adverse events

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	[36]: C: 3.7% OD: 1.3%	NR	Low (n=1)[36]	?	[18]: C: 1.6% OD: 2.9%	NR	High (n=1)[18]	?	[48]:5.9%	High (n=1)[48]	[56]: 1.4%, 2.5%* [55]: 2.9%	Moderate (n=2)[55, 56]
Endoscopically proven NERD and low grade GERD	[42] C: 5.9% OD: 2.6%	NR	Low (n=1)[42]	?	[46]: C: 0% OD: 0%	NR	High (n=1)[46]	?	-	-	[60]: 2.6% [61]: 2.0%, 3.0%†	Moderate (n=1)[61] NA (n=1)[60]
Endoscopically uninvestigated GERD	-	-	-	?	-	-	-	?	[50]: 0%	Low (n=1)[50]	[57]: 0%	Moderate (n=1)[57]

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, ?: no data/statistical comparison

* % short-term adverse events in the esomeprazole 40 mg group and the esomeprazole 20 mg group, respectively; † % short-term adverse events in the pantoprazole 20 mg group and the esomeprazole 20 mg group, respectively

Table 30: Long-term safety - Cancer

Population	Continuous vs. on-demand comparison studies Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically uninvesttigated GERD	-	-	-	?	-	-	-	?	Adenocarcinoma: 0.16% - SIR (95% CI): 6.87 (6.13-7.67) Squamous cell carcinoma:0.06% - SIR (95% CI): 3.35 (2.76-4.03)[49]	NA (n=1)[49]	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, SIR = standardised incidence ratio (relative to the entire Swedish background population of same age, sex and calendar period), ?: no data/statistical comparison

Table 31: Long-term safety - Death

Population	Continuous vs. on-demand comparison studies. Identical PPI and dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Continuous vs. on-demand comparison studies. Different PPI and/or dosage			CONCLUSION ON WHICH THERAPY IN FAVOUR	Non-comparison studies			
									Continuous		On-demand	
	Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Significant difference	Risk of bias (nr studies)		Outcome	Risk of bias (nr studies)	Outcome	Risk of bias (nr studies)
Endoscopically proven NERD	-	-	-	?	-	-	-	?	[48]: Death after completing or prematurely discontinuing study: 1.3% (none treatment-related)	High (n=1)[48]	-	-
Endoscopically proven NERD and low grade GERD	-	-	-	?	-	-	-	?	-	-	-	-
Endoscopically uninvestigated GERD	-	-	-	?	-	-	-	?	-	-	-	-

Keys: C: continuous therapy, GERD: gastroesophageal reflux disease, NA: not applicable, NERD: non-erosive reflux disease, NR: not reported, OD: on-demand therapy, ?: no data/statistical comparison

Summary statement efficacy, effectiveness and safety

In the clinical review 28 articles published between 2000 and 2019 were included: 12 RCTs (risk of bias low n=6, moderate n=2, high n=4) directly comparing continuous and on-demand PPI therapy, and 16 single arms of studies comparing continuous or on-demand PPI with another treatment. For most outcomes of interest it was not possible to draw a conclusion in favour of continuous or on-demand PPI therapy (Table 32), because none of the comparison studies reported on a specific PICO outcome, statistical comparison was lacking, no significant or clinically relevant difference was found, or results contradicted each other. Indeed, the efficacy evidence showed that on-demand therapy results in lower PPI pill consumption per day compared with continuous therapy. The difference in favour of continuous therapy for the outcome heartburn symptom relief may largely be attributed to the specifications of the therapy modality; with on-demand therapy a dose of PPI is taken when clinical symptoms occur, which may explain the higher symptom load. Based on efficacy and effectiveness outcomes, the overall satisfaction of the patients with both treatment modalities and health-related quality of life was in general high and differences between continuous and on-demand PPI therapy were quite small, resulting in a lacking clinically relevant difference between these two therapy modalities. No major safety issues were reported in the included studies.

Table 32: Overview of the evidence on the efficacy, effectiveness, and safety of continuous versus on-demand long-term PPI therapy in in adult patients with NERD or GERD

Study outcomes of interest	Number of comparison studies included on study outcome	CONCLUSION ON WHICH THERAPY IS IN FAVOUR*		
		C	OD	?
1. PPI pill consumption per day	6[18, 36, 40, 42, 43, 45]		x	
2. Number of endoscopic investigations per year	1[40]			x
3. Patient-reported therapy satisfaction	8[10, 18, 36, 39-41, 43, 45]			x
4. PPI intake or compliance during study	1[39]			x
5. Health-related quality of life	6[36, 38, 39, 41, 43, 46]			x
6a. Symptom relief: Heartburn	3[10, 39, 40]	x		
6b. Symptom relief: Regurgitation	2[10, 40]			x
6c. Symptom relief: Perception of flow of gastric content into oesophagus	0			x
7a. Safety: Short-term adverse events (<6 months)	5[10, 18, 36, 42, 46]			x
7b. Safety: Long-term adverse events (longer than 6 months)	0			x

* The conclusion on which therapy is in favour for the outcomes of interest was based on the statistically significant differences found between continuous and on-demand PPI therapy, the clinical relevance of these differences (e.g. relatively high general patient satisfaction and HRQoL levels were found at the end of continuous as well as on-demand PPI therapy with small differences between both treatment modalities), and finally it was taken into account if other studies reported inconclusive results.

8 Costs, cost-effectiveness and budget impact

8.1 Methodology costs, cost-effectiveness and budget impact

For the cost-effectiveness search besides comparison studies we also included non-comparison studies to inform the key HTA questions posed. We used the same categorisation as in the efficacy, effectiveness, and safety literature review search:

- Comparison studies which compare continuous with on-demand long-term PPI therapy;
- Non-comparison studies (i.e. comparison is possible within these studies, but no direct comparison between continuous and on-demand PPI therapy), which include one arm with continuous PPI therapy or one arm with on-demand PPI therapy.

8.1.1 Databases and search strategy

The literature search was conducted using the databases PubMed (MEDLINE), Embase.com, and NHS/EED. The search filters for cost-effectiveness and costing studies were embedded onto the search strategy of the efficacy, effectiveness, and safety evidence, as discussed above in Section 7.1.1.

The applied search filters were publication period (from 2000-2019) and the language of the publications (English, Dutch, French, and German). Furthermore, animal studies, case reports, and non-pertinent publication types (e.g. editorials, letter, and comments) were excluded with additional search strings. The full search strategies for each database are outlined in Appendix 15.2. The database output, including all indexed fields per record (e.g. title, authors, abstract), was exported to Endnote version X7.4 where the hits were de-duplicated.

Selection procedure

For the cost-effectiveness search, the same selection procedure as for the effectiveness review was applied.

Inclusion and exclusion criteria

The list of inclusion and exclusion criteria applied during the selection process is presented in Table 33.

Note that the population as presented in the PICO table in Section 5 is extended, in order to increase the number of hits by including the studies analysing mixed adult population with endoscopically proven NERD and low grade GERD.

Quality assurance approach

The following quality control measures were applied during the selection process:

- Two independent researchers from iMTA screened all titles and abstracts. The results were compared and discussed before proceeding to the full-text review phase. In case of discrepancy or disagreements during the selection phase, a third researcher was consulted. The study was discussed until consensus was reached.

- Two independent researchers from iMTA assessed the selected full-text articles for relevancy and critically appraised them. In case of discrepancy or disagreements during the selection phase, a third researcher was consulted. The study was discussed until consensus was reached.

- The economic filter, suggested on the Canadian Agency for Drugs and Technologies in Health (CADTH) website, for economic evaluations and cost/economic models on the Ovid Medline interface were used instead of the original economic filter for PubMed (MEDLINE) as given in Appendix 15.2, in order to check if any additional relevant studies were missed. Using the CADTH search filter did not yield any other additional relevant hits.

- The title and abstract screening conducted on the unfiltered efficacy, effectiveness, and safety search hits (as explained in Section 7.1.1) did not yield any additional cost-effectiveness studies other than the ones identified from the cost-effectiveness search using cost-effectiveness search filters.

Table 33: Inclusion and exclusion criteria for cost-effectiveness systematic review

	Inclusion	Exclusion
Period publication	• From 2000-2019	
Country of study	• All countries	
Language of the study	• English • French • German • Dutch	• All other languages
Study design/type	• Economic evaluations • Cost-effectiveness • Cost-minimisation • Cost-benefit • Other costing studies • Resource use measurement	• All other study design/types
Study quality		• No exclusion based on study quality
Study population	• Patients ≥18 years with NERD • Patients ≥18 years with uninvestigated GERD	• Healthy population • Patients <18 years • Population with other diagnosis than NERD/uninvestigated GERD

	• Mixed population of patients ≥18 years with endoscopically proven NERD and low GRADE† GERD	
Study intervention	• Continuous (daily) PPI long-term therapy (i.e. longer than 6 months) OR On-demand PPI long-term therapy (i.e. longer than 6 months)	• All other interventions (e.g. intermittent PPI therapy) • PPI short-term therapy (i.e. <6 months)
Study comparison		
Study outcomes	• See outcomes in PICO table (Section 5)	

Keys: NERD = non-erosive reflux disease, GERD = gastroesophageal reflux disease, PPI = proton pump inhibitor, PICO = Patients - Intervention – Comparator – Outcome
* Relevant meta-analyses and systematic reviews were selected during the screening of title and abstract phase. During the full-text phase, reference lists of these reviews were checked for possibly missed relevant individual articles; † According to the Savary-Miller classification. Grade I: Single or isolated erosive lesion(s), oval or linear, but affecting only one longitudinal fold; Grade II: Multiple erosive lesions, non-circumferential, affecting more than one longitudinal fold, with or without confluence; or according to the Los Angeles classification. Grade A: One or more mucosal breaks < 5 mm in maximal length; Grade B: One or more mucosal breaks > 5mm, but without continuity across mucosal folds

8.1.2 Other sources

Not applicable.

8.1.3 Assessment of quality of evidence

In an attempt to provide insight in the quality of the studies at a glance, the studies were assessed on their reported information (Table 37). The well-established guidelines on the evaluation of economic evaluations by Drummond and Jefferson (1996) were used in conjunction with the more recent checklist for critical assessment of economic evaluation from 'Methods for the Economic Evaluation of Health Care Programmes' by Drummond et al. (2005). The guidelines from 1996 contain a clear and well-structured overview of the crucial elements that every full economic evaluation should provide. In 2005, the checklist was extended to provide additional guidance on the usefulness of the evaluations. Hence, the focus of the checklist is on the methodology employed, which enables the reader to make a preliminary judgement on the validity of the stated results. An alternative to the Drummond checklist(s) is the CHEERS checklist[b] that was developed by the ISPOR task force and published in 2013. The CHEERS checklist aimed to consolidate guidelines, to optimise reporting, and to provide a user-friendly manual to the assessors. The CHEERS checklist provides a practical guide to assess submitted economic evaluations of health interventions regarding the reporting of crucial elements. The CHEERS list overlaps with the lists of Drummond et al. (1996, 2005). However, Drummond's lists are more exhaustive and explicitly encourages the reviewer to critically assess the reported data (e.g. in Drummond's lists there

[b] http://www.equator-network.org/wp-content/uploads/2013/04/Revised-CHEERS-Checklist-Oct13.pdf

are questions such as: “Is the methodology coherent with the outlined aim?”). Therefore, we continued with the well-established Drummond checklists, merging criteria whenever there was an overlap.

8.1.4 Methodology health economic analyses

Data extracted from the studies were summarised in tables. The summary tables were compiled for study characteristics and outcomes and were drafted separately for trial- and model-based studies. For the trial-based studies the PICO outcomes were reported. For the model-based studies medication cost, direct and indirect cost, total cost, and QALYs gained were stated. All summary tables distinguish between the four different study types: 1) on-demand versus continuous comparison studies on identical PPI and dosage, 2) on-demand versus continuous comparison studies on different PPI and/or dosage, 3) non-comparison studies on continuous PPI therapy, and 4) non-comparison studies on on-demand PPI therapy.

Data was synthesised for outcomes that were shared across the studies. Since the studies were not homogenous we did not pool the outcomes, but describe the cost ranges and where possible compared on-demand PPI therapy costs with continuous PPI therapy costs. The outcomes were reported for trial-based and model-based studies separately and were further distinguished in: 1) on-demand versus continuous comparison studies on identical PPI and dosage, 2) on-demand versus continuous comparison studies on different PPI and/or dosage, 3) non-comparison studies on continuous PPI therapy, and 4) non-comparison studies on on-demand PPI therapy. For trial-based studies PICO outcomes were reported. For the model-based studies medication cost, direct and indirect cost, total cost, total QALYs and QALYs gained were extracted. Cost per QALY were calculated based on total costs and total QALYs, if they had been reported in the study.

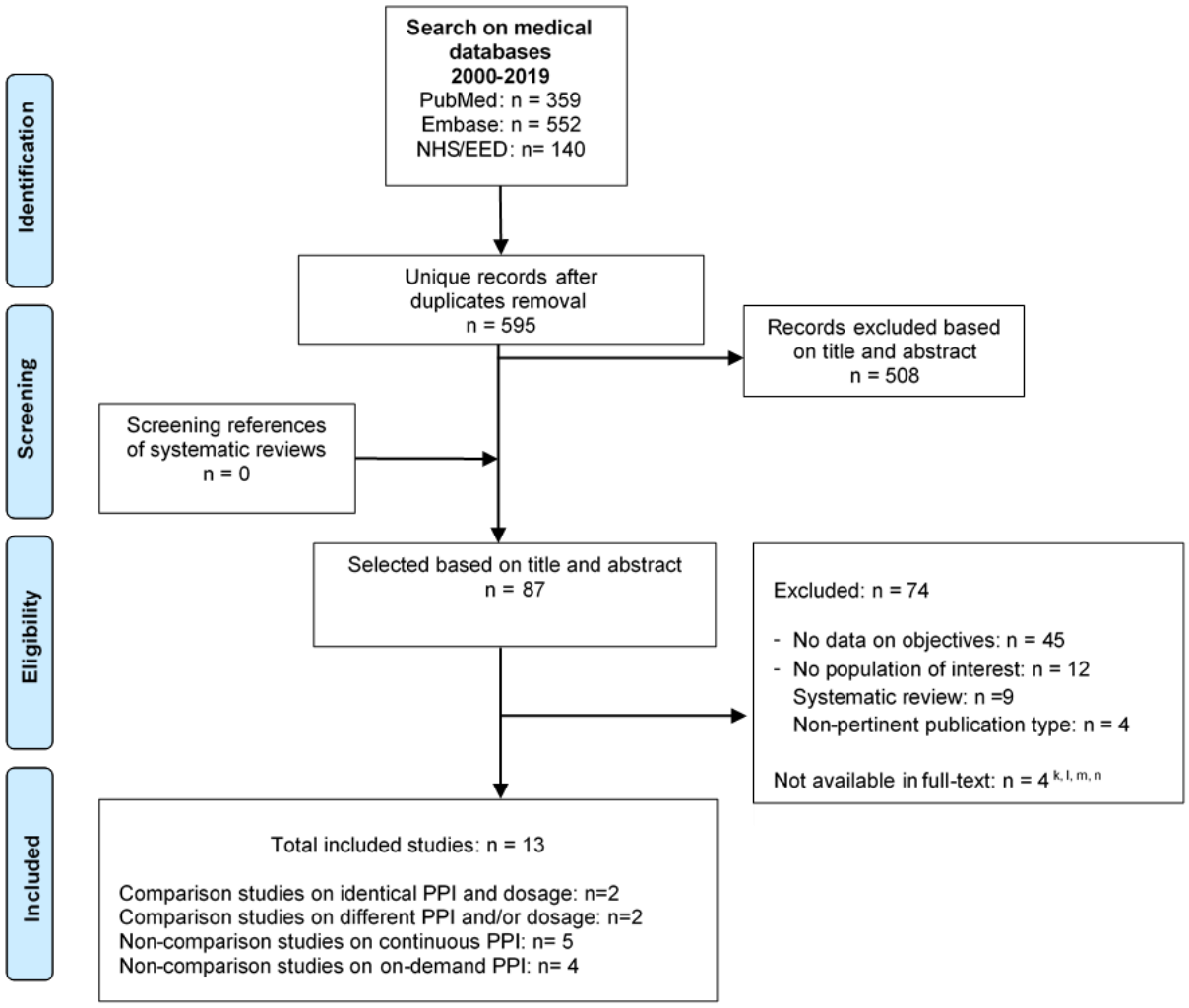
8.2 Results costs, cost-effectiveness and budget impact

8.2.1 PRISMA flow diagram

The systematic search on cost-effectiveness created 595 unique records (Figure 3). Of those, 508 were excluded based on their title, abstract/title, or abstract. This resulted in 87 studies that were read in full-text. After applying the inclusion and exclusion criteria, 13 studies were included in the cost-effectiveness review; six trial-based and seven model-based studies. Of the trial-based studies, four compared continuous versus on-demand PPI long-term therapy in adult patients with uninvestigated GERD (two studies) or NERD (two studies). The other two trial-based studies were non-comparison studies with uninvestigated GERD population. Of the seven model-based studies, all were non-comparison studies

with uninvestigated GERD (four studies) or NERD (three studies) population. The main reason for exclusion was the lack of data on the research objective, e.g. the PPI therapy strategy was not clearly described as on-demand or continuous, the intervention or comparator was not PPI therapy, or the study focused only on the initial therapy phase during which the PPI therapy is administered empirically for a duration of four to eight weeks. Studies that were not an economic evaluation or costing study were also excluded. Other reasons for exclusion were patient population, e.g. patients with erosions, helicobacter pylori or dyspepsia, and non-availability of study in full-text. Literature reviews were screened only for additional references, but were otherwise excluded.

Figure 3: PRISMA flow diagram cost effectiveness review



Keys: PPI = Proton Pump Inhibitor

Not available in full-text (n=4):

[k] **Buijt I, Al MJ, Rutten FF**. Do proton pump inhibitors reduce costs? Costs and effects of esomeprazol in the treatment of gastroesophageal reflux disease. Pharmaceutisch Weekblad 2003;138(35):1194-99;

[l] **Kripke C.** Comparison of short-term treatments for GERD. American family physician 2005;71(7):1303-4;

[m] **Negrini C, Wahlqvist P, Rossi C, et al.** Economic evaluation of on-demand treatment with esomeprazole in gastroesophageal reflux disease. ONE economic longitudinal study in Italy. Pharmacoeconomics - Italian Research Articles 2005;7(1):67-80;

[n] **Sugano K, Kobayashi M.** Economic evaluation of maintenance therapies for reflux esophagitis: comparison between step-up therapies and step-down therapies. Japanese Pharmacology and Therapeutics 2001;29(6):459-68;

8.2.2 Study characteristics table

For the study characteristics of the included studies separate tables were drafted for the trial- and model-based studies. The study characteristics tables were further distinguished into the different study types: 1) continuous versus on-demand comparison studies on identical PPI and dosage; 2) continuous versus on-demand comparison studies on different PPI and/or dosage; 3) non-comparison studies on continuous PPI therapy; 4) non-comparison studies on on-demand PPI therapy. Additionally, a table on the quality of the trial- and model-based studies was included.

Study characteristics of trial-based studies

Four of the six trial-based studies compared continuous PPI therapy with on-demand PPI therapy. Among these four studies, two studies used identical PPI medication and dosage [40, 63], one study compared on-demand and continuous PPI therapies using different PPI medications and different dosages [18] , and one remaining study compared on-demand and continuous PPI therapies using the same PPI medication but with different dosages.[45] The other two trial-based studies were non-comparison studies; one with continuous PPI therapy[47] and one with on-demand PPI therapy[52] as intervention.

The PPI therapy used in both comparison studies with identical PPI and dosage was esomeprazole 20 mg.[40, 63] In the comparison studies with different PPI and/or dosage, in the first study, on-demand esomeprazole 20 mg was compared to continuous lansoprazole 15 mg treatment[18], and in the second study, on-demand lansoprazole 30 mg was compared to continuous lansoprazole 15 mg treatment[45]. In the non-comparison studies, in the first study, the continuous PPI treatment was esomeprazole 20 mg[47], and in the second study, the on-demand PPI treatment was esomeprazole 20 mg.[52]

The PPI treatment duration across studies ranged from 6 months to 11 months. All studies, but Tsai et al., were open-label RCTs. Tsai et al. study was conducted as a single-blind RCT[18]. The studies were from Norway, Switzerland, the United Kingdom, Poland, the United States, Denmark, and one was a multi-country study (Denmark, Finland, Norway, and Sweden).

In four studies[40, 47, 52, 63] uninvestigated GERD was the population of interest. The other two studies[18, 45] focused on endoscopically investigated NERD patients. All studies but one conducted a cost consequence evaluation. On the contrary, Meineche-Schmidt et al. conducted a cost minimisation analysis[52]. An overview of all study characteristics is provided in Table 34.

Table 34: Study characteristics of the trial-based studies

Reference	Country	Study design	Study period	Type of evaluation	Currency year	Study population	Intervention	Comparator
	Comparison studies on identical PPI and dosage							
Hansen (2005)[63]	NO	Open-label RCT	26 weeks	Cost consequence analysis	2001 (1 Euro = 8'049 NOK).*	Uninvestigated GERD	Group 1: Esomeprazole 20 mg, on-demand	Group 2: Continuous esomeprazole 20 mg once daily Group 3: Continuous ranitidine 150 mg twice-daily (6 months)
Szucs (2009)[40]	CH	Open-label RCT	6 months	Cost consequence analysis	NR (CHF)	Uninvestigated GERD	Esomeprazole 20 mg, on-demand	Continuous esomeprazole 20 mg once daily
	Comparison studies on different PPI and/or dosage							
Tsai (2004)[18]	UK	Single-blind RCT	6 months	Cost consequence analysis	June 2002 (GBP)	Endoscopically proven NERD	Esomeprazole 20 mg, on-demand	Continuous lansoprazole 15 mg (6 months)
Cibor (2006)[45]	PL	Open-label RCT	11 months	Cost consequence analysis	NR (PLN)	Endoscopically proven NERD	Group 1: Lansoprazole 30 mg on-demand	Group 2: Lansoprazole 15 mg daily Group 3: Lansoprazole 30 mg in four-week courses during a relapse
	Non-comparison studies continuous PPI							
Kaplan Machilis (2000)[47]	US	Open-label RCT	6 months	Cost consequence analysis	1998 (USD)	Uninvestigated GERD*	Omeprazole 20 mg once daily	Ranitidine hydrochloride, 150 mg twice daily
	Non-comparison studies on-demand PPI							
Meineche-Schmidt (2004)[52]	DK	Open-label RCT	6 months	Cost minimisation	2001 (1 Euro = 7.44 DKK)*	Uninvestigated GERD†	Group 1: Esomeprazole 20 mg, on-demand	Group 2: Intermittent treatment, 4 weeks long 40 mg Esomeprazole course on symptom recurrence Group 3: Intermittent treatment, 2 weeks long 40 mg esomeprazole course on symptom recurrence

Keys: NO = Norway, DK = Denmark, CH = Switzerland, UK = United Kingdom, PL = Poland, US = United States, FI = Finland, NO = Norway, SE = Sweden, RCT = Randomised Controlled Trial, GERD = Gastroesophageal Reflux Disease, NERD = Non-Erosive Reflux Disease, NR = Not Reported, GBP = British pound sterling, NOK = Norwegian krone, PLN = Polish złoty, USD = United States dollar, DKK = Danish krone* These were the conversion rates that were used in the studies, as they presented results in euros.

* Patients were included based on clinical diagnosis. Diagnosis of GERD was based on frequency of heartburn and/or acid regurgitation despite non-prescription treatment for 2 weeks or more; † Patients were included if their symptoms were suggestive of GERD for three days or more during the 7 days prior to inclusion.

Study characteristics of model-based studies

All seven model-based studies are non-comparison studies. Among those, four studies[64-67] focused on continuous PPI treatments, and three studies[68-70] were analysing on-demand PPI treatments.

PPI medication used in these studies were esomeprazole 20 mg, lansoprazole 15 mg, rabeprazole 10 mg, pantoprazole 20 mg, omeprazole 10 mg and omeprazole 20 mg treatment, as well as a combination of several different PPIs and dosages (Table 35).

In the model-based studies, the patient population was often not based on the actual patients enrolled in a trial, but rather it was based on the description of the assumptions on the baseline characteristics. In two of the studies, the population of interest was endoscopically proven NERD patients.[68, 70] Two studies examined a mixed population, consisting of both endoscopically proven NERD and low grade GERD patients.[65, 69] The other three studies[64, 66, 67] focused on an uninvestigated GERD population. Comay et al. included an endoscopically uninvestigated GERD patient population, which was diagnosed based on a 24 hours pH study and empirical PPI treatment.[64] Doan et al. described an uninvestigated GERD population that was stratified based on reported symptom severity.[67] You et al. described a hypothetical uninvestigated GERD population in remission.[66]

The study countries were Canada, China, Italy, the United Kingdom, and the United States.

Six of the seven studies were cost-effectiveness analyses (CEA) and used either a decision tree model [68, 69] or a Markov model.[64-66, 70] Doan et al. conducted a costing study with a decision-tree model.[67]

The time horizon was set between six months and lifetime (i.e. 30 years), and cycle lengths were two weeks, one month, or six months.

Most studies took the payer's perspective including the UK National Health Service[65, 68, 70] and other third party payers.[64, 66] Hughes et al.[69] and Doan et al.[67] considered a healthcare service & societal perspective, and an employer perspective, respectively. An overview of all study characteristics is provided in Table 35 and Table 36.

Table 35: Study characteristics of the model-based studies

	Hughes (2005a)[69]	Hughes (2005b)[68]	Wahlqvist (2002)[70]
Country	IT	UK	UK
Model type	Decision tree model	Decision tree model	Markov model
Type of EE	CEA	CEA	CEA
Model population	Mixed population endoscopically proven NERD and low grade GERD*	Endoscopically proven NERD	Endoscopically proven NERD
Time horizon	12 months	1 year	6 months
Cycle length	n/a	n/a	2 weeks
Perspective	Healthcare service & society	UK NHS	UK NHS
Discounting	n/a	n/a	n/a
Currency year	1998 (GP visits) 1996 (Endoscopy, gastroenterologist) 2004 (Medicine costs) (EUR)	2003 (EUR)	1998 (Primary care, gastroenterologist and endoscopy) 2000 (Medicine costs) (GBP)
Intervention	Group 1: On-demand use of esomeprazole 20 mg	Group 1: On-demand use of esomeprazole 20 mg	Group 1: On-demand use of esomeprazole 20 mg
Comparator	Group 2: On-demand use of lansoprazole 15 mg Group 3: On-demand use of pantoprazole 20 mg Group 4: On-demand use of rabeprazole 10 mg Group 5: On-demand use of omeprazole 10 mg Group 6: On-demand use of omeprazole 20 mg	Group 2: On-demand use of pantoprazole 20 mg Group 3: On-demand use of rabeprazole 10 mg Group 4: On-demand use of lansoprazole 15 mg Group 5:On-demand use of omeprazole 10 mg Group 6: On-demand use of omeprazole 20 mg	Group 2: Intermittent 4-week acute treatment courses of omeprazole 20 mg once daily; Group 3: No drug treatment followed by a continuous omeprazole treatment (20 mg once daily) upon relapse

Keys: UK = United Kingdom, IT = Italy, EE = Economic Evaluation, CEA = Cost-Effectiveness Analysis, GERD = Gastroesophageal Reflux Disease, NERD = Non-Erosive Reflux Disease, NHS = National Health System, n/a = not applicable, GBP = British pound sterling, EUR = euro

* The population in the study consisted of low grade GERD 0 or I and I or II who achieved a complete resolution of their symptoms in the first four weeks of the empirical treatment and entered as investigated NERD the maintenance therapy.

Table 36: Study characteristics of the model-based studies (cont'd)

	Comay (2008)[64]	Doan (2008)[67]	You (2003)[66]	Bojke (2007)[65]
Country	CA	US	CN	UK
Model type	Markov model	Decision tree model	Markov model	Markov model
Type of EE	CEA	Costing study	CEA	CEA
Model population	Uninvestigated GERD*	Uninvestigated GERD†	Uninvestigated GERD	Mixed population endoscopically proven NERD and low grade GERD‡
Time horizon	5 years	1 year	12 months	Lifetime (30 years)
Cycle length	6 months	4 weeks and 6 months	1 month	1 month
Perspective	Ministry for Health	Employer perspective	Public health organization in Hong Kong	UK NHS
Discounting	3%	n/a	NR	3.50%
Currency year	2006 (CAD)	2005 (USD)	2003 (USD)	2004 (GBP)
Intervention	Stretta procedure	PPI continuous, standard dose	Standard-dose histamine-2 receptor antagonist	Continuous use of different PPIs and dosages¶
Comparator	G1: Continuous use of omeprazole 20 mg G2: Laparoscopic Nissen fundoplication	No treatment	G1: Continuous low-dose proton pump inhibitor G2: Continuous standard-dose proton pump inhibitor	Laparoscopic surgery

Keys: CEA = Cost-Effectiveness Analysis, EE = Economic Evaluation, US = Unites States, CA = Canada, CN = People's Republic of China, NR = Not Reported, n/a = not applicable, GERD = Gastroesophageal Reflux Disease, NERD = Non-Erosive Reflux Disease, PPI = Proton-Pump-Inhibitor, CAD = Canadian dollar, USD = United States dollar, GBP = British pound sterling

* Patients with an abnormal 24 hours pH study and response to empirical treatment were included. The study was included since patients were not endoscopically investigated; † Patients were stratified into mild, moderate, severe, and no GERD symptoms. The study was included since patients were not investigated; ‡ The investigation was not specified. We included the study since the population of interest (mixed population NERD and low grade GERD or endoscopically proven NERD) might be included in the patient population; ¶ An average daily PPI dose was calculated per patient

All included studies, model- and trial-based, were critically appraised by the Drummond checklist. Table 37 provides an overview of the criteria. Criteria which were not fulfilled by the majority of the studies were on the relevance of productivity changes to the study question (B8). These were not discussed in most of the studies also due to their perspective (payer perspective, i.e. National Health Service) rather than societal perspective. Although all of the studies described their sources of resource utilisation, the selection of choice for the inputs were often not justified, as required by Drummond's checklist (B10). Capital costs and operating cost (B11) were also not reported in most studies. Details on inflation adjustments (B15) and details of statistical test and confidence intervals for stochastic data (C6) were also commonly not reported.

Table 37: Critical appraisal with the Drummond Checklist

#	Criteria	Hansen (2005)[61]	Meineche-Schmidt (2004)[52]	Szucs (2009)[40]	Tsai (2004)[18]	Kaplan Machi-lis(2000)[47]	Cibor (2006)[45]	Hughes[a] (2005)[69]	Hughes[b] (2005)[68]	Wahlqvist (2002)[70]	Comay (2008)[64]	Doan (2008)[67]	You (2003)[66]	Bojke (2007)[65]
A														
1	The research question is clearly stated.[71, 72]	Yes	Yes	Yes	Not Clear	Yes	Not Clear	Yes	Yes	Yes	Not Clear	Yes	Yes	No
2	The economic importance of the research question is stated.[71, 72]	Not Clear	Not Clear	Yes	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes
3	The viewpoint(s) of the analysis are clearly stated and justified.[71, 72]	Yes	Yes	Yes	No	No/Not Clear	Not Clear	Not Clear	Yes	Yes	Yes	Yes	Yes	Yes
4	The rationale for choosing alternative programmes or interventions compared is stated.[71, 72] (Should do nothing alternative considered?)[72]	No	No	Yes	No	Yes	No	Not Clear	Not Clear	Yes*	Yes	No	Yes	Yes
5	The alternatives being compared are clearly described.[71, 72]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	The form of economic evaluation used is stated, i.e. the study examines both the costs & consequences.[71, 72]	Yes	Yes	Yes	No	Yes	No	Yes	Not Clear	Yes	Yes	Yes	Yes	Yes
7	The choice of form of economic evaluation is justified in relation to the questions addressed.[71, 72]	Yes	Yes	Yes	No	No	No	Yes	Not Clear	Yes	Yes	Yes	Yes	Yes
B														
1	Details of the design and results of effectiveness study are given[71, 72] (if based on a single study, if done through an RCT did it reflect regular practice.[72])	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Details of the methods of synthesis or meta-analysis of estimates are given[71, 72] (if based on a synthesis of a number of effectiveness studies) (Search strategies and rules for inclusion/exclusion are outlined[72]).	Yes	Yes	Yes	Yes	N/A	N/A	N/A	N/A	N/A	No	Yes	No	Yes
3	Details of potential biases are given (if based on observational data)[72]	N/A	N/A	N/A	N/A	Yes	No	Yes	Yes	Not Clear	N/A	N/A	N/A	N/A
4	The primary outcome measure(s) for the economic evaluation are clearly stated and justified.[71]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Methods to value effects are stated (e.g. TTO, SG ...).[71]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
6	Details of the subjects from whom valuations were obtained were given.[71]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No
7	Productivity changes (if included) are reported separately).[71]	Yes	No	Yes	No	No	No	Yes	N/A	N/A	No	Yes	No	N/A
8	The relevance of productivity changes to the study question is discussed. [71]	Yes	No	Yes	No	No	No	No	N/A	N/A	No	Yes	No	No
9	Sources of resource utilisation were described and justified. [72]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not Clear	Yes	Yes	Yes	Yes
10	Details of identified items omitted and/or special circumstances that made measurement difficult were described.[72]	Yes	Yes	No	No	Yes	No	No	No	No	No	Yes	No	No
11	Capital costs and operating costs were included.[72]	Yes	Yes	No	No	No	No	No	No	No	No	N/A	No	Not Clear

12	Quantities of resource use are reported separately from their unit costs.[71]	No	Yes	Yes	Not Clear	No	No	Yes	Yes	No	No	Yes	Yes	No
13	Methods for the estimation of quantities and unit costs are described.[71]	Yes	Yes	Yes	Not Clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14	Currency and price data are recorded.[71]	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
15	Details of currency of price adjustments for inflation or currency conversion are given.[71]	Yes *	Yes *	No	No	No	N/A	No	No*	No	No	No	No	No
16	Details of any model used are given. (e.g. decision tree, epidemiological model, …)[71]	N/A	N/A	N/A	N/A	N/A	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17	The choice of model used and the key parameters on which it is based are justified.[71]	N/A	N/A	N/A	N/A	N/A	N/A	Not Clear	Not Clear	Yes	Not Clear	Yes	Not Clear	No
C														
1	The time horizon of costs & benefits is stated.[71, 72]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	The discount rate(s) is stated.[71, 72]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	Yes
3	The choice of rate(s) is justified.[71, 72]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Yes	N/A	N/A	No
4	An explanation is given if costs or benefits are not discounted.[71, 72]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
5	Incremental analysis is reported (comparing relevant alternatives).[71 72]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes*	Yes	Yes	Yes	Yes
6	Details of statistical test and confidence intervals are given for stochastic data.[71]	No	Yes	No	No	No	N/A	Not Clear	Not Clear	No	No	No	Yes	Yes
7	The approach to sensitivity analysis is given.[71]	Yes	No	No	No	No	No	Not Clear	Yes	Yes	Yes	Yes	Yes	Yes
8	The choice of variables and the ranges/distribution of values for the sensitivity analysis is justified.[72]	No	N/A	N/A	No	N/A	N/A	Not Clear	Yes	No	No	Yes	Yes	No
9	The ranges over which the variable are varied are stated.[72]	Yes	N/A	N/A	No	N/A	N/A	Not Clear	Not Clear	Yes	Yes	Yes	Yes	Yes
10	Major outcomes are presented in a disaggregated as well as aggregated form.[71]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
11	The answer to the study question is given.[71]	Yes	Yes	Yes	Not Clear	Yes	Yes	Yes	Not Clear	Yes	Yes	Yes	Yes	Yes
12	Conclusions follow from the data reported.[71]	Yes	Yes	Yes	Not Clear	Yes	Not Clear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13	Conclusions are accompanied by the appropriate caveats.[71]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Keys: N/A = Not Applicable

8.2.3 Findings costs

The trial- and model-based studies reported on several cost categories such as medication costs, direct and indirect costs as well as effectiveness (i.e. QALYs).

For the trial-based studies, the PICO outcomes (Section 5) were extracted and compared between continuous and on-demand PPI therapy. PICO outcomes on costs related to progression to ERD, adverse events/side effects, quality-adjusted cost comparison, informal caregiver cost, QALYs, LYs and ICER were not available for any of the trial-based studies.

For the model-based studies we extracted and provided information on medication cost, direct cost (e.g. costs for endoscopy or hospital visits) and indirect cost (e.g. productivity costs), total cost, and total QALYs. Furthermore, cost per QALY values (overall and per year) were calculated for the model-based studies, if the total cost and total QALYs were reported in these studies. Since all model-based studies were non-comparison studies (i.e. on-demand PPI therapy and continuous PPI therapy were not compared with each other in none of the identified studies), the ICER (on-demand vs continuous PPI therapy) was not reported in none of the identified model-based studies.

The extracted PICO outcomes from the identified trial-based studies and model-based studies are presented below, respectively.

Trial-based studies - Medication cost, endoscopy costs, and hospitalisation costs

Medication cost during the follow-up period (6 and 6.5 months) were higher in the continuous PPI therapy arm than in the on-demand PPI therapy arm in both comparison studies with identical PPI medication and dosage (Table 38).[40, 63] The same finding was found in the comparison study, using the same PPI medication with different dosages, by Cibor et al., in which the medication costs for the continuous PPI therapy arm (15 mg lansoprazole) were higher than those for the on-demand therapy (30 mg lansoprazole).[45] In the comparison study using different PPI medications as well as different dosages, by Tsai et al., the medication costs for continuous PPI therapy (15 mg lansoprazole) were also higher than those in the on-demand therapy arm (20 mg esomaprazole).[18] For the non-comparison studies, Meineche-Schmidt et al. [52] found similar medication costs for on-demand PPI as in the comparison study on identical PPI and dosage by Hansen et al. [63] In both studies, esomeprazole 20 mg was used for on-demand PPI therapy.

For over-the-counter PPI medication costs, in comparison to the continuous PPI therapy, Hansen et al.[63] reported higher costs for on-demand PPI therapy, whereas in Szucs et al.[40] lower costs were found for on-demand PPI therapy.

Costs for endoscopy varied between the two comparison studies using identical PPI medication and dosage. Hansen et al. [63] found lower costs for on-demand PPI treatment when compared to continuous

PPI treatment, whereas Szucs et al.[40] reported higher costs for on-demand PPI. No other studies reported on costs for endoscopy.

Costs for hospitalisations were reported in the comparison study using identical PPI medication and dosage by Szucs et al. [40]. It was found that hospitalisation costs were higher for the on-demand PPI arm than for the continuous PPI arm. The findings from the non-comparison studies could not be used to confirm the cost outcomes reported in the comparison study due to different currencies and years of publications (Table 38).

Table 38: PICO outcomes: Medication costs, endoscopy costs, and hospitalisation costs - trial-based studies

	Study population	Study period	Medication costs within 6 months, 2 years, 5 years, …, lifetime (PPIs)*		Costs of endoscopic investigations		Costs related to hospitalisations	
			Continuous	On-demand	Continuous	On-demand	Continuous	On-demand
Comparison studies on identical PPI and dosage								
Hansen (2005)[63]	Uninvestigated GERD	26 weeks	€223.7 SM €1.9 CCM €0.4 OTC	€146.3 SM €2.7 CCM €0.6 OTC	€7.5	€7.3	No hospitalisations occurred	
Szucs (2009)[40]	Uninvestigated GERD	6 months	CHF509.4 SM CHF7.1 MP CHF0.9 OTC	CHF352.7 SM CHF8.8 MP CHF0.7 OTC	CHF26.1†	CHF33.1†	CHF1.1	CHF61.2
Comparison studies on different PPI and/or dosage								
Cibor (2006)[45]	Endoscopically proven NERD	11 months	PLN151.6	PLN110.2	NR	NR	NR	NR
Tsai (2004)[18]	Endoscopically proven NERD	6 months	£64.71 £84.63**	£37.85	NR	NR	NR	NR
Non-comparison studies continuous PPI								
Kaplan Machilis (2000)[47]	Uninvestigated GERD	6 months	$592	n/a	NR	n/a	Inpatient $7,174 Outpatient $1,198	n/a
Non-comparison studies on-demand PPI								
Meineche-Schmidt (2004)[52]	Uninvestigated GERD	6 months	n/a	€143.7 SM €6.5 MP €0.9 OTC	n/a	NR	n/a	€14.7

Keys: SM = Study Medication, MP = Medication Prescribed, OTC = Over-The-Counter, CCM = Concomitant Medication, NR= Not Reported, n/a = not applicable, GERD = Gastroesophageal Reflux Disease, NERD = Non-Erosive Reflux Disease, FI = Finland, NO = Norway, SE = Sweden, DK = Denmark, CHF = Swiss franc, PLN = Polish zloty

* Medication costs were differentiated into study medication (SM), GERD-related concomitant medication (CCM), GERD-related medication prescribed (MP) and GERD-related over-the-counter medication (OTC), if reported. ** For lansoprazole based on licensed usage (1 capsule per day); † Tests and procedures.

Trial-based studies - Costs of adverse events/side effects, costs of progression to ERD, and other costs

The studies did not report costs of adverse events/side effects and costs of progression to ERD. Other resource use costs, like GP costs and healthcare contact costs were reported in the two comparison studies using identical PPI medication with the same dosage.[40, 63] In both studies, costs for on-demand PPI were slightly lower over the course of the study duration (Table 39).

Table 39: PICO outcomes: Costs of adverse events/side effects, progression costs to ERD, and other costs - trial-based studies

	Study population	Study period	Costs of adverse events/side effects		Costs related to progression to ERD		Other resource use costs (e.g. formal caregiver, general practitioners, etc.)	
			Continuous	On-demand	Continuous	On-demand	Continuous	On-demand
Comparison studies on identical PPI and dosage								
Hansen (2005)[63]	Uninvestigated GERD	26 weeks	NR	NR	NR	NR	€15.3*	€15.0*
Szucs(2009)[40]	Uninvestigated GERD	6 months	NR	NR	NR	NR	CHF39.0 †	CHF38.2†
Comparison studies on different PPI and/or dosage								
Cibor (2006)[45]	Endoscopically proven NERD	11 months	NR	NR	NR	NR	NR	NR
Tsai (2004)[18]	Endoscopically proven NERD	6 months	NR	NR	NR	NR	NR	NR
Non-comparison studies continuous PPI								
Kaplan Machilis (2000)[47]	Uninvestigated GERD	6 months	NR	n/a	NR	n/a	$606§ ($4.7 per person)	n/a
Non-comparison studies on-demand PPI								
Meineche-Schmidt (2004)[52]	Uninvestigated GERD	6 months	n/a	NR	n/a	NR	n/a	€10.2*

Keys: NR= Not Reported, n/a = not applicable, GERD = Gastroesophageal Reflux Disease, NERD = Non-Erosive Reflux Disease, FI = Finland, NO = Norway, SE = Sweden, DK = Denmark, CHF = Swiss franc

* General practitioner costs; † Healthcare contacts; § Includes outpatient physician and urgent care center visits. Costs are per treatment group.

Trial-based studies - Quality adjusted cost comparison and indirect costs

None of the studies reported on the outcome quality adjusted cost comparison. For indirect costs, three studies provided insights on productivity and travel costs; two comparison studies using identical PPI medication with the same dosage[40, 63] and one non-comparison study of on-demand PPI therapy.[45] One of the two comparison studies using identical PPI medication with the same dosage[63] found productivity costs in favour of continuous PPI treatment, and travel costs in favour of on-demand PPI treatment. The other comparison study using identical PPI medication with the same dosage[40] reported only on travel costs, which were found to be lower for continuous PPI therapy.

The non-comparison study on on-demand PPI therapy[52], reported almost 50% lower productivity costs and slightly higher travel costs for on-demand PPI therapy than Hansen et al.[63] reports. The reason of the discrepancy between productivity costs was unclear, since the details of the productivity cost calculations were not presented in those studies. These studies were published one year after each other, the costs in those studies were presented in Euro as currency, the baseline characteristics were similar, although the studies were held in two different Scandinavian countries (Denmark and Norway), and the studies investigated the same PPI therapy, which is 20 mg esomeprazole, on-demand therapy (Table 40).

Table 40: PICO outcomes: Quality adjusted cost comparison, and indirect costs - trial-based studies

	Study population	Study period	Quality adjusted cost comparison after 6 months, 2 years, 5 years, life-time		Productivity costs		Travel costs		Informal caregiver costs	
			Continuous	On-demand	Continuous	On-demand	Continuous	On-demand	Continuous	On-demand
Comparison studies on identical PPI and dosage										
Hansen (2005)[63]	Uninvestigated GERD	26 weeks	NR	NR	€39.0	€42.0	€1.5	€1.2	NR	NR
Szucs(2009)[40]	Uninvestigated GERD	6 months	NR	NR	NR	NR	CHF3.0	CHF3.3	NR	NR
Comparison Studies On Different PPI And/Or Dosage										
Cibor (2006)[45]	Endoscopically investigated NERD	11 months	NR	NR	NR	NR	NR	NR	NR	NR
Tsai (2004)[18]	Endoscopically investigated NERD	6 months	NR	NR	NR	NR	NR	NR	NR	NR
Non-Comparison Studies Continuous PPI										
Kaplan Machilis (2000)[47]	Uninvestigated GERD	6 months	NR	n/a	NR	n/a	NR	n/a	NR	n/a
Non-Comparison Studies On-Demand PPI										
Meineche-Schmidt (2004)[52]	Uninvestigated GERD	6 months	n/a	NR	n/a	€21.0	n/a	€1.7	n/a	€6.9*

Keys: NR= Not Reported, n/a = not applicable, GERD = Gastroesophageal Reflux Disease, NERD = Non-Erosive Reflux Disease, FI = Finland, NO = Norway, SE = Sweden, DK = Denmark, CHF = Swiss franc

* Indirect costs: Costs for travel and visit time.

Trial-based studies - Incremental/total cost

All comparison studies reported lower total costs for on-demand PPI therapy than for continuous PPI therapy [18, 40, 45, 63] (Table 41). Although some studies found higher indirect costs for on-demand PPI therapy, due to higher productivity or travel costs, these costs were balanced out by lower medication costs while calculating the final total costs of the treatment. The non-comparison study of Meineche-Schmidt et al. [52] reports a similar total cost value to the one reported by Hansen et al. [63] for on-demand PPI therapy (€211.4 and 221.5 and, respectively).

Table 41: PICO outcomes: Incremental/total costs - trial-based studies

	Study population	Study period	Direct costs		Indirect costs		Total costs		Incremental costs
			Continuous	On-demand	Continuous	On-demand	Continuous	On-demand	
Comparison studies on identical PPI and dosage									
Hansen (2005)[63]	Uninvestigated GERD	26 weeks	€250.2	€173.2	€45.6	€48.3	€295.8	€221.5	€74.3
Szucs(2009)[40]	Uninvestigated GERD	6 months	CHF583.5*	CHF497.9*	NR	NR	CHF591.4*	CHF502.8*	CHF88.6
Comparison studies on different PPI and/or dosage									
Cibor (2006)[45]	Endoscopically investigated NERD	11 months	PLN151.6	PLN110.2	NR	NR	PLN151.6	PLN110.2	PLN41.4
Tsai (2004)[18]	Endoscopically investigated NERD	6 months	£84.63† £64.71	£37.85	NR	NR	£64.71 £84.63†	£37.85	£26.86 £46.78
Non-comparison studies continuous PPI									
Kaplan Machilis (2000)[47]	Uninvestigated GERD	6 months	$8,371	n/a	NR	n/a	$8,371	n/a	-
Non-comparison studies on-demand PPI									
Meineche-Schmidt (2004)[52]	Uninvestigated GERD	6 months	n/a	€182	n/a	€28	n/a	€211.4	-

Keys: NR= Not Reported, n/a = not applicable, GERD = Gastroesophageal Reflux Disease, NERD = Non-Erosive Reflux Disease, FI = Finland, NO = Norway, SE = Sweden, DK = Denmark, CHF = Swiss franc, PLN = Polish zloty

* Costs were calculated based on Table 6 in Szucs et al 2009; † License usage (1 capsule per day).

Model-based studies – Direct, indirect, and total costs

In all seven model-based studies direct, indirect, and total cost for on-demand PPI treatment were not compared directly to continuous PPI treatment. Costs were therefore compared across studies when the same PPI medication was investigated for both continuous PPI and on-demand PPI therapies.

In three of the non-comparison studies[64, 68, 69] the PPI treatments of omeprazole 10 mg and/or omeprazole 20 mg were studied. Two of these studies were focusing on the on-demand PPI therapy[68, 69] and

one was analysing continuous PPI therapy[64]. Two of the studies[68, 69] reported costs in currency Euro and one study[64] reported costs in Canadian Dollars.

One year of on-demand PPI treatment led to direct cost of €438 for omeprazole 10 mg and €330 for omeprazole 20 mg.[69] For continuous PPI treatment direct costs were $2'394.10 for 5 years of omeprazole 20 mg treatment.[64]

In the first on-demand study, total PPI therapy costs were €554 for omeprazole 10 mg and €438 for omeprazole 20 mg.[69] The second study did not report mean total costs, however the median total costs for omeprazole 10 mg and omeprazole 20 mg from the second study differed by more than 50% in comparison to the mean costs from the first study, investigating PPI on-demand therapy costs[68, 69]. In the study of Hughes et al. [69] total mean costs for omeprazole 10 mg and omeprazole 20 mg were €528 and €412, respectively, whereas Hughes et al. [68] reported total median cost of €210 for omeprazole 10 mg, and €201 for omeprazole 20 mg (Table 42).

Table 42: Direct, indirect, and total costs - model-based studies

Reference	Continuous PPI	On-demand PPI	Time horizon	Mean direct costs (Median)	In CHF 2018**	% indirect costs (mean)	In CHF 2018	Mean medication costs	In CHF 2018**	Mean total costs (Median)	In CHF 2018**
Non-comparison studies on-demand PPI											
Hughes[a] (2005)[69]	n/a	EP 20mg	**1 year**	€326 (€295)	666.31 (602.95)	34% (€152)	(299.78)	NR	-	€447 (€419)	913.62 (856.40)
		LP 15mg		€282 (€249)	576.38 (508.93)	21% (€84)	(165.67)			€398 (€370)	813.47 (756.24)
		PP 20mg		€250 (€223)	510.98 (455.79)	35% (€129)	(254.42)			€368 (€341	752.16 (696.97)
		RP 20 mg		€212 (€181)	433.31 (369.95)	38% (€125)	(246.53)			€329 (€295)	672.44 (602.95)
		OP 10mg		€438 (€405)	895.23 (827.78)	30% (€166)	(327.39)			€554 (€528)	1132.32 (1'079.18)
		OP 20mg		€330 (€297)	674.49 (607.04)	22% (€96)	(189.34)			€438 (€412)	895.23 (842.09)
Hughes[b] (2005)[68]	n/a	EP 20mg	**1 year**	NR (€190)	(398.56)	NR	-	NR	-	NR (€190)	(398.56)
		LP 15mg		NR (€195)	(409.05)					NR (€195)	(409.05)
		PP 20mg		NR (€176)	(369.19)					NR (€176)	(369.19)
		RP 10mg		NR (€123)	(258.01)					NR (€123)	(258.01)
		OP 10mg		NR (€210)	(440.51)					NR (€210)	(440.51)
		OP 20mg		NR (€201)	(421.63)					NR (€201)	(421.63)
Wahlqvist (2002)[70]	n/a	EP 20mg	**6 months**	£63	172.81	NR	-	£44	120.69	£63	172.81
Non-comparison studies continuous PPI											
Bojke (2007)[65]	Different PPIs and doses*	n/a	**30 years**	£4,890[d]	12'464.37	NR	-	NR	-	£4,890[d]	12'464.37

Comay (2008)[64]	OP 20mg	n/a	**5 years**	CA$2'394.10[d]	3'293.63	NR	-	NR	-	CA$2'394.10[d]	3'293.63
Doan (2008)[67]	Standard dose	n/a	**1 year**	$1'053.66†	1'841.61	$442.45†	773.32	NR	-	$1'496.11†	2'614.93
You (2003)[66]	Low-dose PPI	n/a	**1 year**	$1'372	2'441.52	NR	-	NR	-	$1'372	2'441.52
	Standard-dose PPI	n/a	**1 year**	$904	1'608.70	NR	-	NR	-	$904	1'608.70

Keys: d = discounted, EP=Esomeprazole, LP=Lansoprazole, M = Mild, NR = Not Reported, OP=Omeprazole, PP=Pantoprazole, RP=Rabeprazole, r = reported S = Severe, OP1 = Omeprazole 10 mg, OP2 = Omeprazole 20 mg

* An average daily dose was calculated per patient; † The direct costs $21'073'248, indirect costs $8'849'039, and total cost $29'922'287 were based on a population of 100'000 with 20'000 GERD patients. In the table, these costs were re-calculated for the average patient.
** The original costs from the publications were converted to CHF using the rates of the publication year and were inflated to the corresponding end of 2018 CHF values.

Model-based studies - Cost per QALY

The arm-specific cost per QALY values were calculated only for the model-based studies, since none of the trial-based studies reported on QALYs.

Among the model-based studies, Wahlqvist et al.[70], Hughes et al.[68], and Doan et al.[67] were excluded since they did not report on QALYs. In the remaining model-based studies, arm-specific cost per QALY were calculated (both overall as well as per-year values). However, due to different currencies, discounting assumptions, and underlying PPI therapies, no comparison was done between the cost per QALY values of the on-demand and continuous PPI therapy.

The cost per QALY are reported per study arm and patient population (Table 43). For on-demand PPI therapy in NERD patients cost per QALY ranged from €744.15 for rabeprazole (10 mg) to €1'340.54 for omeprazole (10 mg).[69] None of the studies reported QALYs for NERD patients on continuous PPI therapy. Cost per QALY for continuous PPI therapy was found for the mixed population low grade GERD and uninvestigated GERD populations. The cost per QALY ranged from CA$103 for omeprazole 20 mg[64] to $1'374 for low-dose PPI therapies including omeprazole 10 mg and lansoprazole 15 mg. For standard doses of PPI, including omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, and rabeprazole 20 mg, cost per QALY was $905 (Table 43).[66]

Table 43: Comparison of on-demand vs. continuous PPI therapy based on costs per QALY - model-based studies

	Continuous PPI	On-demand PPI	Time horizon	Currency year	Reported QALYs (mean)	Reported total costs (mean)	Cost per QALY		
							Continuous (overall)	On-demand (overall)	Per year**
Endoscopically proven NERD									
Hughes (2005a)[69]	n/a	**EP** 20 mg **LP** 15 mg **PP** 20 mg **RP** 10 mg **OP1** 10 mg **OP2** 20 mg	1 year	NR	**EP** 0.722 **LP** 0.730 **PP** 0.727 **RP** 0.727 **OP1** 0.740 **OP2** 0.729	**EP** €447 **LP** €398 **PP** €368 **RP** €329 **OP1** €554 **OP2** €438	n/a	**EP** €1'071 calculated **LP** €932 calculated **PP** €850 calculated **RP** €744 calculated **OP1** €1'341 calculated **OP2** €1'054 calculated	**EP** €1'071 calculated **LP** €932 calculated **PP** €850 calculated **RP** €744 calculated **OP1** €1'341 calculated **OP2** €1'054 calculated
Mixed population low GRADE GERD and uninvestigated GERD									
Bojke (2007)[65]	Different PPIs and doses*	n/a	30 years	2004	12.36	£4,890[d]	£396 calculated	n/a	£13 calculated
Comay (2008)[64]	**OP** 20 mg	n/a	5 years	2006	4.6357	CA$2,394.10[d]	CA$516.45 reported	n/a	CA$103 calculated
You (2003)[66]	**LD**: OP 10 mg LP 15 mg **SD**: OP 20 mg LP 30 mg PP 40 mg RP 20 mg	n/a	1 year	2003	**LD** 0.998 **SD** 0.999	**LD** $1,372 **SD** $904	**LD** $1'374 reported **SD** $905 reported	n/a	**LD** $1'374 reported **SD** $905 reported

Keys: PPI = Proton-Pump Inhibitor, EP = Esomeprazole, LP = Lansoprazole, PP = Pantoprazole, RP = Rabeprazole, OP = Omeprazole, LD = Low Dose, SD = Standard Dose, n/a = not applicable, NR = Not Reported [d] discounted

* An average daily dose was calculated for each drug and each patient.
** Per year cost per QALY is calculated by dividing the overall cost per QALY (calculated from total costs and total QALYs accumulated over the whole time horizon) to the length of the time horizon.

8.2.4 Findings cost-effectiveness

The PICO outcome for incremental cost-effectiveness ratio (ICER), comparing continuous PPI therapy with on-demand PPI therapy, was not available in any of the identified studies from the cost-effectiveness literature review. Therefore, we conducted a de novo model to estimate the cost-effectiveness of continuous PPI long-term therapy compared to on-demand PPI long-term therapy in the Swiss setting (see section 8.3).

8.2.5 Findings budget impact

From the cost-effectiveness literature review no budget impact analyses were found for the Swiss setting on the comparison of continuous and on-demand PPI therapy. Therefore, a budget impact analysis was conducted for the Swiss setting (see section 8.4).

8.3 De novo cost-effectiveness model

For the de novo cost-effectiveness model a healthcare insurer perspective was taken. As it was not possible to distinguish the amount of per patient deductibles specific to GERD and PPI medications in the current Swiss medical insurance co-payment system, it was assumed that all the GERD related healthcare costs were covered fully by the health insurance in the standard of care, and we focused on the impact of the disinvestment of continuous PPI therapy for the sake of on-demand PPI therapy in the uninvestigated GERD patient population.

The on-demand PPI therapy was operationalised by the reimbursement restriction applied in terms of the number of pills to be paid per year. For the reimbursement restriction, in the base-case, it was assumed that the health insurances in Switzerland would cover for a maximum number of 200 pills per year for uninvestigated GERD or NERD patients using on-demand therapy, and if a patient consumed more than 200 pills per year, the remaining PPIs would be bought out of pocket by the patients. This threshold of 200 pills per year was considered, since it has been shown in the literature that NERD or univestigated GERD patients take in average approximately between 120 to 200 pills per year[1], however different reimbursement restriction levels (i.e. 100 pills per year, 365 pills per year or no restriction) were also considered in the analyses. It was assumed that this change in reimbursement would have no impact on the medication use and clinical effectiveness for the on-demand patients.

In the base-case, it was also assumed that the reimbursement restriction level was applicable to the on-demand PPI therapy patients in all endoscopically uninvestigated states (patients receiving on-demand

PPI therapy both before their first relapse as well as after their first relapse, when they receive on-demand PPI therapy as part of the usual care). Additionally, the reimbursement restriction affected the patients receiving on-demand PPI therapy in the endoscopically investigated NERD state. Different subgroup analyses, for instance when the reimbursement restriction level was applied only to uninvestigated GERD patients before their first relapse is provided in the subgroup analysis section.

8.3.1 Methodology cost-effectiveness model

Model structure

A Markov model has been developed to compare the cost-effectiveness of continuous versus on-demand PPI therapy for the treatment of uninvestigated GERD in Switzerland.

The model was divided into short-term and long-term parts, the short-term part (mainly the first 6 months) focused on the short-term outcomes of the GERD diseases such as the control of the symptoms, or the relapse of the disease or the referral to the endoscopy. On the other hand, the long-term part (after 6 months) of the model focused on the extrapolation of the GERD disease, such as the progression or the regression of the GERD disease stages, or the incidence of Barret's oesophagus. The short-term and the long-term parts of the model used differing sources for populating clinical and cost inputs.

The cycle length of the model was assumed to be one month and the time horizon of the cost-effectiveness model was considered to be lifetime. In both of the models, in all states, the patients were at risk of death, following general population mortality trends.

The structure of the economic model and the overall selection of the input sources were presented to two clinical GERD experts from the Netherlands. The experts agreed that the conceptual model represented the natural history of the disease, validated the structure of the model, and considered the preliminary choice of the inputs as plausible. Their feedback on the structure and on the inputs were incorporated in the economic model. Additionally, after the programming of the model was complete, the black-box model verification tests given in Appendix 15.7 were conducted on the model in line with the recommendations as outlined in the TECH-VER.[73] Conducted verification tests provided results in line with a priori expectations.

In the base-case, only direct health-care related costs were included. The costs and health outcomes were not discounted in the base-case, and standard half-cycle correction was applied.

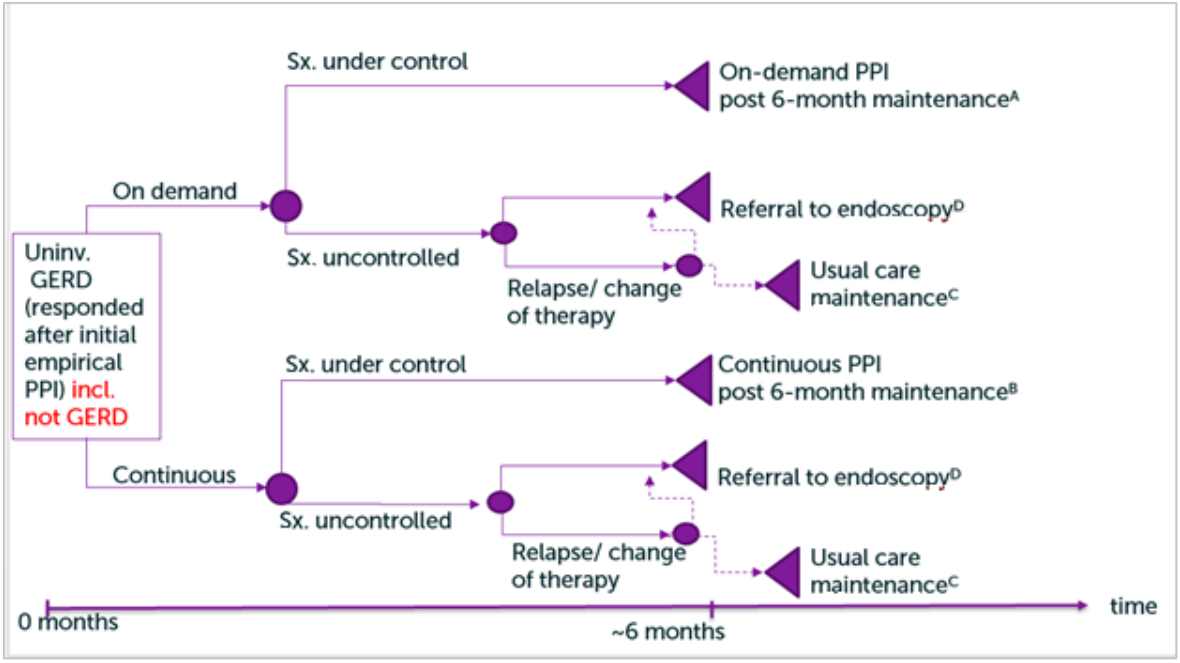
Our economic model is different from the previously published cost-effectiveness models in the sense that it models the natural history of the disease of a GERD patient in his/her lifetime, using robust evidence from RCTs and other long-term disease registries while populating the clinical and cost inputs of the model.

Short-term model

The short-term model is depicted in Figure 4 below. Patients who had responded to their empirical PPI treatment were allocated to either on-demand or continuous PPI therapy arm and they continued receiving their initially allocated treatment as long as their symptoms were under control. After 6 months, if their symptoms were still under control, these patients would enter the long-term model and be in the *post 6-month maintenance* state of their initially allocated *(on-demand or continuous PPI therapy)* treatment arm. The side effects associated with the PPI therapy were incorporated in the short-term and long-term models.

The trajectory when patients' symptoms were uncontrolled (i.e. when patients relapse) was the same in both the short-term and the long-term model. When patients relapsed, they first visited a GP. Afterwards, they either were referred to endoscopy (due to alarm symptoms) or they started receiving high-dose drug therapy for a month (28 days continuous high-dose PPI therapy) and then they visited the GP again. If patients did not respond to the high-dose drug therapy, they were referred to endoscopy and if they responded to the high-dose drug therapy, their dose was re-adjusted and they continued receiving the adjusted drug therapy that had controlled their symptoms (i.e. usual care maintenance).

Figure 4: Short-term model



Keys: incl.= including; PPI = Proton-Pump Inhibitors; Sx = symptoms; Uninv.= uninvestigated
[A, B, C, D] refers to the starting points in the long-term model

In the short-term model, if the patients' symptoms were under control after 6 months with their initially assigned therapies (on-demand or continuous PPI), then they would start the long-term model from "on-demand PPI maintenance" or the "continuous PPI maintenance" therapy states (starting points A and B, respectively). Upon relapse, patients would enter the long-term model (can occur before 6 months), however their starting point in the long term model would be dependent on patient's response on the high-dose drug therapy after relapse. Patients who were directly referred to endoscopy or who did not respond to the high-dose drug therapy after relapse, would enter the long-term model from the *endoscopy* state (starting point D) and patients whose symptoms responded to the high-dose drug therapy after relapse, would enter the long-term model from the *usual-care* maintenance state (starting point C).

Long-term model

The long-term model is depicted in Figure 5 below. The patients could enter the long-term model in one of the following states:

- On-demand PPI maintenance therapy
- Continuous PPI maintenance therapy
- Usual-care PPI maintenance therapy
- Endoscopy

These entering states and the transitions in and out from these states are explained below.

On-demand/continuous PPI maintenance therapy: At each cycle, patients could stay at this state, or they could relapse, or they could taper and eventually discontinue their drug treatment (and therefore would enter the off-treatment state, where they were exposed to a different risk of relapse).

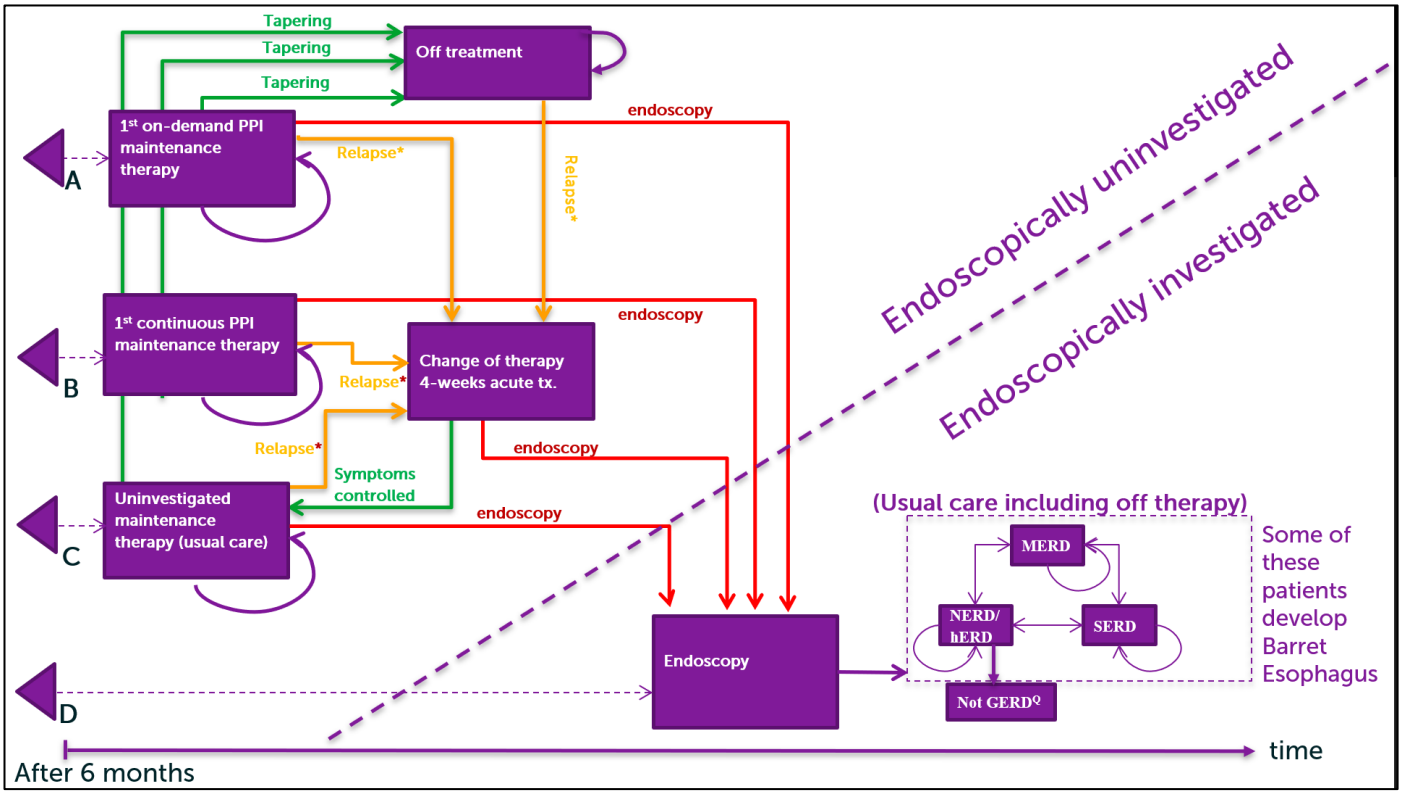
Usual care maintenance therapy: Patients who relapsed from their treatment and who had their symptoms controlled after the high-dose drug therapy (i.e. who showed response to high-dose drug therapy) following that relapse would enter the usual care maintenance state. At each cycle, patients could stay in this state, or they could relapse, or they could taper and eventually discontinue their drug treatment (and therefore would enter the off-treatment state, where they were at a different risk of relapse). Due to the vast number of drug type & dosage forms, for usual care, an umbrella "treatment basket" form was assumed, reflecting the treatment patterns of the uninvestigated GERD population. This umbrella treatment basket was assumed to be formed of on-demand and continuous PPI therapy as well as other GERD medications, such as H_2RA/antacids.

Endoscopy: Patients could enter to the endoscopy state directly after their symptoms deteriorate (with additional alarm symptoms) or upon not responding to the high dose therapy after GP visit due to symptoms' relapse. After the endoscopy, the esophagitis/erosion level of the patients were revealed and the

patients would enter the post-endoscopy states, which are non-erosive/healed reflux disease (NERD/HERD), mildly erosive reflux disease (MERD: LA classification A and B), and severely erosive reflux disease (SERD: LA classification C and D). In addition, the existence of any Barrett's oesophagus would be confirmed by the endoscopy. After endoscopy, patients were assumed to remain in the post-endoscopy states and to have transitions among these post-endoscopy states until the end of the time horizon.

Additionally, some of the NERD patients could be later re-diagnosed as 'not GERD' (e.g. functional dyspepsia or other underlying disease that causes reflux-like symptoms).

Figure 5: Long-term model



Keys: incl.= including; PPI = Proton-Pump Inhibitors; tx = treatment; hERD = healed erosive reflux disease; MERD = mild erosive reflux disease; NERD = non-erosive reflux disease; SERD = severe erosive reflux disease; Not GERD = not gastroesophageal reflux disease (such as functional dyspepsia)

Modelling process

The conceptual model was developed based on the literature and the clinical guidelines, and it was validated by the clinical experts. A draft version of the conceptual model was implemented in Microsoft Excel and Visual Basic for Excel 2013® software. The model was a cohort-based model, and the prognosis of a hypothetical cohort was simulated under on-demand and continuous PPI therapy. The model cohort's baseline characteristics were identical to the baseline characteristics of the patients enrolled in the Szucs et al. study.[40] Heterogeneity (e.g. based on age/sex) was not investigated as subgroup-specific clinical effectiveness data was lacking from the study findings used in populating the model.

Overview of the base-case and sensitivity and scenario analyses

The summary box below outlines the general characteristics of the cost-effectiveness and budget-impact models:

Type of model = Markov

Perspective = health insurance payer

Time horizon = lifetime for cost-effectiveness analysis, 5 years for budget impact analysis

Discounting = Results with 0%, 3% and 6% discounting rates were presented

Year of costs = 2019

Software used = Microsoft Excel®

The list of key base-case assumptions is provided in Section 15.4:

Model inputs

Inputs for the model are divided into the following categories:

- Transition probability inputs
- Cost inputs
- Utility inputs
- Safety inputs

Each of these categories will be explained in following subchapters.

The inputs of the economic model were derived from a variety of sources, which were identified by systematic reviews on the clinical and cost-effectiveness as well as other sources discussed with the clinical experts.

For the short-term model, the most frequently used source was the Szucs et al. study[40], a Swiss study that is based on the largest randomized clinical trial that was conducted on uninvestigated GERD population that compared on-demand and continuous PPI treatment.

Populating the model with synthesized evidence from the clinical effectiveness search results was not possible, since the type and detail of the outcomes from the identified studies in the clinical effectiveness search were varying from each other. None of the publications were reporting necessitated data for the economic model as granular as the Szucs et al. study did.[40]

For the long-term model, the most frequently used sources were the publications associated with the ProGERD study.[74-76] The ProGERD study is a large (n=6'215) prospective multicentre open cohort study conducted in Germany, Austria, and Switzerland and the treatment patterns, resource use/costs, and natural history of the disease were followed from baseline (year 0) to year 5. These studies provided necessitated data for populating most of the post-endoscopy state inputs.

Transition probability inputs

Relapse probabilities (for on-demand and continuous PPI therapy): In the Szucs et al. study[40], 55 (out of 913 patients) and 60 (out of 991 patients) relapses (defined as the need for treatment change) were observed during 6 months, in the continuous and on-demand arms, respectively. These relapses that had been observed within 6 months were transformed to monthly relapse probabilities, assuming that the rate of relapse was constant in time. The relapse rate difference between the continuous and on-demand PPI therapy arms was stated to be "non-significant", however, it was decided to use the treatment-specific relapse rates together with their uncertainty margins in the economic model. Using the same relapse probabilities would have been slightly more in favour of the on-demand PPI therapy.

Response probability of high-dose drug therapy: The overall response probability of high-dose drug therapy was assumed to be 71.2%, which was obtained from a prospective study, Heading et al.[77], which reported that 1'344 out of 1'888 patients achieved symptom response after receiving high dose (40 mg) pantoprazole between 4 to 8 weeks.

Direct endoscopy probabilities (for on-demand and continuous PPI therapy): In the Szucs et al. study[40], 28 patients in each arm (continuous and on-demand PPI) were referred to endoscopy. However, in the study, it was not mentioned how many among these 28 patients were referred to endoscopy directly, before a high dose drug therapy was initiated. Therefore, we derived the direct endoscopy referrals (before high dose therapy) from the total number of endoscopies from the equations below, for each treatment arm.

total endoscopy # = direct endoscopy # before high dose drug therapy + endoscopy # after high dose drug therapy

total endoscopy # = direct endoscopy # before high dose drug therapy + # relapse * (probability of no response after high dose drug therapy)

direct endoscopy # before high dose drug therapy = total endoscopy # - # relapse * (probability of no response after high dose drug therapy)

From these equations, the number of direct endoscopy referrals could be estimated as 12 (out of 926 patients) and 11 (out of 991 patients) during 6 months, in continuous and on-demand PPI treatment

arms, respectively. These endoscopy numbers observed within 6 months were transformed to monthly endoscopy probabilities, assuming constant rate in time.

Probability of endoscopy outcomes: The probability of possible endoscopy outcomes in terms of the esophagitis/erosion levels (i.e. NERD/HERD, MERD, or SERD) were derived from the Zagari et al. study[78], which is a population based study that was conducted in Italy. The probabilities for possible endoscopy outcomes for GERD patients with reflux symptoms (after they stop GERD medication) were calculated from the number of patients reported in the article (p.1'356-1'357, from Zagari et al.[78]). These calculated probabilities for possible endoscopy outcomes, also represented the underlying esophagitis/erosion level of any uninvestigated GERD patient, at any point in time, in the economic model.

Probability of going off-treatment (for on-demand and continuous PPI therapy): The probability of going off-treatment (defined as PPI remission) from on-demand and continuous PPI therapy was calculated from the Nocon et al. study.[75] This study focused on the long-term pattern of GERD medication use in GERD patients receiving routine care. The medication patterns from year 1 to year 4 from the ProGERD study were analysed for each medication type (continuous PPI, on-demand PPI, other medication, and no medication) as well as for each esophagitis level (NERD/HERD, MERD, SERD). In Nocon et al. (p. 719, Table 2)[75] the number of patients who were having on-demand/continuous PPI treatment at year 1 and among those, the number of patients who went off-treatment at year 4 were presented for each esophagitis/erosion level. From these numbers in the paper, the monthly probability of going from on-demand/continuous PPI treatment to off-treatment could be derived by using the endoscopy outcome probabilities from Zagari et al.[78], assuming constant rate in time.

Transition among post-endoscopy states: After the endoscopy, the esophagitis/erosion level (if any) of the patients were revealed. The transitions among the post-endoscopy states were derived from Malfertheiner et al. (p.158, Table 2)[76], which reported the grade of esophagitis/erosion level of the enrolled patients in the ProGERD study at baseline, year 2 and year 5. From these observed transitions, monthly transition probability matrices were obtained for years 0-2 and years 2-5 (using linear algebra methods such as eigenvalue decomposition)[j]. These transition probability matrices obtained from ProGERD study were used to inform the model for post-endoscopy state transitions.

[j] The details of the Eigenvalue decomposition is provided in the Appendix 15.6

Probability of developing Barrett's oesophagus: The probability of developing Barrett's oesophagus (BE) was also derived from the five year BE incidences reported in the Malfertheiner et al. study[76]. These five year (BE) probabilities (p.161, Table 3) specific to different esophagitis/erosion levels were used in the model calibration, so that the model, with the calibrated BE probability inputs, generated the same overall BE probability as the figure from the study, after five years.

Probability of not having acid reflux among newly diagnosed NERD patients: The probability of not having acid reflux among newly diagnosed NERD patients were obtained from Savarino et al.[79], where the 200 patients with typical reflux symptoms and negative endoscopy results underwent impedance-pH monitoring while off proton pump inhibitor treatment. Among 200 NERD patients, from the pH-monitoring results, it was detected that 54 (27%) of these patients were actually not having acid reflux (hence having functional dyspepsia).

Probabilities associated with usual care and off-treatment states: In the model, it was assumed that usual care could be represented by the different GERD medication types observed in the ProGERD study, which were continuous PPI therapy, on-demand PPI therapy and other GERD medications (assumed 75% H_2RA and 25% antacids, in line with ProGERD as discussed in Nocon et. al[75]). Note that the patients who received no medication in the ProGERD study were considered to be in the "off-treatment" state in the model and hence were excluded from the 'usual care' state.

Treatment distributions in the usual care: For calculating the oesophagitis/erosion level specific usual care treatment distributions, the re-weighted percentages of the observed medication types for each oesophagitis/erosion level were derived from the year-specific GERD medication intake percentages for NERD/HERD, MERD, and SERD patients as given in Nocon et al.[75] (p.718, Figure 2). Note that in the usual care state, it was assumed that the distribution of the oesophagitis/erosion levels of the patients would be same as the distribution observed in Zagari et al.[78].

Relapse probability during usual care: The conditional 4-year relapse rates (given an oesophagitis level and a medication type) were calculated using the data presented in Nocon et al.[75] (p. 719, Table 2). The overall monthly relapse probability during usual care was calculated by scaling the weighted sum of these conditional 4-year relapse rates, taking the endoscopy outcome probabilities from Zagari et al.[78] and the usual care treatment distribution percentages from Nocon et al.[75] into account. The equation below demonstrates the derivation of the overall relapse rate during the usual care.

P(relapse during usual care) =

P(NERD)*P(PPI continuous|NERD)*P(relapse|PPI continuous, NERD) + P(NERD)*P(PPI on-demand|NERD)*P(relapse|PPI on-demand, NERD)+ P(NERD)*P(other|NERD)*P(relapse|other, NERD)+

P(MERD)*P(PPI continuous|MERD)*P(relapse|PPI continuous, MERD) + P(MERD)*P(PPI on-demand|MERD)*P(relapse|PPI on-demand, MERD)+ P(MERD)*P(other|MERD)*P(relapse|other, MERD)+

P(SERD)*P(PPI continuous|SERD)*P(relapse|PPI continuous, SERD) + P(SERD)*P(PPI on-demand|SERD)*P(relapse|PPI on-demand, SERD)+ P(SERD)*P(other|SERD)*P(relapse|other, SERD)

Relapse during off-treatment: The oesophagitis/erosion level specific relapse rates for patients during off-treatment period (i.e. when patients do not receive GERD medication) was also derived from the data presented in Nocon et al.[75] (p. 719, Table 2). From these conditional four-year relapse rates, overall monthly relapse probability under no GERD therapy was calculated by taking the weighted average of these conditional relapse rates according to the underlying oesophagitis levels. Based on the discussions with the clinical experts, it was further assumed that the patients who were off-treatment would not be directly referred to the endoscopy but would first undergo a high-dose drug therapy upon relapse.

P(relapse during off treatment) =

P(NERD) *P(off treatment & relapse|NERD) + P(MERD) *P(off treatment & relapse|MERD) + P(SERD) *P(off treatment & relapse|SERD)

Probability of going off-treatment from usual care: A similar approach was followed to obtain the probabilities to go off-treatment from the usual care state. Underlying oesophagitis level and medication type specific, conditional 4-year going off-treatment rates were calculated using the data presented in Table 2 from Nocon et al.[75] From these conditional 4-year rates, overall monthly going off-treatment probability under usual care was calculated by taking the weighted average of these conditional 4-year rates and rescaling the rate to the monthly probability.

P(off-tx under usual care) =

P(NERD)*P(PPI continuous|NERD)*P(off-tx |PPI continuous, NERD) + P(NERD)*P(PPI on-demand|NERD)*P(off-tx |PPI on-demand, NERD)+ P(NERD)*P(other|NERD)*P(off-tx |other, NERD)+

P(MERD)*P(PPI continuous|MERD)*P(off-tx |PPI continuous, MERD) + P(MERD)*P(PPI on-demand|MERD)*P(off-tx |PPI on-demand, MERD)+ P(MERD)*P(other|MERD)*P(off-tx |other, MERD)+

P(SERD)*P(PPI continuous|SERD)*P(off-tx |PPI continuous, SERD) + P(SERD)*P(PPI on-demand|SERD)*P(off-tx |PPI on-demand, SERD)+ P(SERD)*P(other|SERD)*P(off-tx |other, SERD)

Direct endoscopy probability during usual care: Oesophagitis/erosion level and medication type specific, conditional 4-year direct endoscopy rates were calculated using the treatment type distributions per oesophagitis/erosion level. The direct endoscopy rate was then assumed to be contingent solely on the treatment type. For on-demand and continuous PPI treatment, these direct endoscopy probabilities were already calculated based on the numbers observed in the Szucs et al. study[40]. For other GERD medication, the treatment specific direct endoscopy rate was assumed to be the arithmetic average of the on-demand and continuous PPI direct endoscopy rates. The overall monthly direct endoscopy probability under usual care was calculated by taking the weighted average of these conditional rates according to the underlying medication types and oesophagitis/erosion level.

P(direct endoscopy during usual care) =

P(NERD)*P(PPI continuous|NERD)*P(direct endoscopy |PPI continuous, NERD) +
P(NERD)*P(PPI on-demand|NERD)*P(direct endoscopy |PPI on-demand, NERD)+
P(NERD)*P(other|NERD)*P(direct endoscopy |other, NERD) +

P(MERD)*P(PPI continuous|MERD)*P(direct endoscopy |PPI continuous, MERD) +
P(MERD)*P(PPI on-demand|MERD)*P(direct endoscopy |PPI on-demand, MERD)+
P(MERD)*P(other|MERD)*P(direct endoscopy |other, MERD) +

P(SERD)*P(PPI continuous|SERD)*P(direct endoscopy |PPI continuous, SERD) + P(SERD)*P(PPI on-demand|SERD)*P(direct endoscopy |PPI on-demand, SERD)+ P(SERD)*P(other|SERD)*P(direct endoscopy |other, SERD)

Mortality: It was assumed that the patients in the model, in all states, were subject to a mortality risk identical to the general Swiss population. The age and gender specific mortality risks (based on the baseline characteristics of the Szucs et al. trial[40], baseline age of 55 and baseline sex ratio of male to female patient numbers is one) were derived from the WHO 2016 database, based on the 2008-2013 data from the Swiss Federal Statistical Office.[80]

A list of the model inputs used for transition probabilities is given in Appendix 15.4.

Cost Inputs

Monthly drug acquisition costs

Drug acquisition costs were calculated for each state, by multiplying the per pill drug acquisition costs with average per month drug use (number of pills) for each type of GERD medication used. Below, we explain how the per pill drug acquisition costs were calculated for the different GERD medication types used (i.e. regular dose PPIs, high-dose GERD medication and H2RAs/ antacids). Note that other formulations than tablet form were not taken into consideration (e.g. liquid or other IV formulations).

Per pill drug acquisition costs

Per pill drug acquisition costs were calculated from the yearly market sales data for all types of PPI/ H_2RA and antacid brand/package formulations available in Switzerland (including generic formulations), obtained from Tarifpool: © SASIS AG.[29] These sales data were not disaggregated according to the

indication (since these drugs are indicated for other diseases than GERD, such as ulcer). Therefore, we assumed that overall sales pattern would represent the GERD-specific sales pattern for these drugs.

For each formulation (i.e. in terms of the active substance and dosage) and for each brand, the package size (in terms of pill number), annual sales data in terms of CHF and number of packages (2018) were available from Tarifpool: © SASIS AG.[29]

From these detailed level data for each formulation/brand combination, formulation-specific per pill drug acquisition costs and market shares were calculated. Afterwards, overall per pill drug acquisition costs were calculated by taking the weighted average of formulation-specific costs according to their market shares. The formulae used in the calculation of the per pill drug acquisition costs, which were applied to each medication type, are provided below.

i = formulation i, j = brand j

tablets sold (i,j) = sales in packages (i,j)*package size (i,j)

per pill price (i,j) = sales in CHF(i,j) /# tablets sold (i,j)

$$\#\text{ tablets sold (i)} = \sum_j \#\text{ tablets sold (i, j)}$$

$$\#\text{ sales in CHF(i)} = \sum_j \text{sales in CHF(i, j)}$$

per pill price (i) = sales in CHF(i) /# tablets sold (i)

$$\text{market share (i)} = \text{tablets sold (i)} / \sum_i \text{tablets sold (i)}$$

$$\text{per pill price} = \sum_i \text{per pill price (i)} * \text{market share (i)}$$

Overall and for each formulation per pill drug acquisition costs and market shares for regular-dose PPIs are given in Table 91 in Appendix 15.4.

For high-dose drug therapy, which was applied after relapse, it was assumed that the highest dose of each PPI active substance was used. Hence, per pill drug acquisition cost for high-dose drug therapy included only the market share and price per pill from dexlansoprazolum 60 mg, esomeprazolum 40 mg, lansoprazolum 30 mg, omeprazolum 40 mg, pantoprazolum 40 mg, and rabeprazolum 20 mg. The resulting re-weighted market shares and overall per pill drug acquisition costs for the high-dose drug therapy are given in Table 92 in Appendix 15.4.

For H_2RAs and antacids, overall and for each formulation per pill drug acquisition costs and market shares are given in Table 93 and Table 94, respectively (Appendix 15.4).

Drug use per month

Drug use per month for continuous PPI therapy and on-demand PPI therapy were obtained from the Szucs et al study.[40] In that study (p. 279, Figure 2), the distribution of patients according to the number of PPI tablets taken per day during the maintenance phase (6 months) was plotted for both on-demand and continuous PPI therapy arms. The specific values from this plot were digitally extracted for both on-demand and continuous PPI therapy arms. From these extracted values, the distribution of the patients in both on-demand and continuous PPI therapy arms across different per day tablet use levels was obtained as given in Table 95 in Appendix 15.4.

From these distributions, pseudo patient level data was generated for both continuous PPI therapy and on-demand PPI therapy arms, assuming that each generated patient would consume exactly the mid-point of the corresponding tablet range. After the pseudo-level patient generation, the empirical distribution of the pill use per day could be calculated. From this distribution, average PPI drug use per month for both arms as well as the estimated payer spending for PPI acquisition under a given reimbursement restriction level, and the resulting out of pocket payments for the on-demand PPI therapy arm could be derived.

It was assumed that the resource use in the Szucs et. al. 2009[40] open-label trial reflected the real world resource use in the Swiss clinical setting. In Szucs et al. 2009[40], the authors stated that the average PPI usage of the on-demand patients in their trial was higher than the average PPI usage from another trial investigating on-demand PPI therapy (Talley et al. 2002).[56] The authors considered that this overestimation could be due to the differences in drug dispensation (i.e. in the Szucs et al[40], patients could receive the whole supply (200 tablets) at randomization), differences between drug consumption assessment (e.g. in Szucs et al.[40] tablets not returned were counted as consumed) and differences between trial populations (Szucs et al. study[40] focused on the uninvestigated GERD population, whereas the other study analysed the NERD population). For the purpose of this HTA, the settings of the Szucs et al. trial[40] (and the drug dispensation) were considered to be reflective of the clinical practice and the planned implementation of the on-demand PPI therapy in Switzerland.

For both H_2RA and antacids, it was assumed that patients would receive one pill per day. Based on these calculations, the monthly drug acquisition costs for on-demand PPI therapy, continuous PPI therapy, other continuous GERD medication therapy and high dose medication therapy (upon relapse) were calculated as given in Table 44 below.

Table 44: Average drug acquisition costs in CHF per month per patient for different therapies

Average on-demand PPI drug cost per month (payer +out of pocket)	**13.07**
Average continuous PPI drug cost per month	**19.08**
Average cost other GERD medication drugs	**14.04**
Average high dose medication costs per month	**22.36**
Average pill consumption per day in the continuous PPI arm	**0.95**
Average pill consumption per day in the on-demand PPI arm	**0.65**

Drug acquisition costs under usual care: The monthly drug acquisition costs under usual care were calculated from a similar formula used while calculating usual-care state specific transition probability inputs as explained above. It was assumed that there were no drug acquisition related costs associated with patients in the "off-treatment" state and patients who were re-diagnosed as having non-acid reflux.

Average monthly drug acquisition costs under usual care =

P(NERD)*P(PPI continuous|NERD)* Average monthly drug acquisition costs under continuous PPI + P(NERD)*P(PPI on-demand|NERD)* Average monthly drug acquisition costs under on-demand PPI + P(NERD)*P(other|NERD)* Average monthly drug acquisition costs under other GERD medication +

P(MERD)*P(PPI continuous|MERD)* Average monthly drug acquisition costs under continuous PPI + P(MERD)*P(PPI on-demand|MERD)* Average monthly drug acquisition costs under on-demand PPI + P(MERD)*P(other|MERD)* Average monthly drug acquisition costs under other GERD medication +

P(SERD)*P(PPI continuous|SERD)* Average monthly drug acquisition costs under continuous PPI + P(SERD)*P(PPI on-demand|SERD)* Average monthly drug acquisition costs under on-demand PPI + P(SERD)*P(other|SERD)* Average monthly drug acquisition costs under other GERD medication

Other healthcare resource use costs:

Resource use frequency under continuous and on-demand PPI therapy for pre-endoscopy states:

In Szucs et al.[40], 6-month resource use under continuous and on-demand PPI therapy were reported (p. 278, Table 4). These 6-month resource use figures were transformed into monthly resource use frequency per patient. The resulting resource use frequency values for on-demand PPI therapy and continuous PPI therapy are given in Table 45 below.

Table 45: Monthly resource use frequencies for on-demand PPI and continuous PPI therapy

Resource use type	Frequency in 1 month for on-demand PPI	Frequency in 1 month for continuous PPI
Clinician visit	0.0725	0.0696
Telephone	0.0229	0.0243
Specialist visit	0.0040	0.0031
Hospital admission (all types)	0.0005	0.0004
Helicobacter Pylori test	0.0037	0.0033

It was assumed that the monthly resource use frequency under other GERD medication would be equal to the average of the on-demand PPI therapy and continuous PPI therapy monthly resource use frequency values.

Unit cost for resource use in pre-endoscopy states

The unit resource use cost for endoscopy and telephone contact were retrieved from the Swiss Federal Statistical Office and the Swiss standard rates for outpatient medical services (Tarmed) reported in the Szucs et al. study.[40]

The doctor visit (specialist and primary care) unit costs were also retrieved from Tarmed, reported in the Matter-Walstra et al. study.[81] The stated unit costs were adjusted for inflation to 2018 prices, using inflation rates from the Swiss Federal Statistical Office, accessed from the OECD website.[k]

[k] https://data.oecd.org/

It was assumed that upon hospital admission, a patients' length of stay would be equal to 4.5 days. This value was taken from hospital specific hospital cost declarations obtained from Swiss DRG specific database records.[82] Similarly, per day hospital stay cost was calculated by dividing average hospital cost per patient (for patients who are coded for gastroscopy or endoscopic anti-reflux procedure) with the average length of stay from Swiss DRG specific database records. For Helicobacter Pylori tests, the unit cost was calculated from the weighted average of the unit costs of different type of tests (i.e. urease test, breath test, bacteria culture negative/positive tests, and stool test), where the weights were based on the number of the test analyses conducted between 2012-2017.[83]

The resulting unit costs for resource use are given as below in Table 46.

Table 46: Unit resource use costs in CHF

Resource use type	Costs
Endoscopy	569.46
Primary care visit	165.70
Telephone contact	27.39
Specialist visit	165.70
Hospital per day	1'566.84
Helicobacter pylori test	70.49

After these unit costs were multiplied with the corresponding health care unit resource use (HCRU) frequency values, their sum would give the monthly HCRU costs for each of the treatment types (on-demand, continuous PPI and other GERD medication therapy) analysed.

The HCRU costs corresponding to the usual care state were calculated in a similar way to the other usual care related calculations.

Average monthly HCRU costs under usual care =

P(NERD)*P(PPI continuous|NERD)* Average monthly HCRU costs under continuous PPI +
P(NERD)*P(PPI on-demand|NERD)* Average monthly HCRU costs under on-demand PPI +
P(NERD)*P(other|NERD)* Average monthly HCRU costs under other GERD medication +

P(MERD)*P(PPI continuous|MERD)* Average monthly HCRU costs under continuous PPI +
P(MERD)*P(PPI on-demand|MERD)* Average monthly HCRU costs under on-demand PPI +
P(MERD)*P(other|MERD)* Average monthly HCRU costs under other GERD medication +

P(SERD)*P(PPI continuous|SERD)* Average monthly HCRU costs under continuous PPI +
P(SERD)*P(PPI on-demand|SERD)* Average monthly HCRU costs under on-demand PPI +
P(SERD)*P(other|SERD)* Average monthly HCRU costs under other GERD medication

Health-care resource use costs associated with other model states

In the relapse state, it was assumed that the patient would visit the GP twice (once at the beginning and once at the end of the high-dose drug therapy). In the direct endoscopy state, unit endoscopy cost from Table 46 was assigned.

For the post-endoscopy GERD states, the annual HCRU costs were directly taken from Willich et al[74] (p. 373, Table 3), which is a cost-of-disease analysis, conducted on the patients enrolled in the ProGERD study. The HCRU annual costs provided in the paper (in Euros) were first translated to monthly costs and then they were transformed to CHF using the 2005 exchange rates from the purchasing power parity adjusted exchange rates list from the OECD database.[84] Afterwards, the inflation adjustment was conducted using the rates from the Swiss Federal Statistical Office.[85] It was also assumed that patients who were diagnosed to have Barrett's oesophagus would have additional HCRU costs, which were derived as well from Willich et al.[74]. The resulting monthly HCRU costs for the post-endoscopy states are given in Table 96 in the Appendix 15.4.

For the patients who are diagnosed as not acid reflux patients, it was assumed that the HCRU costs would be the same as for the NERD patients, however, an additional expected one-off cost for pH-manometry was assigned before they enter that state. The unit cost for pH-manometry was sourced from Ho et al.[86] (800 Pounds), converted to CHF and inflation adjusted. This unit cost was multiplied by the lifetime probability of pH-manometry for non-acid reflux patients, calculated from the six-month pH-

recording number from the continuous PPI therapy arm and the total number of patients in the trial, extrapolated to lifetime, using the median remaining lifetime estimate of 30 years.

Utility Inputs

The baseline utility value for GERD patients adopted in the model was assumed to be the general French speaking Swiss population utility for age band 50 to 55 years, estimated from the regression coefficient estimates from the Perneger et al. study[87], given in Table 47 below. Each year, the utility values of the GERD patients were adjusted according to the age of the cohort.

Table 47: Age-related utility adjustments

Covariate	Coefficient
Sex (0 for male, 1 for female)	0.0209
Age	-0.00008
Age^2	-0.00002
Constant	0.90222

The relapse in the model was assumed to cause a utility decrement of 0.1, which was deduced from the one year utility value change from the baseline of the medication therapy arm of the Goeree et al. study (p.269, Figure 1).[88] This study compared the impact of symptom resolution of symptomatic GERD patients, which were either treated with PPI therapy or had a fundoplication surgery. The utility decrement for relapse state was applied during the whole cycle length (1 month).

Additionally, it was assumed that endoscopy would have an impact on patients HRQoL. No established value could be found from the literature for the disutility associated with endoscopy, however it is assumed that endoscopy would cause patients increased worry and therefore would increase patients' anxiety/depression. Therefore, it was assumed that the decrements were associated with anxiety and depression domain in the UK EQ-5D-5L value set.[89] The average decrement for a one level increase in anxiety and depression was 0.072 (note that the average decrement for losing one level of any item is 0.064). These utility decrements were applied only for one cycle.

Safety Inputs

In the base-case, additional utility decrements and costs associated with PPI related adverse events were not included in the economic model. This was based on the fact that the healthcare resource use estimates from the Szucs et al. study[40] included all healthcare resource use, and additional inclusion of the adverse event associated costs would lead to double-counting. Furthermore, in Szucs et al.[40] and in all other RCTs that compared on-demand and continuous PPI therapy, no established, clinically relevant difference in adverse events were observed.

Cost-effectiveness analysis results

The deterministic results of the cost-effectiveness analysis in the base-case will include total costs, life years and QALYs pertaining to on-demand and continuous PPI therapy as well as the incremental costs, life years, QALYs and ICER, under the base-case assumptions. In addition to these, disaggregated costs according to different disease states/ cost types and the accrued out-of pocket costs in a patient's lifetime under on-demand therapy are also provided in Section 8.3.2.

Probabilistic sensitivity analysis

Given the parametric uncertainty surrounding the input parameters utilised in the model, probabilistic sensitivity analysis (PSA), consisting of 1'000 iterations was run to test parameter uncertainty within the model. All parameters except drug prices and discount rates were included in the PSA. As is standard practice, appropriate distributions were fitted to the included parameters. Beta distributions were used for probabilities, proportions, risks and utilities, gamma distributions for costs, Dirichlet distribution for multinomial/ categorical outcomes such as the post-endoscopy transition probabilities. Where standard errors were unknown, they were estimated as 20% of the mean value. For daily intake of the PPI, these values were bootstrapped replicating the daily intake of PPI medication as observed in the Szucs et al. trial.[40] The details of the distributions used in the PSA sampling are provided in Appendix 15.4.

The mean results from the PSA iterations, cost-effectiveness scatter plots and the cost-effectiveness acceptability curves are presented in Section 8.3.2.

One-way sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted by variating the upper and lower bounds (based on the 95% confidence intervals, calculated from the distributions used while sampling for iterations in the PSA) sequentially for all model input parameters (all parameters sampled in the PSA, except for the multinomial ones) one by one, keeping others constant at their base-case values. Since the ICER values are extremely high due to the negligible QALY difference, we conducted the one-way sensitivity analysis on incremental costs and on incremental QALYs, separately. The results of these OWSAs are presented in the form of tornado diagrams, showing the top ten influential parameters on incremental results for costs and QALYs in Section 8.3.2.

Scenario analyses

In order to explore the impact of structural and methodological uncertainty on the cost-effectiveness results, the following scenario/subgroup analyses were conducted.

- Different time horizons (6 months, 2 years, and 5 years)
- Different discount rates (3% and 6% for both cost and health outcomes)
- Different reimbursement restriction levels (no restriction on the pills reimbursed, max 365 pills per year reimbursed, 100 pills per year reimbursed)
- Adjusting for treatment switching from on-demand to continuous PPI treatment
- Short-term, one-year cost-effectiveness model (cost per relapse free, pre-endoscopy days)
- Reimbursement restriction affecting only uninvestigated GERD patients before their first relapse.

The details and the results of the scenario analyses are presented separately for each of the scenario listed above in Section 8.3.2.

8.3.2 Results de novo cost-effectiveness analysis

Base-case results

Below we present the total costs, life years, and QALYs for both continuous PPI therapy and on-demand PPI therapy for the base-case analysis with the reimbursement level restriction of 200 pills per year. In the base-case (lifetime, no discounting) incremental QALYs are negligible (0.0005) and incremental costs are 896 CHF. The corresponding ICER, due to the extremely small QALY difference, is 1’694’104 CHF per QALY gained for continuous PPI compared to on-demand PPI therapy (Table 48).

Table 48: Base-case cost-effectiveness results

Technologies	Total costs (CHF)	Total LYG	Total QALYs	Incremental costs (CHF)	Incremental LYG	Incremental QALYs	ICER (CHF) versus baseline (QALYs)
On-demand PPI	8'613	29.35	23.58				
Continuous PPI	9'508	29.35	23.58	896	0.0000	0.0005	1'694'104

Disaggregated costs

Disaggregated results (in terms of costs) from the base-case analysis are given in Table 49 below. Post-endoscopy related medication and other HCRU (e.g. GP visits, hospitalisation) costs are the biggest components, however they hardly have an impact on the incremental costs.

As expected, incremental costs between continuous PPI and on-demand PPI therapy is mostly due to the difference in medication costs until the first relapse (attributes to almost 75% of the total difference). Other cost components are similar in both arms. The reimbursement restriction (200 pills per year) would lead to an average additional lifetime out of pocket payment for medication acquisition costs of around 379 CHF for on-demand PPI therapy per patient. Note that the majority (around 60%) of this out-of-pocket PPI medication spending is made in the 'on-demand PPI' states, before the first relapse, and the remaining out of pocket spending is accrued in the states after the first relapse, namely during the on-demand PPI therapy in the "usual care" states before endoscopy and in the suspected NERD states after the endoscopy.

Table 49: Disaggregated costs in CHF

Health state	Cost on-de-mand PPI	Cost continuous PPI	Increment
Medication costs – until first re-lapse	496.1	1173.4	677.3
Other health care resource use (HCRU) costs-until first relapse	933.4	953.8	20.4
Medication costs- relapse	42.7	41.1	-1.6
Other HCRU costs- relapse	316.1	304.4	-11.7
Medication costs- usual care pre-endoscopy	875.0	916.3	41.3
Other HCRU costs -usual care pre-endoscopy states	952.0	917.6	-34.5
Endoscopy state costs	195.9	198.4	2.5
Medication costs – post-endos-copy	1635.2	1763.3	128.0
Other HCRU costs-post-endos-copy	3027.9	3098.4	70.5
Other costs (Barrett's oesopha-gus)	138.3	141.6	3.3

Indirect costs	0.0	0.0	0.0
Total	8612.6	9508.2	895.6
Average out of pocket costs	379.3	0.0	-379.3
Average lifetime out of pocket costs for those who consume more PPIs than the reimbursement restriction	613.8	0.0	-613.8

Sensitivity and Scenario Analyses

Probabilistic Sensitivity Analysis

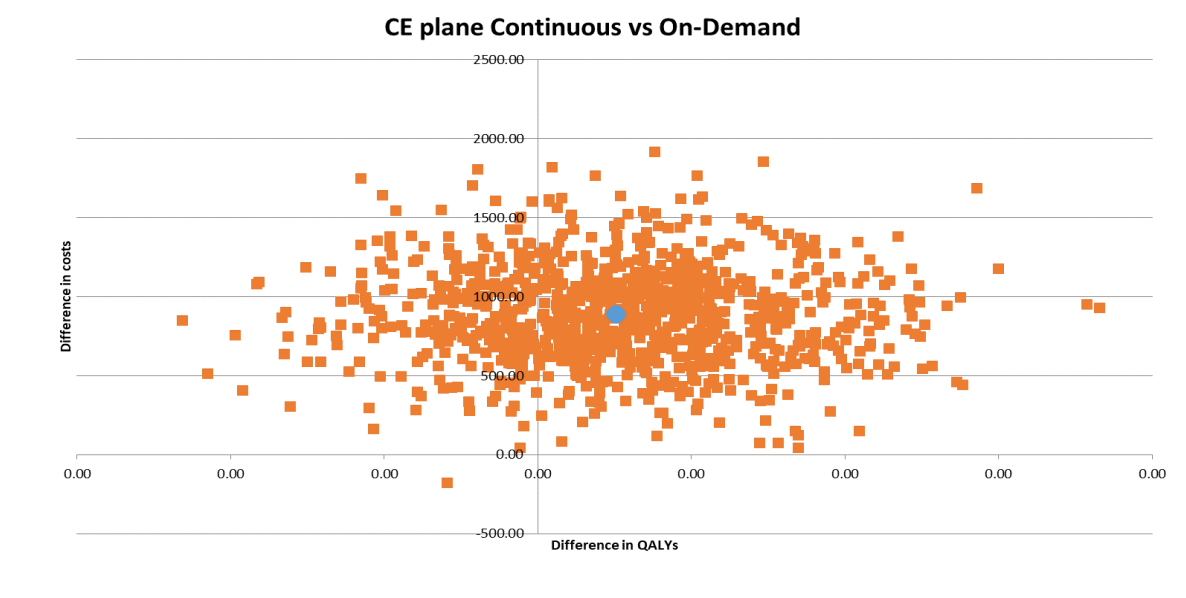
Cost-effectiveness scatter plots and cost-effectiveness acceptability curves (CEAC) are provided to examine the uncertainty related to the decision (Figure 6 and Figure 7). The mean cost-effectiveness results according to the PSA results are provided in Table 50.

Table 50: **Cost-effectiveness results, PSA mean results**

Technologies	Total costs (CHF)	Total LYG	Total QALYs	Incremental costs (CHF)	Incremental LYG	Incremental QALYs	ICER (CHF) versus baseline (QALYs)
On-demand PPI	8'588	29.35	23.58				
Continuous PPI	9'478	29.35	23.58	890	0.0000	0.0005	1'730'570

From Table 50, it can be seen that mean incremental QALYs from continuous PPI therapy are negligible (0.0005). Mean incremental costs are 890 CHF. The resulting probabilistic ICER from 1’000 iterations is 1’730’570 CHF per QALY gained (comparable to the deterministic, base-case ICER of 1’694’104 CHF per QALY gained).

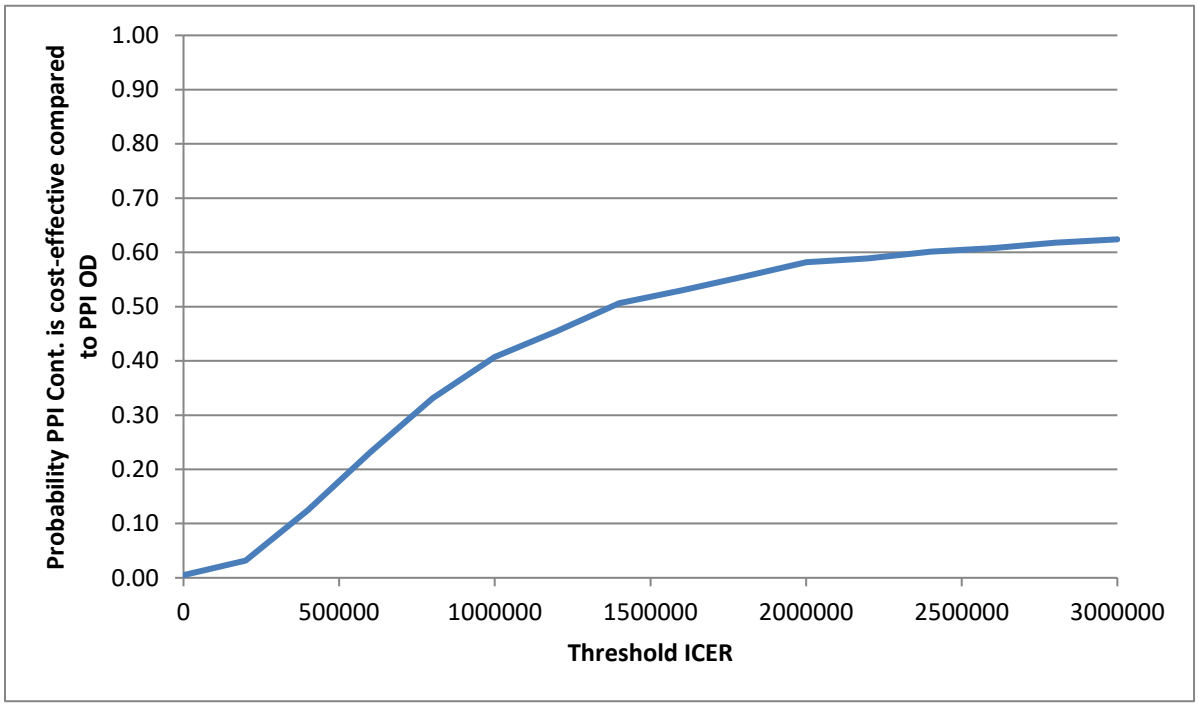
Figure 6: Cost-effectiveness Scatter Plot (base-case, discounting rate = 0%)



The scatterplot cloud from the PSA iterations is spread mostly in the northeast and northwest quadrants of the cost-effectiveness plane (Figure 6). Almost in all iterations, continuous PPI therapy led to a higher cost, however, there is a substantial proportion of iterations where on-demand PPI therapy led to higher QALYs than continuous PPI therapy. Nevertheless, the QALY differences in all iterations were negligible.

Due to the negligible QALY difference, and that some of the iterations yielded a negative QALY gain for continuous PPI therapy, the CEAC curve does not approximate to 1, even under extremely high willingness to pay thresholds (e.g. 3'000'000 CHF per QALY gained). The probability that continuous PPI therapy is cost-effective against on-demand is around 18%, 40%, 55%, and 62% for 500'000 CHF, 1'000'000 CHF, 2'000'000 CHF, and 3'000'000 CHF per QALY gained thresholds, respectively (Figure 7).

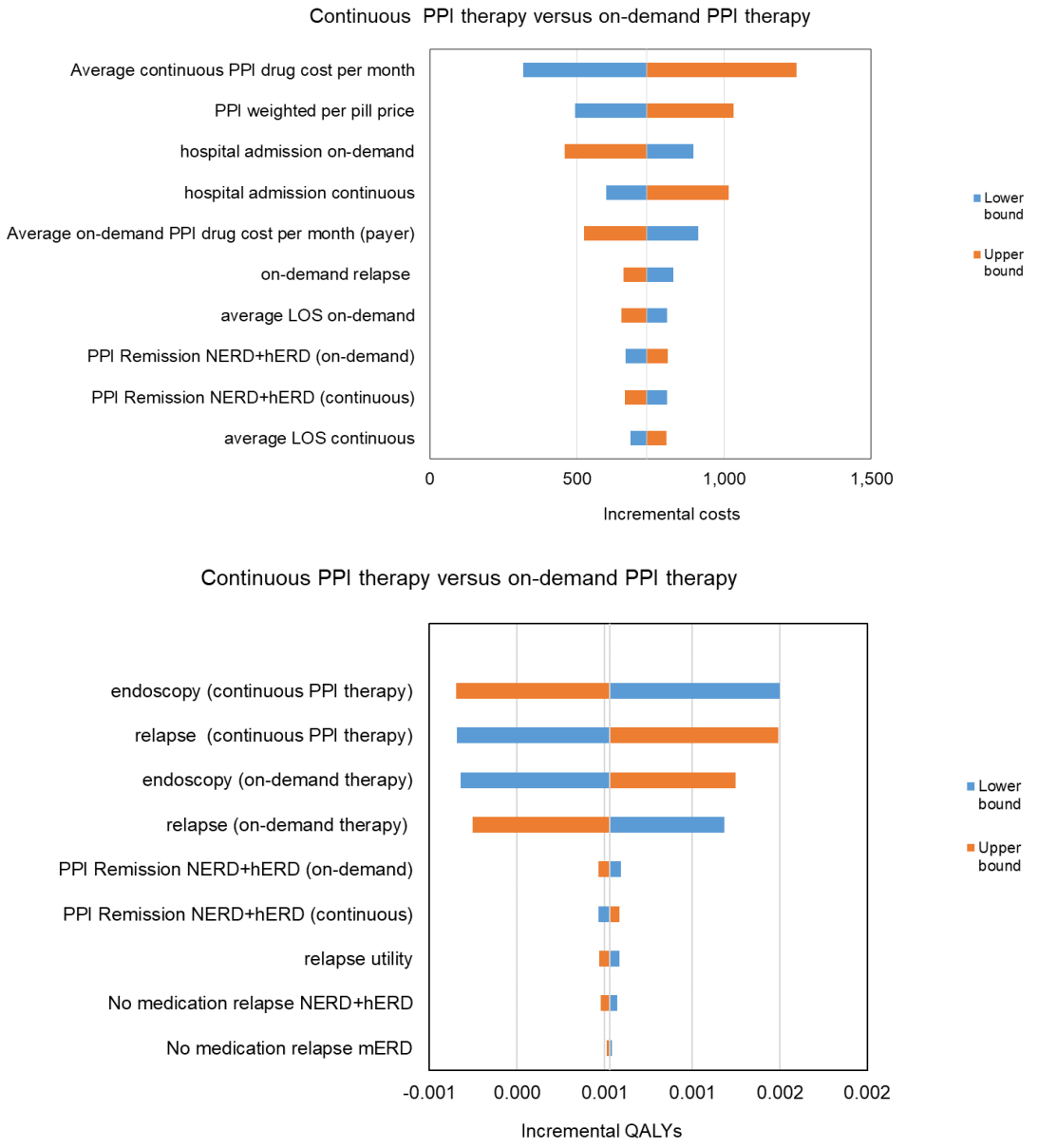
Figure 7: Cost effectiveness Acceptance Curve



One-way Sensitivity Analysis

In Figure 8, the tornado diagrams that show the top 10 most influential parameters on the incremental costs and incremental QALYs from the OWSA are presented. The top influencing parameters are average PPI cost per month for continuous PPI therapy and on-demand PPI therapy, and the per pill price for PPIs. Additionally, hospital admission and relapse rates for the on-demand PPI therapy and continuous PPI therapy arms are also influential on the incremental costs. For incremental QALYs, treatment specific endoscopy and relapse probabilities are the most influential ones, however their impacts are rather negligible (less than 0.002 incremental QALY difference between the upper and lower ranges).

Figure 8: Tornado diagrams resulting from the one-way sensitivity analysis on incremental costs (above) and incremental QALYs (below)



Scenario Analyses

The details and the results of the scenario analyses are presented in subheadings below.

Different time horizon

Cost-effectiveness analysis scenarios were conducted using different time horizons (6-months, 2 years, and 5 years). The results of these analyses are provided in Table 51. The incremental costs and QALYs decrease with shorter time horizons, and ICER gets more extreme values with shorter time horizons. At

6-month time horizon, the on-demand PPI therapy even dominates the continuous PPI therapy. This is because of the fact that the endoscopy rate of the continuous PPI therapy is slightly higher than that of the on-demand PPI therapy. However, in longer time horizons, the continuous PPI therapy leads to higher QALYs, since the impact of the lower relapse rates overweigh the impact of higher endoscopy rates for the continuous PPI therapy.

Table 51: Cost effectiveness analysis results with different time horizons

	Incremental costs (CHF)	Incremental LYG	Incremental QALYs	ICER (CHF) versus base-line (QALYs)
6 months	49	0.0000	0.0000	-289'965'236
2 years	181	0.0000	0.0000	29'395'511
5 years	393	0.0000	0.0000	9'840'170
Life time (base-case)	896	0.0000	0.0005	1'694'104

Different discount rates

Cost-effectiveness analysis scenarios were conducted using different discount rates (3% and 6%). The results of these analyses are provided in Table 52. The incremental costs and QALYs decrease, and ICER gets higher with higher discount rates. The PSA results under these discount rates are also provided in Appendix 15.5.

Table 52: Cost effectiveness analysis results with different discount rates

	Incremental costs (CHF)	Incremental LYG	Incremental QALYs	ICER (CHF) versus baseline (QALYs)
0% (base-case)	896	0.0000	0.0005	1'694'104
3%	724	0.0000	0.0003	2'127'899
6%	612	0.0000	0.0002	2'614'228

Different reimbursement restriction levels

The impact of different reimbursement restriction levels (no restriction, 365 pills per day, and 100 pills per day) were explored in the following scenario analyses. Note that in the base-case it was assumed that up to 200 pills per year would be reimbursed for on-demand PPI therapy patients. The results of these analyses are provided in Table 53. In addition to the incremental cost-effectiveness results, life-time out of pocket costs per patient and lifetime out of pocket costs per 'above restriction-level PPI user' patient are also given in Table 53. It should be noted that in these scenarios, the costs related to the comparator strategy (on-demand PPI) were modified and not the intervention strategy (continuous PPI).

It can be observed that as the reimbursement restriction level becomes tighter, the incremental costs as well as the ICER increase, since the total payer-level costs for on-demand PPI therapy decrease, as a bigger proportion of PPI medication costs are paid out of pocket from the patients. Life-time out-of-pocket costs per patient in the base-case increase with tighter reimbursement restriction levels, to around 760 CHF when only 100 pills per year are reimbursed for on-demand patients. Note that, even when the restriction level is one pill per day, there will be still some out-of-pocket PPI medication costs payments, since there are some patients who took more than one PPI pill per day on the average, in the on-demand therapy arm in Szucs et al[40].

Table 53: Scenario analysis results with different reimbursement restriction levels

	Incremental costs (CHF)	On-demand out of pocket per patient (in CHF)	On-demand out of pocket per patient who uses above restriction level PPI (in CHF)*	Incremental QALYs	ICER (CHF) versus baseline (QALYs)
Unrestricted pill use	516	0	0	0.0005	976'548
365 pills per year	588	72	403	0.0005	1'112'334
200 pills per year (base-case)	896	379	614	0.0005	1'694'104
100 pills per year	1'276	760	913	0.0005	2'413'428

*Total out of pocket costs are divided by the number of patients who use more PPI pills than the reimbursement restriction level

Adjusting for treatment switching from on-demand PPI therapy to continuous PPI therapy

In the Szucs et al. study[40], many patients (around 26%), who were assigned to the on-demand PPI therapy arm, actually used PPI pills as if they were on the continuous PPI therapy arm (i.e. around one pill per day or more). Therefore, in this scenario, the patients who use PPIs every day were considered as 'not appropriate' for the on-demand PPI therapy. At the end of the sixth month, if a patient's allocated PPI pills for that year (n=200) were more or less finished, then that patient would be considered as a 'continuous PPI user' from month seven and onwards. Such a patient would not be affected by the reimbursement restriction level until the next relapse or endoscopy event.

Hence, in this scenario, in the economic model, the patients who use more PPIs than the yearly reimbursement restriction level of 200 pills, contact their healthcare provider. Afterwards, these patients are transferred to the 'continuous PPI' state at the 7th month. Those patients can relapse and have an endoscopy at similar rates to the continuous PPI therapy patients, in the remaining cycles. The relapse and endoscopy rates of the 'actual on-demand' PPI users, who did not switch to continuous PPI therapy, for the remaining cycles, are adjusted using the observed relapse and endoscopy rates from the trial and the observed switching probability, according to the formula below:

P(rate observed in on-demand arm of Szucs et al) =

P(rate of actual on-demand PPI patients| actual on-demand PPI in on-demand arm)* P(actual on-demand PPI in on-demand arm)

+ P(rate of actual continuous PPI patients| actual continuous PPI in on-demand arm)* P(actual continuous PPI in on-demand arm)

In Table 54, it can be observed that the incremental costs (733 CHF) and the ICER (1'562'893 CHF) slightly decreased in comparison to the base-case, after the transition probabilities and the costs are adjusted for the treatment switching from the on-demand arm to continuous arm. This is only due to the increase in the total costs of the on-demand PPI therapy arm, since a proportion of the allocated patients are switched to continuous therapy arm, and for those patients, the PPI medication costs are fully reimbursed. The life-time out-of-pocket costs per patient under this scenario are around 330 CHF, where the 50% of this out-of-pocket PPI medication spending is made in the 'on-demand PPI' states before the first relapse.

Table 54: Scenario analysis results with treatment switching adjustment

Technologies	Total costs (CHF)	Total LYG	Total QALYs	Incremental costs (CHF)	Incremental LYG	Incremental QALYs	ICER (CHF) versus baseline (QALYs)
On-demand PPI	8'775	29.35	23.58				
Continuous PPI	9'508	29.35	23.58	733	0.0000	0.0005	1'562'893

Short-term cost-effectiveness model (cost per relapse free/pre-endoscopy days)

In the scenario analysis below, we first explored the cost-effectiveness of on-demand PPI versus continuous PPI therapy using a different outcome than QALY, namely relapse-free pre-endoscopy days in a year. For this purpose, the relapse-free days in the pre-endoscopy states were calculated in each cycle in one year. The ICER was found by dividing the incremental costs in one year to the incremental relapse-free days in one year before endoscopy.

From Table 55 it can be noticed that after one year, on-demand PPI therapy slightly dominates continuous PPI therapy. This is due to the fact that continuous PPI therapy has a higher endoscopy rate in comparison to the on-demand PPI therapy arm, which leads to a decrement of approximately 0.5 relapse-free, pre-endoscopy days in a year.

Table 55: One-year cost-effectiveness analysis based on relapse-free pre-endoscopy days gained

Technologies	Total costs (CHF)	Total LYG	Total relapse free, pre-endoscopy days	Incremental costs (CHF)	Incremental LYG	Incremental relapse free, pre-endoscopy days	ICER (CHF) versus baseline (relapse free, pre-endoscopy days)
On-demand PPI	351	0.998	351.4				
Continuous PPI	446	0.998	350.9	95	0.0000	-0.5389	Dominated

If we focus only on the relapse-free days (pre- or post-endoscopy days combined), from Table 56, one can see that continuous PPI therapy leads to slightly higher relapse-free (around 0.07 days in a year) days in total. These results generate an ICER value of 1'332 CHF per relapse free days gained, for continuous PPI therapy in comparison to on-demand PPI therapy (Table 56).

However, interpreting these ICER values based on relapse-free days is challenging, since there is no Swiss population based WTP study, specifically on GERD symptoms/ clinical outcomes.

Table 56: One-year cost-effectiveness analysis based on relapse-free, pre-/post-endoscopy days gained

Technologies	Total costs (CHF)	Total LYG	Total relapse free, pre-/post- endoscopy days	Incremental costs (CHF)	Incremental LYG	Incremental relapse free, pre-/post-endoscopy days	ICER (CHF) versus baseline (relapse free, pre-/post-endoscopy days)
On-demand PPI	351	0.998	360.77				
Continuous PPI	446	0.998	360.84	95	0.0000	0.0715	1'332

Subgroup Analyses

Below we investigate the following subgroup analysis:

- Uninvestigated GERD subpopulation when reimbursement restriction is applied only for patients until their first relapse (hence not during on-demand therapy in the usual care and NERD states)

In this subgroup analysis, the reimbursement restriction is applied only for the starting patients until their first relapse. The cost-effectiveness results of this scenario are provided in Table 57 below. One can note from the table, that the incremental costs and ICER have slightly decreased since out of pocket payment would be only for the states before the patients relapse. This analysis results in a lifetime out of pocket cost estimate of 216 CHF.

Table 57: When reimbursement restriction applies only for uninvestigated GERD patients before their first relapse

Technolo-gies	Total costs (CHF)	Total LYG	Total QALYs	Incremen-tal costs (CHF)	Incremen-tal LYG	Incremen-tal QALYs	ICER (CHF) versus baseline (QALYs)
On-demand PPI	8'776	29.35	23.58				
Continuous PPI	9'508	29.35	23.58	733	0.0000	0.0005	1'385'686

8.4 Budget impact analysis

8.4.1 Methodology budget impact model

Model structure budget impact model

The budget impact model (BI model) allows the calculation of the projected population-level five-year overall costs of introducing on-demand PPI therapy to the Swiss uninvestigated GERD population, who uses PPI on a continuous basis (i.e. one PPI pill every day) at baseline.

The BI model was built as an extension to the cost-effectiveness model, which was described previously. Hence, the core model characteristics for the BI model are largely the same as those used for the cost-effectiveness model (i.e. 1-month cycle time, no discounting, same transition probabilities, same resource use and unit costs). The time horizon of the BI model is restricted to 5 years.

At each cycle, the BI model estimates the number of patients that are using continuous PPI therapy and the number of patients using on-demand PPI therapy. These population-level numbers can be calculated from the specific input parameters of the BI model, which are listed as below:

1. Prevalence of the GERD patients who are endoscopically uninvestigated and who are on continuous PPI therapy
2. Incidence of the GERD patients who are endoscopically uninvestigated and who are on continuous PPI therapy (for the upcoming five years)
3. Proportion of the cohort of patients that are expected to be receiving on-demand PPI therapy (for the upcoming five years).

The prevalence of the GERD patients at baseline is the estimated number of patients that is assumed to be present at the start of the time horizon and should reflect the current number of GERD patients that are endoscopically uninvestigated and are treated with continuous PPI therapy in Switzerland.

The entries for incidence are the expected number of new endoscopically uninvestigated patients that will need continuous PPI therapy, over the course of the 5-year time horizon of the BI model. Because incidence levels might change over time, separate annual numbers of incident patients can be entered for each of the 5 years. Since the incidence of the GERD is a gradual process, not all incident patients will arrive simultaneously at the start of each year, but instead, newly incident patients each year are spread over that year, i.e. each month, $1/12^{th}$ of the annual incident patients enter the BI model.

Similar to the incidence, the proportion of patients receiving on-demand PPI therapy can be uniquely defined for each year. This enables the calculation of budget impact under different policy implementation scenarios, such as a sudden implementation policy (i.e. 100% patients on continuous PPI therapy

are transferred to on-demand PPI therapy, already in the first year) or a gradual implementation policy (i.e. proportion of the patients using on-demand PPI therapy increases 20% each year). These year-specific proportion values apply to all patients in the model (i.e. both prevalent and incident patients), for all cycles.

From these inputs, the BI model can calculate the following results:

1. The projected (cumulative) population level budget impact estimates for up to 5 years, which incorporate the total amount of cumulative costs from the cost-effectiveness model, as well as the estimated number of patients on continuous PPI therapy and on on-demand PPI therapy, at each year, under a given policy implementation scenario.
2. The difference between the budget impact estimate of a given policy implementation scenario and the budget impact of the status quo, where all patients receive continuous treatment with PPIs. This difference returns the projected reduction in the overall budget spent on the uninvestigated GERD patients in Switzerland, when on-demand PPI therapy is introduced to patients who are on continuous PPI therapy.

Budget impact model and reimbursement policy related inputs

For the budget impact model, a prevalence of 17.6% for reflux disease from Schwenkglenks et al.[90] was assumed. This study also reported that mean disease duration was 9.8 years. When this value was multiplied by the Swiss population projections made by the Swiss Federal Statistical Office[91], approximately 1.5 million patients were estimated to have GERD symptoms. The percentage of patients who were on continuous PPI therapy among GERD patients was calculated to be around 34%, which was calculated from the endoscopy outcomes from Zagari et al.[78] and the erosion/oesophagitis level treatment percentages from Nocon et al.[75]. Hence, it was estimated that approximately 500'000 GERD patients in Switzerland would be on continuous PPI therapy. The percentage of the endoscopically uninvestigated GERD patients was estimated by the cost effectiveness model prediction of the number of patients in endoscopically uninvestigated states at 9.8 years (mean disease duration) under continuous PPI treatment (56.6%). When multiplied with this percentage, the prevalence for the budget impact model for uninvestigated GERD population in Switzerland (on continuous PPI therapy) would be approximately 290'000 patients.

For incidence rates, we assumed the annual incidence of GERD to be 5 new GERD incidences per 1'000 patient years, which was taken from a systematic review on the epidemiology of GERD.[92] This value was multiplied with predicted non-GERD Swiss population and the percentage of continuous PPI users, which yielded the estimate of 12'000 new uninvestigated GERD patients each year.

In the base-case, for the budget impact model, we assumed that the proportion of patients that were on on-demand PPI therapy would go from 0% in year 0 to 100% (of the continuous PPI users among endoscopically uninvestigated population) in year 5 gradually, with an increase of 20% each year.

For the reimbursement restriction, in the base-case, it was assumed that the health insurances in Switzerland would cover for a maximum number of 200 pills per year for uninvestigated GERD or NERD patients using on-demand PPI therapy. If a patient consumed more than 200 pills per year, the remaining PPIs would be bought out of pocket from that patient. It was assumed that this change in reimbursement would have no impact on the medication use and clinical effectiveness for the on-demand patients.

Budget impact analysis scenarios

The population-level, per-year and cumulative budget impact of implementing on-demand PPI therapy (with corresponding reimbursement restriction levels) to the baseline continuous PPI therapy population with no reimbursement restrictions were explored for the five-year horizon. The list of the budget impact analyses is given below:

- Budget impact analysis base-case (200 pills per year and per patient, gradual implementation of changing continuous PPI to on-demand PPI)
- Budget impact analysis scenario 1 (200 pills per year and per patient, sudden implementation of changing continuous PPI to on-demand PPI)
- Budget impact analysis scenario 2 (365 pills per year and per patient, gradual implementation of changing continuous PPI to on-demand PPI)
- Budget impact analysis scenario 3 (365 pills per year and per patient, sudden implementation of changing continuous PPI to on-demand PPI)
- Budget impact analysis scenario 4 (200 pills per year and per patient, gradual implementation of changing continuous PPI to on-demand PPI and treatment switching from on-demand to continuous PPI therapy is allowed).

8.4.2 Results budget impact analysis

Below we present the budget impact analysis (base-case and scenarios) results.

Base-case (200 pills per year and per patient, gradual implementation of changing continuous PPI to on-demand PPI)

In the first analysis (see Table 58), we explored the budget impact of the base-case, where the reimbursement restriction is set at 200 pills per year per patient, and the implementation of on-demand PPI therapy is conducted gradually in five years. From the table below, at the end of the five years, it can be noticed that around 70 million CHF can be saved from gradual implementation of the on-demand PPI therapy to the continuous PPI therapy population.

Table 58: Budget impact analysis base-case (200 pills per year and per patient, gradual implementation of changing continuous PPI to on-demand PPI)

	1st year BI (20% on demand)	2nd year BI (40% on demand)	3rd year BI (60% on demand)	4th year BI (80% on demand)	5th year BI (100% on demand)
Per-year medication costs	127'080'973	121'867'709	115'357'271	110'082'249	106'032'472
Per-year difference in budget compared to 100% continuous PPI and no reimbursement restriction	5'671'781	10'768'040	15'322'339	19'197'363	22'382'368
Cumulative medication costs	127'080'973	248'948'682	364'305'953	474'388'202	580'420'674
Cumulative difference in budget compared to 100% continuous PPI and no reimbursement restriction	5'671'781	16'439'821	31'762'160	50'959'523	73'341'891

Scenario 1 (200 pills per year and per patient, sudden implementation of changing continuous PPI to on-demand PPI)

The impact of sudden implementation of changing continuous PPI therapy to on-demand PPI therapy can be observed in Table 59 below, in which we explored the budget impact of the base-case reimbursement restriction level (200 pills per year per patient), and 100% of the continuous PPI therapy users are switched to on-demand PPI therapy already at year one. At the end of the five years, around 127 million CHF can be saved from sudden implementation of the on-demand PPI therapy to the continuous PPI therapy population.

Table 59: Budget impact analysis scenario 1 (200 pills per year and per patient, sudden implementation of changing continuous PPI to on-demand PPI)

	1st year BI (100% on demand)	2nd year BI (100% on demand)	3rd year BI (100% on demand)	4th year BI (100% on demand)	5th year BI (100% on demand)
Per-year medication costs	104'393'848	105'715'649	105'142'378	105'282'908	106'032'472
Per-year difference in budget compared to 100% continuous PPI and no reimbursement restriction	28'358'906	26'920'100	25'537'232	23'996'704	22'382'368
Cumulative medication costs	104'393'848	210'109'497	315'251'876	420'534'784	526'567'255
Cumulative difference in budget compared to 100% continuous PPI and no reimbursement restriction	28'358'906	55'279'006	80'816'238	104'812'942	127'195'310

Scenario 2&3 (365 pills per year and per patient, gradual/sudden implementation of changing continuous PPI to on-demand PPI)

The impact of different reimbursement restriction levels on the budget impact of the on-demand PPI therapy were analysed in scenario 2 (gradual implementation) and scenario 3 (sudden implementation). In these analyses, the reimbursement restriction level has been changed to 365 pills per year per patient. From Table 60, one can see that, at the end of the five years, around 50 million CHF can be saved from the gradual implementation, and from Table 61, it can be observed that around 85 million CHF can be saved from the sudden implementation of the on-demand PPI therapy to the continuous PPI therapy population.

Table 60: Budget impact analysis scenario 2 (365 pills per year and per patient, gradual implementation of changing continuous PPI to on-demand PPI)

	1st year BI (20% on demand)	2nd year BI (40% on demand)	3rd year BI (60% on demand)	4th year BI (80% on demand)	5th year BI (100% on demand)
Per-year medication costs	129'244'922	125'683'192	120'352'240	115'929'196	112'495'663
Per-year difference in budget compared to	3'507'833	6'952'557	10'327'370	13'350'416	15'919'177

100% continuous PPI and no reimburse-ment restriction					
Cumulative medica-tion costs	129'244'922	254'928'114	375'280'354	491'209'549	603'705'212
Cumulative differ-ence in budget com-pared to 100% con-tinuous PPI and no reimbursement re-striction	3'507'833	10'460'390	20'787'760	34'138'176	50'057'353

Table 61: Budget impact analysis scenario 3 (365 pills per year and per patient, sudden imple-mentation of changing continuous PPI to on-demand PPI)

	1st year BI (100% on demand)	2nd year BI (100% on demand)	3rd year BI (100% on demand)	4th year BI (100% on demand)	5th year BI (100% on demand)
Per-year medication costs	115'213'590	115'254'356	113'467'327	112'591'592	112'495'663
Per-year difference in budget compared to 100% continuous PPI and no reimbursement restriction	17'539'164	17'381'393	17'212'283	16'688'020	15'919'177
Cumulative medication costs	115'213'590	230'467'946	343'935'273	456'526'865	569'022'528
Cumulative difference in budget compared to 100% continuous PPI and no reimbursement restriction	17'539'164	34'920'557	52'132'840	68'820'861	84'740'037

Scenario 4 - (200 pills per year and per patient, gradual implementation of changing continuous PPI to on-demand PPI and treatment switching from on-demand to continuous PPI therapy is allowed)

Finally, in scenario 4, we analysed the budget impact of the scenario, where the reimbursement re-striction is set at 200 pills per year per patient, and the implementation of on-demand PPI therapy is conducted gradually in five years, and the treatment switching from on-demand PPI therapy to continu-ous PPI therapy was allowed. As described previously in section 8.3.2, in this scenario, it was allowed that patients who finished their reimbursed PPIs in the first 6 months would be categorized further as

continuous PPI patients. These patients would not be affected by the reimbursement restrictions anymore. In Table 62, one can notice that, at the end of five years, around 58 million CHF can be saved from gradual implementation of the on-demand PPI therapy to the continuous PPI therapy population.

Table 62: Budget impact analysis scenario 4 (*200 pills per year and per patient, gradual implementation of changing continuous PPI to on-demand PPI and treatment switching from on-demand to continuous PPI therapy is allowed*)

	1st year BI (20% on demand)	2nd year BI (40% on demand)	3rd year BI (60% on demand)	4th year BI (80% on demand)	5th year BI (100% on demand)
Per-year medication costs	127'950'871	124'094'534	118'567'454	114'132'522	110'763'486
Per-year difference in budget compared to 100% continuous PPI and no reimbursement restriction	4'801'883	8'541'216	12'112'156	15'147'090	17'651'354
Cumulative medication costs	127'950'871	252'045'405	370'612'859	484'745'380	595'508'866
Cumulative difference in budget compared to 100% continuous PPI and no reimbursement restriction	4'801'883	13'343'099	25'455'255	40'602'345	58'253'699

Summary statement costs, cost-effectiveness and budget impact

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Based on the cost-effectiveness analysis, it can be deducted that on-demand PPI therapy with a reimbursement restriction of 200 pills per year for uninvestigated GERD and NERD populations is cost-effective in comparison to the continuous PPI therapy. On-demand PPI therapy leads to more or less the same QALYs, with a cost saving of 896 CHF in a patient's lifetime. Under the reimbursement restriction, the additional lifetime out-of-pocket payment for PPIs will be around 380 CHF per patient. From the OWSA, per pill price of the PPI as well as the PPI usage of the on-demand and continuous treatment arms seem to be the most influential parameters on the incremental costs. The PSA reveals that the cost-effectiveness is subject to substantial parametric uncertainty, however, the impact of this parametric uncertainty on the decision uncertainty is

rather limited. The continuous PPI therapy is never cost-effective for plausible willingness to pay threshold levels (up to 100,000 CHF per QALY gained). Since the QALY difference between two arms is extremely small, the cost savings due to on-demand PPI therapy lead to tremendously high ICER values. The main conclusion of the cost-effectiveness results is robust, under different reimbursement restriction levels (e.g. no restriction on reimbursement, restriction to 365, 200 and 100 pills per year), under different discounting levels and time horizons, when using other outcomes than cost per QALY, and when the model is adjusted for the treatment switching from on-demand to continuous PPI therapy arm. For short-term (e.g. 1 year) time horizon scenarios, on-demand PPI therapy leads to slightly higher QALYs, due to the impact of the marginally lower endoscopy rates overweigh the marginally higher relapse rates of the on-demand PPI therapy in comparison to the continuous PPI therapy in the first months.

The 5 year population-level budget impact of changing the uninvestigated GERD and NERD patients' continuous PPI therapy to on-demand PPI therapy, with a reimbursement restriction policy of 200 pills per year, is estimated to be between 70 and 127 million CHF. This budget impact depends on the nature of the policy implementation (sudden or gradual, the budget impact of the latter is smaller). The reimbursement restriction threshold appears to have a considerable effect on the budget impact, as well. If the reimbursement for PPIs is restricted up to 365 pills per year (instead of 200 pills per year as in the base-case), or if reimbursement restriction is not applied to patients who can control their symptoms only by continuous PPI therapy, the 5 year population level budget impact is expected to be between 50 and 85 million CHF.

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9 Legal, social and ethical issues

9.1 Methodology legal, social and ethical issues

9.1.1 Databases and search strategy

For the ethical aspects, following the recommendations in the HTA Core Model Version 3.0[34], modified search filters from Droste et al. 2010[93] were embedded to the clinical search strings explained in Section 7. The search filter for ethical issues is provided in Appendix 15.2.1.

For the legal aspects, the Swiss legislative database was searched for any GERD or PPI related federal, national or European level legislations.[f] Additionally, a search in medical databases was conducted by embedding a legal search filter (provided in Appendix 15.2.1) to the clinical search strings explained in Section 15.1.

For the social aspects, no additional search was conducted, since most of the search terms (or their alternatives) suggested in the HTA Core Model Version 3.0[34] were already included in the search filter for economic or ethical issues (such as 'quality of life', 'patient-choice' or 'patient-decision-making').

9.1.2 Other sources

Additionally, the clinical guidelines and technology assessments from the major national health technology assessment websites were searched (i.e. NICE[g] from the UK, IQWIG[h] from Germany, HAS[i] from France, ZiN[j] from the Netherlands, CADTH[k] from Canada, and PBAC[l] from Australia). This search aimed to check if the published guidelines have included possibly missed relevant evidence on the social, legal, and ethical aspects on the PPI therapy for GERD patients. No missed studies/articles were identified in these guidelines/reviews.

[f] https://www.admin.ch/opc/search/search.php?lang=en

[g] National Institute for Health and Care Excellence (NICE) www.nice.org.uk (https://www.nice.org.uk/guidance/cg184)

[h] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) https://www.iqwig.de/

[i] Haute Autorité de santé (HAS) https://www.has-sante.fr/

[j] Zorginstituut Nederland (ZIN) www.zorginstituutnederland.nl

[k] Canadian Agency for Drugs and Technologies in Health (CADTH) www.cadth.ca/ (1.https://bit.ly/2pQyyZ5 2. https://bit.ly/2A6JSWX)

[l] Pharmaceutical Benefits Advisory Committee (PBAC) www.pbs.gov.au/

9.1.3 Assessment of quality of evidence

Not applicable.

9.1.4 Methodology data analysis legal, social and ethical issues

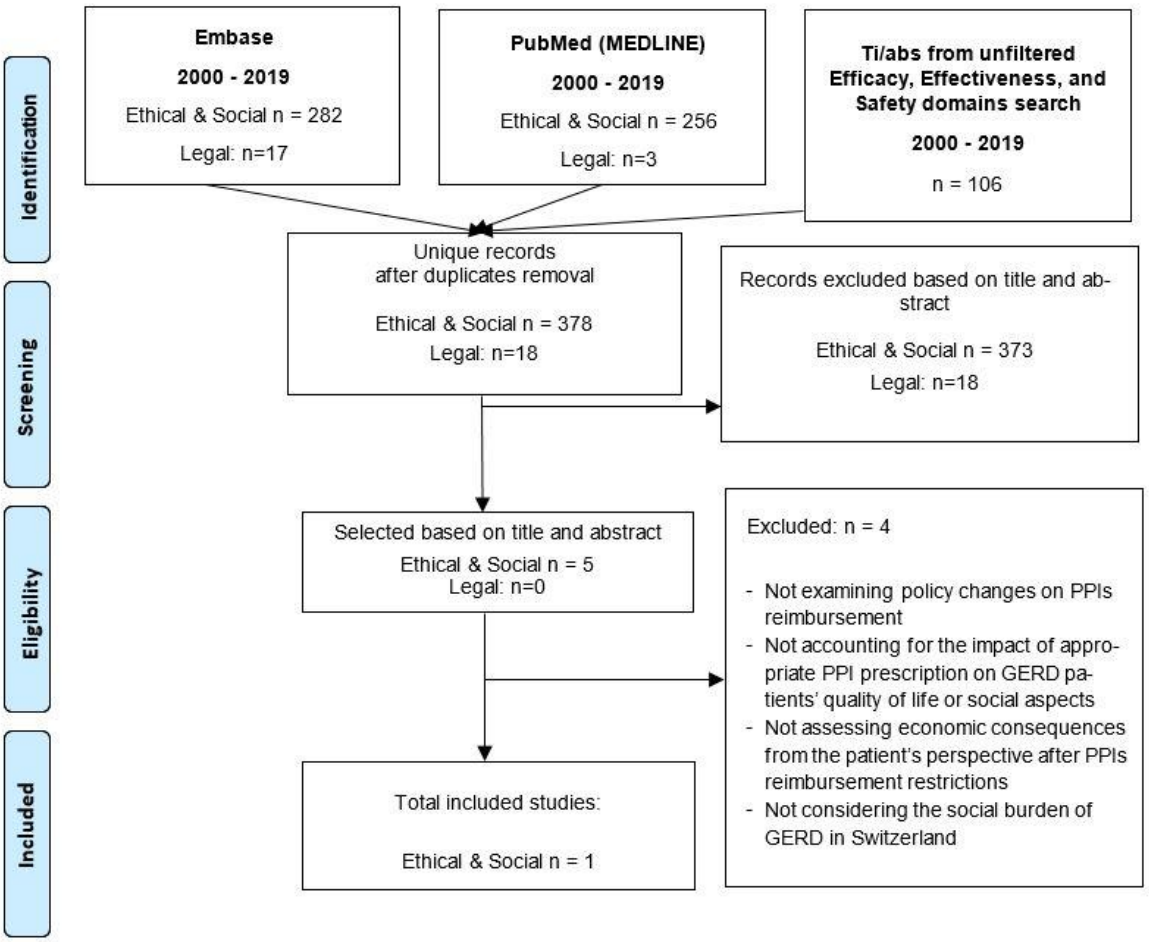
The summary of the findings related to the legal, social, and ethical domains are provided narratively. No statistical tests were applied to the literature search output of the above-mentioned domains. The title/abstract screening phase and the subsequent selection of the relevant studies was performed by two researchers at iMTA.

9.2 Results legal, social and ethical issues

9.2.1 PRISMA flow diagram

The search filters (Section 15.2.1) for ethical and social issues applied to the efficacy, effectiveness, and safety search in Embase.com and PubMed (MEDLINE) yielded 282 and 256 hits, respectively. Similarly, the search filters for legal issues (Section 15.2.1) applied to the efficacy, effectiveness, and safety original search in Embase.com and PubMed (MEDLINE) generated 17 and 3 hits, respectively. Additionally, the hits from the efficacy, effectiveness and safety search were reviewed for potential usefulness for legal, social and ethical issues, which generated 106 hits. Hence, all these searches yielded 396 unique records in total (after excluding duplicates, 378 on ethical & social issues and 18 on legal issues) eligible for title and abstract screening. Of those, 391 were excluded (373 out of 378 hits from the search on ethical and social issues and all 18 hits from the search on legal issues) based on their title and abstract because not pertaining relevant information on the domain under consideration. Following this phase, the remaining five records (all originated from ethical and social search hits) were screened in full-text to identify the relevant studies. The inclusion and exclusion criteria (Section 5) were applied to the screened full-text articles, which finally resulted in the selection of one article. The main reasons for excluding studies in the full-text screening phase were *i)* not considering ethical aspects of policy changes and/or PPI reimbursement restrictions and *ii)* not focussing on continuous versus on-demand PPI therapy as comparator (Figure 9). A preliminary critical appraisal was not applied to the ethical and social systematic search.

Figure 9: PRISMA flow diagram legal, ethical, and social issues review



Keys: PPI = Proton-Pump Inhibitor, GERD = Gastroesophageal Reflux Disease

9.2.2 Study characteristics table

Not applicable.

9.2.3 Findings legal issues

From the literature search outlined above and from the search performed in the Swiss legislative database, no relevant issues were identified with regard to the legal domain.

9.2.4 Findings social issues

Findings on the social domain of policy changes regarding the reimbursement of PPIs are limited to the size of the patient population potentially affected by such changes. Therefore, a study was selected for data extraction in order to provide an estimate of how many people could be potentially affected by a change in reimbursement policy of PPIs. Schwenkglenks et al. conducted a population-based survey in the year 2000 using a computer assisted telephone interview system.[90] The results witnessed that the burden of GERD in Switzerland is in line with the other European countries, with a prevalence of around 18%. From the figures, it was estimated that approximately one million people have GERD symptoms in Switzerland, but only 62.4% resorts to medications to control this condition. Among those undertaking a therapy on a regular basis (38.8%), approximately 32.6% uses prescription drugs, mostly represented by PPIs. Therefore, the number of people that might potentially be affected by a reimbursement restriction on continuous PPI therapy can be roughly estimated between 115'000 and 125'000.

9.2.5 Findings ethical issues

The systematic literature review strategy adopted did not find relevant articles focussing on the differences between continuous and on-demand PPI therapy, in terms of social benefits/disadvantages or ethical issues. Furthermore, none of the articles specifically reported on ethical issues concerning reimbursement restrictions of continuous PPI therapy, nor social consequences of policy changes regarding continuous versus on-demand prescription of PPIs in GERD patients. While not taking the safety arguments into account, from the results of this HTA, we did not find additional ethical considerations, with regard to the reimbursement policy of continuous versus on-demand therapy with PPIs that can be generalised to all reimbursement policies. Nevertheless, potential issues might become relevant once the results of the cost-effectiveness analysis provided in this report are translated into a specific policy.

Summary statement legal, social and ethical issues

None of the references yielded during the systematic literature review specifically reported on ethical issues concerning reimbursement restrictions on PPIs, nor societal consequences of policy changes regarding continuous versus on-demand PPI therapy in GERD patients. Furthermore, the literature search on the legal domain did not find any study. In conclusion, we did not find relevant issues to be reported here.

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10 Organisational issues

10.1 Methodology organisational issues

10.1.1 Databases and search strategy

For the organisational aspects, the studies listed under the MESH subheadings of ‘proton pump inhibitors/organisation and administration’ or ‘proton pump inhibitors/supply and distribution’ on the PubMed (MEDLINE) website were screened.

10.1.2 Other sources

As outlined under Section 9.1.2 major national health technology assessment websites were searched for clinical guidelines and technology assessments to ensure no relevant evidence on the organisational aspects on the PPI therapy for GERD patients was missed. From this search we concluded that no relevant studies/articles were missed.

10.1.3 Assessment of quality of evidence

Not applicable.

10.1.4 Methodology data analysis organisational issues

The evidence on organisational aspects of the technology was described narratively.

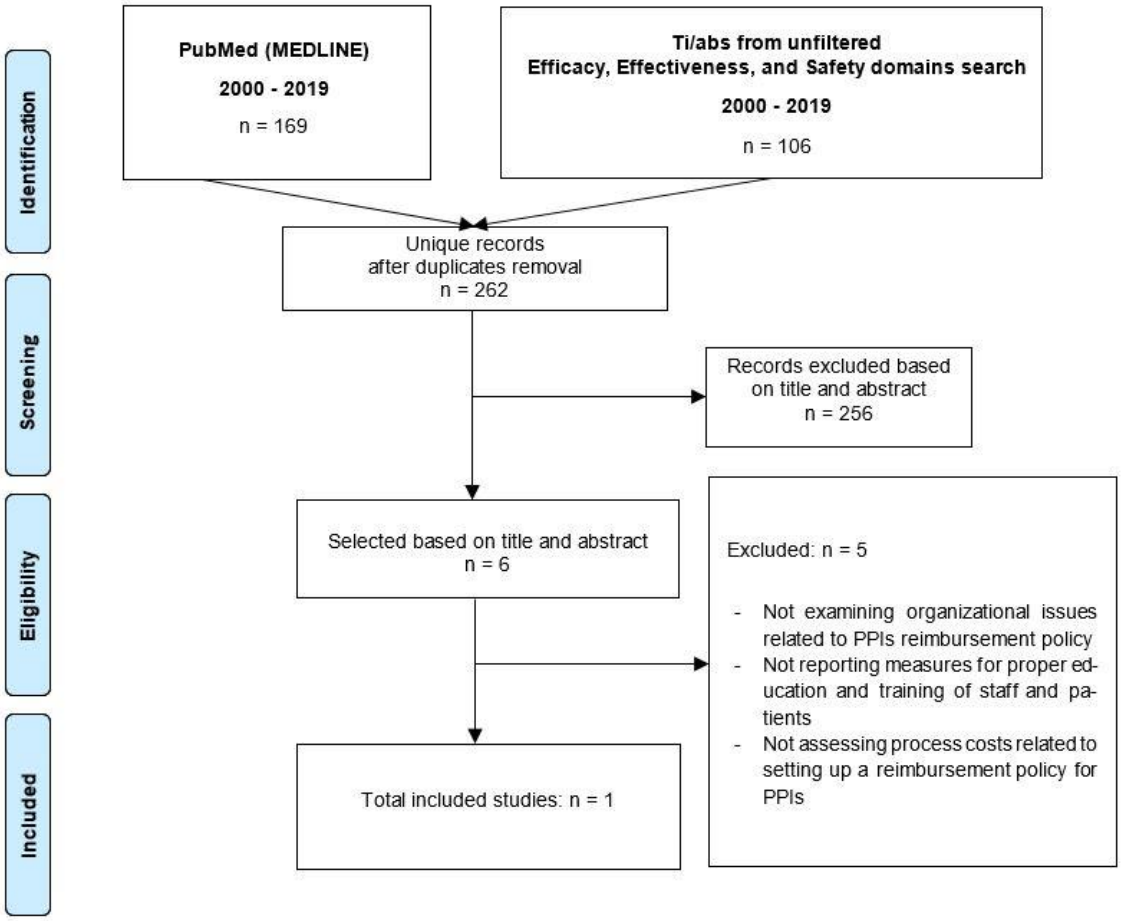
10.2 Results organisational issues

10.2.1 PRISMA flow diagram

A total of 262 references were selected for the systematic literature review on the organisational issues related to continuous versus on-demand therapy with PPIs. After title and abstract screening, six references were considered pertaining the research objective and were screened in full-text. Main reasons for exclusion during the title/abstract screening phase were *i)* including ERD patients and/or Barrett’s oesophagus patients in the population under study, *ii)* comparing PPI treatment with surgery or other anti-acid medications (e.g. H_2RA), *iii)* examining route of administration other than *per os* (namely intravenously), and *iv)* not addressing outcomes relevant for organisational related issues, such as proper

education and training of staff and patients or process costs related to setting up a reimbursement policy for PPIs (Figure 10). Among these six screened publications, five were excluded as they were not related to the organizational issues related to PPI reimbursement policy (Figure 10).[94 95 96 97 98]

Figure 10: PRISMA flow diagram organizational issues review



Keys: PPI = proton pump inhibitor

10.2.2 Evidence table

Not applicable.

10.2.3 Findings organisational issues

The organisational issues related to restricting the reimbursement of continuous therapy with PPIs in favour of on-demand were not taken into consideration by any of the studies examined. Only one study reported the impact of esomeprazole exclusion from the list of reimbursed drugs on healthcare consumption and total costs.[99]

In Alemayehu et al.[99], it was found that after the exclusion of esomeprazole from a USA insurance company list of reimbursed drugs, with the intent to curb costs and favour the prescription of less expensive equivalents, total medical costs, in the following 6 months, rose. The population examined included patients affected from GERD as well as other conditions, such those undertaking ASA therapy chronically and those with dyspepsia. After this new reimbursement policy entered into force, 43% of the entire cohort of patients (GERD and non-GERD) switched to another PPI and 37.5% had no prescription for PPIs. Nevertheless, total healthcare utilisation increased. As observed by the study of Alemayehu et al.[99], unintended costs and healthcare utilisation increment might result from reimbursement restrictions in the form of higher general practitioner consultations, laboratory testing and overuse of cheaper but less effective drugs with similar indications. It is worth noting that the study does not provide inferences about the causes of such an effect. Furthermore, when only GERD patients are considered in this study, total medical costs decreased in the 6 months period examined. Despite the same effect might be observed also in other contexts in which a restriction on PPIs reimbursement system is introduced, an increment in healthcare utilization cannot be interpreted as a direct consequence in light of this study.

In conclusion, specific organisational issues for setting up a policy that regulates the reimbursement of continuous or on-demand therapy with PPIs in GERD patients were not found from the systematic literature search performed.

Summary statement organisational issues

The organisational issues to be considered are strongly dependent on the specific characteristics of the policy change that will be implemented. Specific issues for setting up a policy that regulates the reimbursement of continuous or on-demand PPI therapy in GERD patients were not found from the systematic literature search performed.

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11 Additional issues

PPIs remain, at the moment, the cornerstone for the treatment of GERD. Nevertheless, a percentage of patients with heartburn and acid regurgitation still fail to reach symptoms control, even with a full dosage of PPIs administered in a continuous fashion.[100] In this regard, it is worth noting that only a small percentage of these cases are truly GERD. Indeed, most of these patients, in the beginning defined as GERD based solely on symptoms or on *ex adiuvantibus* criteria, are diagnosed with other conditions than GERD when further investigated with endoscopy and/or pH manometry. Functional heartburn and oesophageal hypersensitivity represent the majority of these conditions that manifest themselves with reflux-like symptoms, but are caused by different pathophysiological mechanisms.[12] Functional heartburn can be described as a condition in which the patient experiences "*burning retrosternal pain for at least 3 months without evidence of continued reflux or underlying motility disorder that is not relieved by optimal anti-secretory therapy*" (p. 2).[100] It was estimated that approximately 60% of the patients refractory to PPI therapy, suffer from functional heartburn.[101] Another category of patients that do not respond to optimal PPI therapy are the patients with oesophageal hypersensitivity. This condition can be described as an abnormal response to normally well-tolerated stimuli of different nature, including pH changes, temperature, mechanical distention, and electrical stimulation.[102] Patients suffering from oesophageal hypersensitivity are probably centrally and peripherally sensitised, because of an increased permeability of the oesophageal mucosae that exposes sensitive nerve terminations to acid.[102] Furthermore, in addition to functional heartburn and oesophageal hypersensitivity, many other factors can affect the oesophageal motility and lower oesophageal sphincter contraction. These factors include among others motility disorders, stress, and psychological comorbidity.[100]

To meet the medical needs of these, above-mentioned group of patients, new compounds have been developed in the last years, namely potassium-competitive acid blockers, transient lower oesophageal sphincter relaxation reducers, prokinetics, mucosal protectants, and oesophageal pain modulators.[103]

Potassium-competitive acid blockers are H+/K+-ATPase competitive inhibitors that showed efficacy similar to PPIs. Nevertheless, due to their kinetics, the plasma peak concentration is reached faster than with PPIs. This profile makes potassium-competitive acid blockers putative drugs particularly useful for on-demand therapy.[103] Till present, no trials established their superiority to PPIs and, therefore, none of the compounds in this category have been approved in Europe. Nevertheless, vonoprazan obtained market authorisation in Japan for the treatment of gastric and duodenal ulcers, reflux oesophagitis, and prevention of low-dose aspirin- or nonsteroidal anti-inflammatory gastritis.[104] Vonoprazan showed the advantage of effectively suppressing acid production at night and did not result in hepatic toxicity, like potassium-competitive acid blockers previously developed.

Another recent category of drugs is represented by those regulating the lower oesophageal sphincter motility. Potential targets of these drugs are gamma-aminobutyric acid B receptors ($GABA_B$), metabotropic glutamate receptor 5 (mGlucR5), cannabinoid (CB), cholecystokinin (CCK), 5-hydroxytryptamine 4 ($5\text{-}HT_4$), muscarinic, and opioid receptors.[103] The clinical relevance of these drugs for patients having GERD like symptoms is not clear and, currently, they are not routinely used in clinical practice.

In patients with refractory symptoms that do not positively respond to PPIs, pain modulators have been advocated as a potential solution. Vanilloid receptor antagonists have been tested for this purpose.[103]

As these new improvements are targeting patients who are refractory to PPIs, the implication of these improvements on the decision problem is not expected to be significant.

Furthermore, improvements in terms of formulations and pharmacokinetics led to the development of extended release PPIs. This new class of PPIs, such as dexlansoprazole MR, an R-enantiomer of lansoprazole, and tenatoprazole, demonstrated a higher efficacy in suppressing night-time acid production than regular control PPIs (esomeprazole and lansoprazole).[103] These drugs might find application particularly in patients with sleep disorders and in those experiencing reflux-related symptoms prevalently during night time.[103] Furthermore, extended release PPIs, which can be administered once daily and without regard to meals, might help addressing the poor compliance with PPIs prescription that is currently observed in a significant percentage of cases and that represents an important cause of treatment dissatisfaction.[105]

The impact of these extended release PPIs on the decision problem is unknown, as the night-time acid production might go unnoticed easier, on-demand PPI therapy effectiveness in comparison to continuous PPI therapy, in terms of controlling night-time symptoms might be less obvious in comparison to the regular PPI formulations, however there is not enough evidence in the literature to substantiate this claim.

Another aspect to take into account in the domain of organisational issues is the implementation of proper training of patients and health staff. The literature review did not identify studies on educational issues for switching from PPIs continuous to on-demand therapy. An additional organizational challenge might be identifying patients' endoscopy status, e.g. in case of (the frequent) patient changes between health insurers. As a health insurer would have no easy way of asserting if a new patient has had an endoscopy previously, this might limit how well the group under study in the HTA can be targeted in practice.

12 Discussion

The present HTA study evaluated the efficacy, effectiveness, safety, and cost-effectiveness of continuous long-term PPI treatment versus on-demand long-term PPI treatment in adult NERD and uninvestigated GERD patients, based on available data from the scientific literature. In this section the main findings reported are discussed in light of possible limitations and discrepancies encountered. First we discuss the efficacy, effectiveness, and safety of the two treatment regimens investigated, then we elaborate on the findings from the cost-effectiveness perspective. Legal, social, ethical, and organisational issues are not discussed in this section, due to the lack of relevant findings.

The decision to set a ceiling for the reimbursement of PPIs in specific subpopulations of GERD patients can be guided, first of all, by the clinical repercussions it might have on the patients' quality of life and health. From the findings gathered across the studies selected, we found a significant heterogeneity in terms of study outcomes and study design that hampered the interpretation of the results, especially in terms of in-between study comparisons or pooling of the data. Furthermore, the clinical manifestations of GERD in the study population (i.e. uninvestigated GERD and NERD patients) are not objective but rather limited to the subjective patient reported symptoms. These factors might have contributed to the mixed findings encountered across studies. Another factor that could have influenced the outcomes is the limited time span of most of the included studies that, for the comparison studies on identical PPI and dosage, did not exceed six months. For the comparison studies on non-identical PPI and dosage, the period of the study was extended to 12 months in some cases, but the risk of bias was high for all the studies included.

Having said that, despite the mixed results found when the single outcomes, such as satisfaction with treatment of heartburn, satisfaction with modality of treatment or compliance are compared, we might assume that the general satisfaction with the treatment can be a valid indicator to assess whether or not on-demand PPI therapy is at least not inferior to continuous PPI therapy. In this regard, the evidence provided by this HTA suggests that relatively high general patient satisfaction levels were found with both continuous as well as on-demand PPI therapy. Only two studies favoured continuous therapy, one of which included also low grade GERD patients.[43]

These findings, together with the comparable safety outcomes of the on-demand PPI therapy compared with the continuous modality might favour the proposal of a ceiling on the number of pills reimbursed per year in specific subpopulations of GERD patients, as on-demand PPI therapy seems not inferior to continuous therapy, at least in NERD patients.

In terms of cost-effectiveness, none of the studies identified from the literature search were transferable to the current Swiss clinical setting. Therefore, a de novo cost-effectiveness model and budget impact model was created.

A separate CE model for NERD subpopulation was not developed since the uninvestigated GERD population included NERD patients as well. The suspected NERD/HERD disease state after endoscopy is included in the economic model and most patients in this state received on-demand PPI therapy (based on the distributions obtained from the ProGERD study). In the base-case, the reimbursement restriction affected these suspected NERD/HERD patients that were on on-demand PPI therapy, as well. However, in one of the subgroup analysis, we investigated when the reimbursement restriction influenced only uninvestigated patients on on-demand PPI therapy. It should be also emphasized that the actual diagnosis of NERD population necessitates not only endoscopy but also other tests such as pH-manometry, in order to rule out other indications such as functional dyspepsia.

Main strengths of this HTA can be listed as follows: 1) comprehensive and systematic search of the evidence on the medical databases on a broad list of outcomes. The strengths of this systematic review include the use of multiple peer-reviewed literature databases to search systematically for literature published from 2000 onwards. A rigorous methodology, adhering to international methodological standards such as Cochrane and PRISMA, was applied to identify, critically appraise, analyse, and summarise the relevant evidence in order to minimise selection and confirmation bias. 2) de novo cost-effectiveness and budget impact models, validated by clinical experts, characterizing the natural history of the disease as well as incorporating the patient and population-level impacts of changing the continuous PPI therapy to a reimbursement restricted, on-demand PPI therapy for the uninvestigated GERD and NERD patients in Switzerland.

Main limitations of this HTA can be listed as follows: 1) the systematic review is mainly limited by the scarcity of the literature found, the heterogeneity in studies and study outcomes, and lack of between-group statistical comparisons. This resulted in mixed results and as a result for most efficacy, effectiveness, and safety outcomes of interest, it was not possible to draw a conclusion in favour of long-term continuous or on-demand PPI therapy. 2) Identified studies from the literature are mostly sponsored by the industry. 3) A couple of the model and input assumptions for the cost-effectiveness model were not based on literature or expert opinion, as they were related to patients' anticipated behaviour under a future reimbursement policy as well as the fact that it is not possible to calculate the actual deductible costs in the current Swiss insurance co-payment system. 4) It was assumed that the resource use in the Szucs et. al. 2009 trial reflected the real world resource use in the Swiss clinical setting, even though the clinical practice for GERD is not expected to change drastically, and this trial was an open-label trial, it is important that this key assumption is emphasized. 5) As the GERD-specific outpatient unit costs for

resource use in Switzerland could not be generated from the available databases, values from different studies found from the literature (e.g. ProGERD) were used in the economic model, additionally it was assumed that the market share of all PPIs used in Switzerland were reflective of the market share of all PPIs used for uninvestigated GERD population in Switzerland. 6) In the cost-effectiveness analysis, wastage costs (i.e. due to leftover tablets in a package) and the implementation costs of reimbursement restriction were not included in the calculations. Hence, the results of this analysis should be interpreted with caution, if the reimbursement restriction policy implementation for on-demand PPI therapy is planned as handing the maximum yearly reimbursed amount of tablets at once, instead of supplying these tablets on a periodic basis. 7) In the literature we did not come across a study based on real-world data, investigating the impact of a reimbursement restriction for the on-demand therapy of uninvestigated GERD and NERD populations. Hence, unobserved effects of a reimbursement rule change (e.g. possible consequence of changing the reimbursement rule on the PPI intake or on the number of endoscopies in the affected patient population or other legal, social, ethical or organisational impacts) might not be captured in the presented studies identified from the literature.

13 Conclusions

In Switzerland long-term continuous PPIs for NERD and uninvestigated GERD patients are presumably over-prescribed. Given alternative treatment with on-demand PPI long-term therapy for non-erosive GERD and uninvestigated GERD patients, santésuisse suggests limiting prescription for this patient population to a maximum of 200 pills per year. The efficacy, effectiveness, safety, costs, and cost-effectiveness of PPI long-term continuous and on-demand therapy for NERD and endoscopically uninvestigated GERD patients was evaluated in an HTA.

With the evidence found in the clinical-effectiveness review, for most outcomes of interest it was not possible to draw a conclusion in favour of long-term continuous or on-demand PPI therapy, amongst others caused by lacking between-group statistical comparisons and heterogeneity in studies and study outcomes, resulting in mixed results. Due to heterogeneity of the studies, overall estimates of the outcomes were not calculated. Heterogeneity was for example caused by differences in population (i.e. endoscopically proven NERD, endoscopically uninvestigated GERD, or a mixed population of endoscopically proven NERD and low grade GERD), prescribed PPIs (i.e. esomeprazole, omeprazole, rabeprazole, pantoprazole, lansoprazole, or any other PPI), PPI dosages (i.e. varying from 10 mg to 60 mg), or differences in the definition, measurement, units, or stratification of outcomes. The efficacy evidence showed that long-term on-demand PPI therapy results in lower PPI pill consumption per day compared with long-term continuous PPI therapy. The observed difference for the outcome heartburn symptom relief was in favour of continuous PPI therapy and may largely be attributed to the specifications of the therapy modality (i.e. with on-demand therapy a dose of PPI is taken when clinical symptoms occur, which may explain the higher symptom load). In conclusion, long-term PPI therapy is effective in managing the symptoms of NERD and uninvestigated GERD patients, either with a continuous or on-demand therapy modality. Based on the efficacy and effectiveness outcomes, the overall satisfaction of the patients with long-term continuous or on-demand PPI therapy and health-related quality of life was in general high. Furthermore, no major safety issues were reported in the included studies.

On-demand therapy appeared to be cost-effective when PPI use is restricted to 200 pills per year. The cost-effectiveness analysis showed that there is no significant difference expected in terms of QALYs, between on-demand and continuous PPI therapy. On the other hand, the on-demand PPI therapy is expected to lead to cost savings of 896 CHF, in comparison to the continuous PPI therapy, over the course of a patient's life time. Since the QALY difference between two arms is extremely small, the cost savings due to on-demand PPI therapy lead to tremendously high ICER values. Under the reimbursement restriction, the additional life time out-of-pocket payment for PPIs will be 380 CHF per patient. The

main conclusion of the cost-effectiveness results is robust, under different reimbursement restriction level assumptions, sensitivity, and scenario analyses.

The 5 year budget saving from changing the uninvestigated GERD and NERD patients' continuous PPI therapy to on-demand PPI therapy, is estimated to be between 50 and 127 million CHF. This budget impact depends on the nature of the policy implementation (sudden or gradual, the budget impact of the latter is smaller) as well as the reimbursement restriction threshold and the scope of the reimbursement restriction (i.e. full reimbursement for patients who switched to continuous PPI therapy after failing on-demand PPI therapy before endoscopy).

The legal, social, and ethical impact of PPI reimbursement restrictions could not be assessed, since no relevant information was available. Organisational issues that would result from the change in reimbursement policy are dependent on the specific characteristics of the policy change and could therefore, not be derived from literature.

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15 Appendices

15.1 Search strategy for the efficacy, effectiveness, and safety review

PubMed (MEDLINE)

#1 P: NERD/GERD

non-erosive reflux disease[tiab] OR nonerosive reflux disease[tiab] OR NERD[tiab] OR gastroesophageal reflux disease[tiab] OR gastrooesophageal reflux disease[tiab] OR gastroesophageal reflux disease[tiab] OR gastrooesophageal reflux disease[tiab] OR GERD[tiab]

#2 I: PPI therapy

"Proton Pump Inhibitors"[Mesh] OR proton pump inhibitor*[tiab] OR PPI*[tiab] OR omeprazole[tiab] OR lansoprazole[tiab] OR esomeprazole[tiab] OR pantoprazole[tiab] OR rabeprazole[tiab] OR dexlansoprazole[tiab] OR ilaprazole[tiab]

Limits

- Publication period: 2000-2019
- Language: English, Dutch, French, German
- No animal studies:

  #3. Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh])
- No case reports and non-pertinent publication types:

  #

  4. case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt]

Number of hits PubMed (MEDLINE) ((#1 AND #2) NOT (#3 OR #4)):

- 3454 hits (26-03-2019)

Embase.com

#1 P: NERD/GERD

'non erosive reflux disease':ab,ti OR 'nonerosive reflux disease':ab,ti OR nerd:ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gastrooesophageal reflux disease':ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gastrooesophageal reflux disease':ab,ti OR gerd:ab,ti

#2 I: PPI therapy

'proton pump inhibitor'/exp OR 'proton pump inhibitor*':ab,ti OR ppi*:ab,ti OR omeprazole:ab,ti OR lansoprazole:ab,ti OR esomeprazole:ab,ti OR pantoprazole:ab,ti OR rabeprazole:ab,ti OR dexlansoprazole:ab,ti OR ilaprazole:ab,ti

Limits

- Publication period: 2000-2019
- Language: English, Dutch, French, German
- No case reports and non-pertinent publication types:

  #3. [article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [erratum]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim

Number of hits Embase.com ((#1 AND #2) NOT (#3)):

- 5070 hits (26-03-2019)

15.2 Search strategy for the cost-effectiveness review

PubMed (MEDLINE)

#1 P: NERD/GERD

non-erosive reflux disease[tiab] OR nonerosive reflux disease[tiab] OR NERD[tiab] OR gastroesophageal reflux disease[tiab] OR gastrooesophageal reflux disease[tiab] OR gastroesophageal reflux disease[tiab] OR gastrooesophageal reflux disease[tiab] OR GERD[tiab]

#2 I: PPI therapy

"Proton Pump Inhibitors"[Mesh] OR proton pump inhibitor[tiab] OR PPI*[tiab] OR omeprazole[tiab] OR*

lansoprazole[tiab] OR esomeprazole[tiab] OR pantoprazole[tiab] OR rabeprazole[tiab] OR dexlansoprazole[tiab] OR ilaprazole[tiab]

#3 Ec: Economic evaluation

(#3i OR #3ii OR #3iii OR #3iv OR #3v OR #3vi OR #3vii OR #3viii OR #3ix OR #3x OR #3xi OR #3xii OR #3xiii in [All fields])

i. economics OR "economic aspect" OR cost OR "health care cost" OR "drug cost" OR "hospital cost" OR socioeconomics OR "health economics" OR "pharmacoeconomics" OR "fee" OR "budget" OR "economic evaluation" OR "hospital finance" OR "financial management" OR "health care financing"

ii. "low cost" OR "high cost" OR "healthcare costs" OR (healthcare AND cost) OR fiscal OR funding OR financial OR finance

iii. (cost AND estimate) OR "cost estimate" OR "cost variable" OR (unit AND cost)*

iv. economic OR pharmacoeconomic* OR price* OR pricing*

v. (healthcare OR "health care") AND (utilization OR utilisation)

vi. cost AND (treat* OR therap*)*

*vii. (direct OR indirect) AND cost**

viii. "cost effectiveness analysis" OR "cost benefit analysis" OR "cost utility analysis" OR "cost minimization analysis" OR "economic evaluation"

ix. (economic OR "cost-benefit" OR "cost-effectiveness" OR "cost-utility") AND (evaluation OR analys* OR model* OR intervention*)*

x. ("cost minimization" OR "cost minimisation") AND (analys OR model*)*

xi. "resource use" OR "resource utilization" OR "resource utilisation"

xii. ("treatment costs" OR "costs of treatment" OR "cost of treatment" OR "costs of therapy" OR "cost of therapy" OR "cost of treating")

xiii. economic AND (evaluation* OR model)

Limits

- Publication period: 2000-2019
- Language: English, Dutch, German and French
- No animal studies:

  #4. Animals[Mesh] NOT (Humans[Mesh] AND Animals[Mesh])

- No case reports and non-pertinent publication types:

  #5. case reports[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR comment[pt]

Number of hits PubMed (MEDLINE) ((#1 AND #2 AND #3) NOT (#4 OR #5)):

- 359 hits (26-03-2019)

Embase.com

#1 P: NERD/GERD

'non erosive reflux disease':ab,ti OR 'nonerosive reflux disease':ab,ti OR nerd:ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gastrooesophageal reflux disease':ab,ti OR 'gastroesophageal reflux disease':ab,ti OR 'gastrooesophageal reflux disease':ab,ti OR gerd:ab,ti

#2 I: PPI therapy

'proton pump inhibitor'/exp OR 'proton pump inhibitor':ab,ti OR ppi*:ab,ti OR omeprazole:ab,ti OR lansoprazole:ab,ti OR esomeprazole:ab,ti OR pantoprazole:ab,ti OR rabeprazole:ab,ti OR dexlansoprazole:ab,ti OR ilaprazole:ab,ti*

#3 Ec: Economic evaluation

*'economics'/de OR 'economic aspect'/de OR 'cost'/de OR 'health care cost'/de OR 'drug cost'/de OR 'hospital cost'/de OR 'socioeconomics'/de OR 'health economics'/de OR 'pharmacoeconomics'/de OR 'fee'/exp OR 'budget'/exp OR 'economic evaluation'/exp OR 'hospital finance'/de OR 'financial man-agement'/de OR 'health care financing'/de OR 'low cost' OR 'high cost' OR health*care NEXT/1 cost* OR 'health care' NEXT/1 cost* OR fiscal OR funding OR financial OR finance OR cost NEXT/1 esti-mate* OR 'cost variable' OR unit NEXT/1 cost* OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti OR (cost* NEAR/3 (treat* OR therap*)):ab,ti OR health*care NEXT/1 (utilisation OR utilization) OR 'health care' NEXT/1 (utilisation OR utilization) OR resource NEXT/1 (utilisation OR utilization OR use)*

Limits

- Publication period: 2000-2019
- Language: English, Dutch, German and French
- No case reports and non-pertinent publication types:

#4. [article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [erratum]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim

Number of hits Embase.com ((#1 AND #2 AND #3) NOT (#4)):

- 552 hits (26-03-2019)

University of York CRD databases (DARE, NHS/EED and HTA databases)

(reflux disease) AND (PPI* OR proton pump inhibitor*) FROM 2000 TO 2018 in Any field

Number of hits CRD databases:

- 140 hits (26-03-2019)

15.2.1 Search filter for ethical and legal issues

- Ethical Issues

PubMed (MEDLINE)

#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18

#1 "Ethics"[Mesh]

#2 "Freedom"[Mesh]

#3 "Healthcare Disparities"[Mesh]

#4 health-care-delivery[majr] OR health-care-access[majr]

#5 "Informed Consent"[Mesh]

#6 "Morals"[Mesh]

#7 "Altruism"[Mesh]

#8 "Beneficence"[Mesh]

#9 "Ethicists"[Mesh]

#10 "Human Rights"[Mesh]

#11 "Ethics, Medical"[Mesh]

#12 quality of life[majr]

#13 (ethic*[tiab] OR moral*[tiab] OR bioethic*[tiab] OR complicit*[tiab] OR humanism[tiab] OR dignity[tiab] OR integrity[tiab] OR human-right*[tiab] OR principlism[tiab] OR normativ*[tiab] OR principle-base*[tiab] OR beneficence[tiab] OR autonomy[tiab])

#14 (non-maleficence[tiab] OR nonmaleficence[tiab] OR philosoph*[tiab] OR aristoteles[tiab] OR socrates[tiab] OR justice[tiab] OR fairness[tiab] OR hope[tiab] OR accessible[tiab] OR accessibility[tiab] OR Beauchamp[tiab] OR childress[tiab] OR equilibrium*[tiab] OR wide-reflective*[tiab] OR socratic[tiab])

#15 (social-shaping[tiab] OR casuistry[tiab] OR coherence-analy*[tiab] OR eclectic*[tiab] OR right-to-die[tiab] OR right-to-life[tiab] OR social-value*[tiab] OR ethnic-value*[tiab] OR personal-value*[tiab])

#16 (elsi[tiab] OR conviction*[tiab] OR harm[tiab] OR benefit-harm[tiab] OR harm-benefit[tiab] OR choice-of-end-point*[tiab])

#17 (rawls[tiab] OR rawlsian[tiab] OR utilitarian*[tiab] OR patient-choice[tiab] OR patient-decision-making[tiab] OR justify*[tiab] OR promise[tiab] OR imperative[tiab] OR normative[tiab] OR peril[tiab]OR conflicting-interests[tiab] OR equity[tiab] OR imperative[tiab] OR peril[tiab] OR promise[tiab] OR stigma[tiab] OR stigmatiz*[tiab] OR stigmatis*[tiab)

#18 (societal-value*[tiab] OR value*-of-society[tiab] OR fraud[tiab] OR falsified[tiab)

Number of hits PubMed (MEDLINE) (together with population and intervention filters):

- 256 hits (26-03-2019)

Embase.com

#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21

#1 ethics/exp

#2 freedom/exp

#3 health-care-disparity/exp

#4 health-care-delivery/mj or health-care-access/mj

#5 informed-consent/exp

#6 morality/exp

#7 altruism/exp

#8 beneficence/exp

#9 ethicist/exp

#10 human-dignity/exp

#11 human-rights/exp

#12 medical-ethics/exp

#13 personal-value/exp

#14 social-attitude/exp

#15 'quality of life'/mj

#16 (ethic* OR moral* OR bioethic* OR complicit* OR humanism OR dignity OR integrity OR human-right* OR principlism OR normativ* OR principle-base* OR beneficence OR autonomy):ti,ab,kw

#17 (non-maleficence OR philosoph* OR aristoteles OR socrates OR justice OR fairness OR hope OR accessible OR accessibility OR Beauchamp OR childress OR equilibrium* OR wide-reflective* OR so-cratic):ti,ab,kw

#18 (social-shaping OR casuistry OR coherence-analy* OR eclectic* OR right-to-die OR right-to-life OR social-value* OR ethnic-value* OR personal-value*):ti,ab,kw

#19 (elsi OR conviction* OR harm OR benefit-harm OR harm-benefit OR choice-of-end-point*):ti,ab,kw

#20 (rawls OR rawlsian OR utilitarian* OR patient-choice OR patient-decision-making OR justify* OR promise OR imperative OR normative OR peril OR conflicting-interests OR equity OR imperative OR peril OR promise OR stigma OR stigmatiz* OR stigmatis*):ti,ab,kw

#21 (societal-value* OR value*-of-society OR fraud OR falsified):ti,ab,kw

Number of hits Embase.com (together with population and intervention filters):

- 282 hits (26-03-2019)

- Legal Issues

PubMed (MEDLINE)

((((legal*[Title/Abstract]) OR law*[Title/Abstract] OR legisl*[Title/Abstract]) OR (Search "Legislation" [Publication Type] OR "Licensure"[Mesh] OR "Liability, Legal"[Mesh] OR "Legal Case" [Publication Type] OR "legislation and jurisprudence" [Subheading] OR "International Law"[Mesh])))

Number of hits PubMed (MEDLINE) (together with population and intervention filters):

- 3 hits (26-03-2019)

Embase.com

legal*:ti,ab OR law*:ti,ab OR legisl*:ti,ab OR 'licensing'/exp OR 'legal liability'/exp OR 'legislation and jurisprudence'/exp OR 'international law'/exp

Number of hits Embase.com (together with population and intervention filters):

- 17 hits (26-03-2019)

15.3 Summary tables for the efficacy, effectiveness, and safety review

15.3.1 Summary tables on-demand vs. continuous comparison studies on identical PPI and dosage.

Table 63: Treatment use (comparison studies identical PPI and dosage)

Table 64: Treatment completion and reasons discontinuation (comparison studies identical PPI and dosage)

Table 65: Health-related quality of life (comparison studies identical PPI and dosage)

Table 66: General symptom relief (comparison studies identical PPI and dosage)

Table 67: Heartburn (comparison studies identical PPI and dosage)

Table 68: Other specific symptoms/outcomes (comparison studies identical PPI and dosage)

Table 69: Treatment satisfaction at end of treatment (comparison studies identical PPI and dosage)

Table 70: Short-term safety (< 6 month comparison studies identical PPI and dosage)

15.3.2 Summary tables on-demand vs. continuous comparison studies on different PPI and/or dosage

Table 71: Treatment use (comparison studies different PPI and/or dosage)

Table 72: Treatment completion and reasons discontinuation (comparison studies different PPI and/or dosage)

Table 73: Health-related quality of life (comparison studies different PPI and/or dosage)

Table 74: General symptom relief (comparison studies different PPI and/or dosage)

Table 75: Heartburn (comparison studies different PPI and/or dosage)

Table 76: Other specific symptoms/outcomes (comparison studies different PPI and/or dosage)

Table 77: Treatment satisfaction at end of treatment (comparison studies different PPI and/or dosage)

Table 78: Short-term safety (comparison studies different PPI and/or dosage)

15.3.3 Summary tables non-comparison studies on continuous PPI therapy

Table 79: Treatment use (non-comparison continuous studies)

Table 80: Health-related quality of life (non-comparison continuous studies)

Table 81: Symptom relief (non-comparison continuous studies)

Table 82: Treatment satisfaction at end of treatment (non-comparison continuous studies)

Table 83: Short-term safety (non-comparison continuous studies)

Table 84: Long-term safety (non-comparison continuous studies)

15.3.4 Summary tables non-comparison studies on on-demand PPI therapy

Table 85: Treatment use (non-comparison on-demand studies)

Table 86: Health-related quality of life (non-comparison on-demand studies)

Table 87: Symptom relief (non-comparison on-demand studies)

Table 88: Treatment satisfaction at end of treatment (non-comparison on-demand studies)

Table 89: Short-term safety (non-comparison on-demand studies)

15.3.1 Summary tables on-demand vs. continuous comparison studies on identical PPI and dosage.

Table 63: Treatment use (comparison studies identical PPI and dosage)

Reference Country	Study population PPI	Sample size	Mean (SD) pills/day	Mean (SD) pills/week	Mean (SD) total nr of pills	% days PPI intake during study	Mean (SD) nr supplemental antacids/day
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Bayerdörffer, 2016[36] Austria, France, Germany, South Africa, Spain	Endoscopically proven NERD Esomeprazole 20 mg (6 m)	- Total: 598 - C: 297 - OD: 301	- C: 0.91 (0.16) - OD: 0.41 (0.25) - No statistical comparison	NR	NR	NR	NR
Nagahara, 2014[37] Japan	Endoscopically proven NERD Omeprazole 20 mg (6 m)	- Total: 35 - C: 18 - OD: 17	NR	NR	NR	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS							
Hansen, 2005[10]; Hansen, 2006[38] Norway	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1902 - C: 658 - OD: 634	NR	NR	NR	NR	NR
Morgan, 2007[39] Canada	Endoscopically uninvestigated GERD Rabeprazole 20 mg (6 m)	- Total: 268 - C: 137 - OD: 131	NR	NR	NR	- C: 97% of days - OD: 45% of days* - No statistical comparison	- C: 0.1 (0.3) - OD: 0.3 (0.4) - p=0.0023
Nagahara, 2014[37] Japan	Endoscopically proven GERD Omeprazole 20 mg (6 m)	Total: 117 - C: 59 - OD: 58	NR	- C: range 6.2-6.9 (NR) - OD: range 1.8-3.0 (NR) - No statistical comparison - Both ranges are a decrease in time	NR	NR	NR
Szucs, 2009[40] Switzerland	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1904 - C: 913 - OD: 991	- C: 1.03‡ - OD: 0.55‡ - No statistical comparison	NR	- C: 174; median=188 (46.9) - OD: 116; median=100 (63.1)§ - No statistical comparison	NR	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS							
Bour, 2005[43] France	Mixed population of endoscopically proven NERD and Grade I-II GERD Rabeprazole 10 mg (6 m)	- Total: 152 - C: 81 - OD: 71	- C: 0.96 (NR) - OD: 0.31 (NR) - p<0.0001	NR	NR	NR	NR

Reference Country	Study population PPI	Sample size	Mean (SD) pills/day	Mean (SD) pills/week	Mean (SD) total nr of pills	% days PPI intake during study	Mean (SD) nr supplemental antacids/day
Janssen, 2005 [42] Germany, France, Switzerland, Hungary	Mixed population of endoscopically proven NERD and Grade I GERD Pantoprazole 20 mg (24 w)	- Total: 432 - C: 217 - OD: 215	- C: 0.93 (0.17) - OD: 0.51 (0.31) - p<0.001	NR	- C: 152.4 (38.2) - OD: 83.2 (52.4) - p<0.001	NR	NR
Pace, 2005 [41] Italy	Mixed population of endoscopically proven NERD and Grade I GERD Esomeprazole 20 mg (6 m)	- Total: 5265 - C: 2628 - OD: 2637	NR	NR	- C: 179 (38.2) - OD: 83.2 (52.4)† - No statistical comparison	NR	NR

Keys: C = continuous therapy, GERD = gastroesophageal reflux disease, m = months, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, SD = standard deviation, w = weeks
* ~1 dose/2.2 days; mean (SD) duration treatment episodes: 4.5 (15.8) days; mean (SD) interval between treatment episodes: 9.7 (22) days; † Nearly 1 dose/2 days; ‡ Calculated by Pallas: median number of total pills divided by the median number of days on maintenance therapy. Median number of days on maintenance therapy in continuous therapy group 182 (SD 37.0 days) and in on-demand group 182 (SD 38.5) days; § 1 dose on 4-5 days of a 7-day week; around one-third of patients took on average 1 tablet/day

Table 64: Treatment completion and reasons discontinuation (comparison studies identical PPI and dosage)

Reference Country	Study population PPI	Sample size	% Treatment completion	% Treatment discontinuation reasons
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS				
Bayerdörffer, 2016[36] Austria, France, Germany, South Africa, Spain	Endoscopically proven NERD Esomeprazole 20 mg (6 m)	- Total: 598 - C: 297 - OD: 301	- C: 90.2% - OD: 92.0% - p=0.15	C / OD: - Eligibility criteria not fulfilled: 2.0% / 1.3% - AE: 2.0% / 0.3% - Improvement/recovery: 0.7% / 0% - LTFU: 2.4% / 2.0% - Protocol non-compliance: 0.7% / 0.7% - Unsatisfied symptom control: 0.7% / 1.0% - Dissatisfaction pill taking/size/taste: 0% / 0% - Other (not specified): 1.3% / 1.0% No difference between treatments (p=0.15); AE (p=0.07)
Nagahara, 2014[37] Japan	Endoscopically proven NERD Omeprazole 20 mg (6 m)	- Total: 35 - C: 18 - OD: 17	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS				
Hansen, 2005[10]; Hansen, 2006[38] Norway	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1902 - C: 658 - OD: 634	- C: 88.9% - OD: 89.9% - No statistical comparison	Due to lack of efficacy: - C: 11.1% - OD: 10.1% - No statistical comparison Due to any AE: - C: 7.9% - OD: 2.5% - No statistical comparison
Morgan, 2007[39] Canada	Endoscopically uninvestigated GERD Rabeprazole 20 mg (6 m)	- Total: 268 - C: 137 - OD: 131	NR	Due to insufficient heartburn control: - C: 2.2% - OD: 4.6% - p=0.8690 Due to non-severe AEs: - C: 2.9% - OD: 0.8% - No statistical comparison
Nagahara, 2014[37] Japan	Endoscopically proven GERD Omeprazole 20 mg (6 m)	Total: 117 - C: 59 - OD: 58	NR	NR
Szucs, 2009[40] Switzerland	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1904 - C: 913 - OD: 991	NR	NR
MIXED POPULATION OF ENDOSCOPICALLY UNINVESTIGATED NERD AND LOW GRADE GERD PATIENTS				
Bour, 2005[43] France	Mixed population of endoscopically proven NERD and Grade I-II GERD Rabeprazole 10 mg (6 m)	- Total: 152 - C: 81 - OD: 71	- C: 88.8% - OD: 84.5% - No statistical comparison	C / OD (p-value): - AEs: 6.2% / 4.2% (0.724) - Recurrence: 0% / 2.8% (0.216) - Lack of efficacy: 0% / 1.4% (0.467) - Withdrawal of consent: 1.2% / 0% (0.100) - Non-compliance: 3.7% / 1.4% (0.623) - Other (not specified): 1.2% / 8.5% (0.051)

Reference Country	Study population PPI	Sample size	% Treatment completion	% Treatment discontinuation reasons
Janssen, 2005 [42] Germany, France, Switzerland, Hungary	Mixed population of endoscopically proven NERD and Grade I GERD Pantoprazole 20 mg (24 w)	- Total: 432 - C: 217 - OD: 215	- C: 92.2% - OD: 94.0% - No statistical comparison	Due to insufficient symptom control: - C: 0.95% - OD: 0.95% - No significant difference
Pace, 2005[41] Italy	Mixed population of endoscopically proven NERD and Grade I GERD Esomeprazole 20 mg (6 m)	- Total: 5265 - C: 2628 - OD: 2637	NR	NR

Keys: AE = adverse event, C = continuous therapy, GERD = gastroesophageal reflux disease, LTFU = lost to follow-up, m = months, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, w = weeks

Table 65: Health-related quality of life (comparison studies identical PPI and dosage)

Reference Country	Study population PPI	Sample size	QOLRAD	PAGI-QoL	Reflux-Qual
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS					
Bayerdörffer, 2016[36] Austria, France, Germany, South Africa, Spain	Endoscopically proven NERD Esomeprazole 20 mg (6 m)	- Total: 598 - C: 297 - OD: 301	Continuous therapy significantly greater improvement in all 5 QoL domains (p<0.001); not clinically relevant	NR	NR
Nagahara, 2014 [37] Japan	Endoscopically proven NERD Omeprazole 20 mg (6 m)	- Total: 35 - C: 18 - OD: 17	NR	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS					
Hansen, 2005[10]; Hansen, 2006[38] Norway	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1902 - C: 658 - OD: 634	Continuous therapy significantly greater improvement in all QoL domains (p<0.05), except physical activity; not clinically relevant	NR	NR
Morgan, 2007[39] Canada	Endoscopically uninvestigated GERD Rabeprazole 20 mg (6 m)	- Total: 268 - C: 137 - OD: 131	NR	Continuous therapy significantly greater improvement in total QoL (p=0.003) and all domains (p<0.05), except the relationships domain	NR
Nagahara, 2014[37] Japan	Endoscopically proven GERD Omeprazole 20 mg (6 m)	Total: 117 - C: 59 - OD: 58	QoL change over time not compared; no statistically significant differences between treatment groups at each visit	NR	NR
Szucs, 2009[40] Switzerland	Endoscopically uninvestigated GERD	- Total: 1904 - C: 913 - OD: 991	NR	NR	NR

	Esomeprazole 20 mg (6 m)				
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS					
Bour, 2005[43] France	Mixed population of endoscopically proven NERD and Grade I-II GERD Rabeprazole 10 mg (6 m)	- Total: 152 - C: 81 - OD: 71	NR	NR	Continuous therapy significantly greater improvement in total QoL (p=0.034) and daily life (p=0.005), sleep (p=0.016) and food/diet (p=0.047), not relationships, wellbeing and mental state and fears
Janssen, 2005 [42] Germany, France, Switzerland, Hungary	Mixed population of endoscopically proven NERD and Grade I GERD Pantoprazole 20 mg (24 w)	- Total: 432 - C: 217 - OD: 215	NR	NR	NR
Pace, 2005[41] Italy	Mixed population of endoscopically proven NERD and Grade I GERD Esomeprazole 20 mg (6 m)	- Total: 5265 - C: 2628 - OD: 2637	Continuous therapy significantly greater improvement in all QoL domains (p<0.0001); marginal difference	NR	NR

Keys: C = continuous therapy, GERD = gastroesophageal reflux disease, m = months, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, PAGI-QoL = Patient Assessment of upper Gastrointestinal disorders - Quality of Life, QOLRAD = Quality of Life in Reflux and Dyspepsia, w = weeks

Table 66: General symptom relief (comparison studies identical PPI and dosage)

Reference Country	Study population PPI	Sample size	Definition symptom relief	Overall symptom relief	Definition relapse	% relapse	Mean (SD) perceived daily symptom load
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Bayerdörffer, 2016[36] Austria, France, Germany, South Africa, Spain	Endoscopically proven NERD Esomeprazole 20 mg (6 m)	- Total: 598 - C: 297 - OD: 301	GSRS	Continuous therapy significantly greater relief in indigestion (p=0.002), abdominal pain (p=0.001) and reflux (p<0.001), not in diarrhoea and constipation; reflux only clinically relevant	-	NR	NR
Nagahara, 2014[37] Japan	Endoscopically proven NERD Omeprazole 20 mg (6 m)	- Total: 35 - C: 18 - OD: 17	GOS, symptom relief = symptom free ≥6 days/w at any week during the 24 w of treatment	No significant difference between groups	-	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS							
Hansen, 2005[10]; Hansen, 2006[38] Norway	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1902 - C: 658 - OD: 634	OTE	% symptom improvement: - C: 80.2% - OD: 77.8% - No significant difference % A good deal, great deal or very great deal better symptoms*: - C: 95% - OD: 86.5% - No statistical comparison	Need for change in treatment	- C: 7.0% - OD: 10.9% - No statistical comparison	NR
Morgan, 2007[39] Canada	Endoscopically uninvestigated GERD Rabeprazole 20 mg (6 m)	- Total: 268 - C: 137 - OD: 131	GSAS	Continuous therapy significantly fewer and less severe GERD symptoms at end of treatment compared to on-demand therapy (p<0.05)	-	NR	NR
Nagahara, 2014[37] Japan	Endoscopically proven GERD Omeprazole 20 mg (6 m)	Total: 117 - C: 59 - OD: 58	GOS, symptom relief = symptom free ≥6 days/w at any week during the 24 w of treatment	Significantly more patients in the continuous therapy group achieved symptom relief during w 1 to w 10 and during w 12, 13, 16, and 17; no difference in other weeks	-	NR	NR
Szucs, 2009[40] Switzerland	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1904 - C: 913 - OD: 991	-	NR	Need for change in treatment	- C: 6.0% - OD: 6.1% - No significant difference	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS							
Bour, 2005[43] France	Mixed population of endoscopically proven NERD and Grade I-II GERD Rabeprazole 10 mg (6 m)	- Total: 152 - C: 81 - OD: 71	Symptom relief = Likert score ≤2 for the symptom that had led to the initial consultation	At study end: - C: 86.4% - OD: 74.6% - p=0.065	Recurrence of main symptom	- C: 13.6% - OD: 21.1% - p=0.218	NR

Reference Country	Study population PPI	Sample size	Definition symptom relief	Overall symptom relief	Definition relapse	% relapse	Mean (SD) perceived daily symptom load
Janssen, 2005 [42] Germany, France, Switzerland, Hungary	Mixed population of endoscopically proven NERD and Grade I GERD Pantoprazole 20 mg (24 w)	- Total: 432 - C: 217 - OD: 215	Symptom relief = no failure to control symptoms	- C: 81.4% - OD: 69.3% - No significant difference	-	NR	- C: 0.82 (1.34) - OD: 1.26 (1.49) - p<0.001; on-demand therapy higher symptom load
Pace, 2005[41] Italy	Mixed population of endoscopically proven NERD or Grade I GERD Esomeprazole 20 mg (6 m)	- Total: 5265 - C: 2628 - OD: 2637	-	NR	-	NR	NR

Keys: C = continuous therapy, GERD = gastroesophageal reflux disease, GOS = Global Overall Symptom scale, GSAS = GERD Symptoms Assessment Scale, GSRS = Gastrointestinal Symptom Rating Scale, m = months, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, OTE = Overall Treatment Evaluation, w = weeks
* % change in symptoms considered as important, very important or extremely important: C: 91 / OD: 84.7 / no statistical comparison

Table 67: Heartburn (comparison studies identical PPI and dosage)

Reference Country	Study population PPI	Sample size	% no heartburn at study end	% heartburn-free days	% weeks with ≤2 days/week heartburn	Mean (SD) nr heartburn episodes	Mean (SD) days heartburn episodes
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Bayerdörffer, 2016[36]	Endoscopically proven NERD Esomeprazole 20 mg (6 m)	- Total: 598 - C: 297 - OD: 301	NR	NR	NR	NR	NR
Nagahara, 2014 [37] Japan	Endoscopically proven NERD Omeprazole 20 mg (6 m)	- Total: 35 - C: 18 - OD: 17	NR	NR	NR	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS							
Hansen, 2005[10]; Hansen, 2006[38] Norway	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1902 - C: 658 - OD: 634	- C: 72.2% - OD: 45.1% - p<0.0001	NR	NR	NR	NR
Morgan, 2007[39] Canada	Endoscopically uninvestigated GERD Rabeprazole 20 mg (6 m)	- Total: 268 - C: 137 - OD: 131	NR	- C: 90.3% - OD: 64.8% - p<0.0001	Max mild severity: - C: 84% - OD: 41% - p<0.0001	- C: 7 (9.1) - OD: 26 (15.7) - p<0.0001	- C: 1.4 (2) - OD: 4.4 (15.7) - p=0.0319
Nagahara, 2014[37] Japan	Endoscopically proven GERD Omeprazole 20 mg (6 m)	Total: 117 - C: 59 - OD: 58	NR	NR	NR	NR	NR

Szucs, 2009[40] Switzerland	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1904 - C: 913 - OD: 991	- C: 86% - OD: 80% - p<0.001[a]	NR	NR	NR	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS							
Bour, 2005[43] France	Mixed population of endoscopically proven NERD and Grade I-II GERD Rabeprazole 10 mg (6 m)	- Total: 152 - C: 81 - OD: 71	NR	NR	NR	NR	NR
Janssen, 2005 [42] Germany, France, Switzerland, Hungary	Mixed population of endoscopically proven NERD and Grade I GERD Pantoprazole 20 mg (24 w)	- Total: 432 - C: 217 - OD: 215	NR	NR	NR	NR	NR
Pace, 2005[41] Italy	Mixed population of endoscopically proven NERD and Grade I GERD Esomeprazole 20 mg (6 m)	- Total: 5265 - C: 2628 - OD: 2637	NR	NR	NR	NR	NR

Keys: C = continuous therapy, GERD = gastroesophageal reflux disease, m = months, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, w = weeks; [a] No significant difference in % mild, moderate or severe heartburn

Table 68: Other specific symptoms/outcomes (comparison studies identical PPI and dosage)

Reference Country	Study population PPI	Sample size	% no regurgitation at study end	% no epigastric pain at study end	Mean (SD) nr of reflux days	% mucosal breaks at study end	% reflux esophagitis at study end
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Bayerdörffer, 2016[36]	Endoscopically proven NERD Esomeprazole 20 mg (6 m)	- Total: 598 - C: 297 - OD: 301	NR	NR	NR	- C: 0% - OD: 5% - p<0.0001	NR
Nagahara, 2014[37] Japan	Endoscopically proven NERD Omeprazole 20 mg (6 m)	- Total: 35 - C: 18 - OD: 17	NR	NR	NR	NR	- C: 0% - OD: 0% - No significant difference
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS							
Hansen, 2005[10]; Hansen, 2006[38] Norway	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1902 - C: 658 - OD: 634	- C: 78% - OD: 62% - No statistical comparison	NR	NR	NR	NR
Morgan, 2007[39] Canada	Endoscopically uninvestigated GERD Rabeprazole 20 mg (6 m)	- Total: 268 - C: 137 - OD: 131	NR	NR	NR	NR	NR
Nagahara, 2014[37] Japan	Endoscopically proven GERD Omeprazole 20 mg (6 m)	Total: 117 - C: 59 - OD: 58	NR	NR	NR	NR	NR
Szucs, 2009[40] Switzerland	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1904 - C: 913 - OD: 991	- C: 89% - OD: 86% - No significant difference[a]	- C: 89% - OD: 89% - No significant difference[a]	- C: 0.37 (1.2) - OD: 0.43 (1.2) - No significant difference	NR	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS							
Bour, 2005[43] France	Mixed population of endoscopically proven NERD and Grade I-II GERD Rabeprazole 10 mg (6 m)	- Total: 152 - C: 81 - OD: 71	NR	NR	NR	NR	NR
Janssen, 2005[42] Germany, France, Switzerland, Hungary	Mixed population of endoscopically proven NERD and Grade I GERD Pantoprazole 20 mg (24 w)	- Total: 432 - C: 217 - OD: 215	NR	NR	NR	NR	NR

Reference Country	Study population PPI	Sample size	% no regurgitation at study end	% no epigastric pain at study end	Mean (SD) nr of reflux days	% mucosal breaks at study end	% reflux esophagitis at study end
Pace, 2005[41] Italy	Mixed population of endoscopically proven NERD and Grade I GERD Esomeprazole 20 mg (6 m)	- Total: 5265 - C: 2628 - OD: 2637	NR	NR	NR	NR	NR

Keys: C = continuous therapy, GERD = gastroesophageal reflux disease, m = months, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, w = weeks; [a] No significant difference in % mild, moderate or severe epigastric pain

Table 69: Treatment satisfaction at end of treatment* (comparison studies identical PPI and dosage)

Reference Country	Study population PPI	Sample size	Definition satisfaction	General	% satisfied with treatment of heartburn	% satisfied with way taking treatment
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS						
Bayerdörffer, 2016[36]	Endoscopically proven NERD Esomeprazole 20 mg (6 m)	- Total: 598 - C: 297 - OD: 301	Upper two of 5 answer options	% satisfied: - C: 84.8% - OD: 78.7% - No significant difference	& regurgitation: - C: 86.2% - OD: 82.1% - No significant difference	- C: 82.8% - OD: 81.7% - No significant difference
Nagahara, 2014[37] Japan	Endoscopically proven NERD Omeprazole 20 mg (6 m)	- Total: 35 - C: 18 - OD: 17	-	NR	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS						
Hansen, 2005[10]; Hansen, 2006[38] Norway	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1902 - C: 658 - OD: 634	Upper two of 7 answer options	% very satisfied: - C: 82.2% - OD: 75.4% - p<0.01	NR	NR
Morgan, 2007[39] Canada	Endoscopically uninvestigated GERD Rabeprazole 20 mg (6 m)	- Total: 268 - C: 137 - OD: 131	Upper two of 5 answer options	NR	- C: 92% - OD: 79% - p=0.0070 % (very) good effect patient / physician: - C: 89% / 89% - OD: 83% / 81% - p=0.2803 / p=0.1173 % of weeks satisfactorily or completely controlled: - C: 96% - OD: 84% - p<0.0001 % of weeks (very) satisfied: - C: 92% - OD: 76% - p<0.0001	NR

Reference Country	Study population PPI	Sample size	Definition satisfaction	General	% satisfied with treatment of heartburn	% satisfied with way taking treatment
Nagahara, 2014[37] Japan	Endoscopically proven GERD Omeprazole 20 mg (6 m)	Total: 117 - C: 59 - OD: 58	-	NR	NR	NR
Szucs, 2009[40] Switzerland	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1904 - C: 913 - OD: 991	Satisfied: upper 4 of 7 answer options Very satisfied: upper 2 of 7 answer options	NR	Satisfied: - C: 93% - OD: 94% Very satisfied: - C: 77% - OD: 74% No significant difference in overall satisfaction score (1-7)	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS						
Bour, 2005[43] France	Mixed population of endoscopically proven NERD and Grade I-II GERD Rabeprazole 10 mg (6 m)	- Total: 152 - C: 81 - OD: 71	Analogue visual scale 0-100 mm; higher score = more satisfied	Patient: - C: 90 mm - OD: 83 mm - p=0.026 Physician: - C: 90 mm - OD: 83 mm - p=0.005	NR	NR
Janssen, 2005 [42] Germany, France, Switzerland, Hungary	Mixed population of endoscopically proven NERD and Grade I GERD Pantoprazole 20 mg (24 w)	- Total: 432 - C: 217 - OD: 215	-	NR	NR	NR
Pace, 2005[41] Italy	Mixed population of endoscopically proven NERD and Grade I GERD Esomeprazole 20 mg (6 m)	- Total: 5265 - C: 2628 - OD: 2637	Upper two of 7 answer options	NR	- C: 64.5% - OD: 59.7% - Significant difference (p-value NR)	NR

Keys: C = continuous therapy, GERD = gastroesophageal reflux disease, m = months, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, w = weeks
* Satisfaction assessed by patient, unless stated otherwise

Table 70: Short-term safety (<6 months; comparison studies identical PPI and dosage)

Reference Country	Study population PPI	Sample size	% AEs	% SAEs	% patients with endoscopy during treatment
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS					
Bayerdörffer, 2016[36]	Endoscopically proven NERD Esomeprazole 20 mg (6 m)	- Total: 598 - C: 297 - OD: 301	- C: 35.4% - OD: 36.2% - Similar AE profile, p-value NR	- C: 3.7% - OD: 1.3% - No statistical comparison - All SAEs considered not related to treatment	NR
Nagahara, 2014[37] Japan	Endoscopically proven NERD Omeprazole 20 mg (6 m)	- Total: 35 - C: 18 - OD: 17	NR	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS					
Hansen, 2005[10]; Hansen, 2006[38] Norway	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1902 - C: 658 - OD: 634	- C: 46.0% - OD: 47.8% - Similar AE incidence, p-value NR	NR	NR
Morgan, 2007[39] Canada	Endoscopically uninvestigated GERD Rabeprazole 20 mg (6 m)	- Total: 268 - C: 137 - OD: 131	No overall % reported; treatment groups not statistically compared	NR	NR
Nagahara, 2014[37] Japan	Endoscopically proven GERD Omeprazole 20 mg (6 m)	Total: 117 - C: 59 - OD: 58	NR	NR	NR
Szucs, 2009[40] Switzerland	Endoscopically uninvestigated GERD Esomeprazole 20 mg (6 m)	- Total: 1904 - C: 913 - OD: 991	No tolerability concerns, and no clinically relevant differences between the treatment groups regarding the profile or incidence of AEs; not further specified	NR	% endoscopies without biopsy: - C: 0.8% - OD: 0.9% - No statistical comparison % endoscopies with biopsy: - C: 2.3% - OD: 1.9% - No statistical comparison
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS					
Bour, 2005[43] France	Mixed population of endoscopically proven NERD and Grade I-II GERD Rabeprazole 10 mg (6 m)	- Total: 152 - C: 81 - OD: 71	NR	NR	NR
Janssen, 2005[42] Germany, France, Switzerland, Hungary	Mixed population of endoscopically proven NERD and Grade I GERD Pantoprazole 20 mg (24 w)	- Total: 432 - C: 217 - OD: 215	- C: 37.3%* - OD: 29.9%* - No significant difference, p-value NR	- C: 5.9% - OD: 2.6% - No statistical comparison - All SAEs considered not related to treatment	NR

Reference Country	Study population PPI	Sample size	% AEs	% SAEs	% patients with endos-copy during treatment
Pace, 2005[41] Italy	Mixed population of endoscopically proven NERD and Grade I GERD Esomeprazole 20 mg (6 m)	- Total: 5265 - C: 2628 - OD: 2637	NR	NR	NR

Keys: AE = adverse event, C = continuous therapy, GERD = gastroesophageal reflux disease, m = months, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, SAE = severe adverse event, w = weeks
* AE relation to continuous therapy / on-demand therapy (no significant difference): Unrelated: 84.8 / 77.2; Not likely related: 11.2 / 16.8; Likely related: 3.9 / 6.0; Definitely related: 0 / 0. AE intensity continuous therapy / on-demand therapy (no significant difference): Mild: 43.3 / 41.6; Moderate: 45.5 / 47.7; Severe: 11.2 / 10.7

15.3.2 Summary tables on-demand vs. continuous comparison studies on different PPI and/or dosage

Table 71: Treatment use (comparison studies different PPI and/or dosage)

Reference Country	Study population PPI	Sample size	Mean (SD) pills/day	Mean (SD) pills/week	Mean (SD) total nr of pills	% days PPI intake during study	Mean (SD) nr supplemental antacids/day
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Cibor, 2006[45]	Endoscopically proven NERD Lansoprazole 15 mg or 30 mg (11 m)	- Total: 60 - C: 20 - OD: 20	- C: NR - OD: 0.3 (0.3)	NR	NR	NR	NR
Tepeŝ, 2009[46]	Endoscopically proven NERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 56 - C: 25 - OD: 23	NR	NR	NR	NR	NR
Tsai, 2004[18]	Endoscopically proven NERD Lansoprazole 15 mg or esomeprazole 20 mg (6 m)	- Total: 622 - C: 311 - OD: 311	- C: 0.8 (NR) - OD: 0.3 (NR) - No statistical comparison	NR	NR	NR	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS							
Tepeŝ, 2009[46]	Mixed population of endoscopically proven NERD and LA Grade A-B GERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 196 - C: 102 - OD: 94	NR	NR	NR	NR	NR

Keys: C = continuous therapy, GERD = gastroesophageal reflux disease, m = months, NERD = non-erosive reflux disease, NR: = not reported, OD = on-demand therapy, SD = standard deviation, UK = United Kingdom

Table 72: Treatment completion and reasons discontinuation (comparison studies different PPI and/or dosage)

Reference Country	Study population PPI	Sample size	% Treatment completion	% Treatment discontinuation reasons
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS				
Cibor, 2006[45]	Endoscopically proven NERD Lansoprazole 15 mg or 30 mg (11 m)	- Total: 60 - C: 20 - OD: 20	NR	NR
Tepeŝ, 2009[46]	Endoscopically proven NERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 56 - C: 25 - OD: 23	NR	NR
Tsai, 2004[18]	Endoscopically proven NERD Lansoprazole 15 mg or esomeprazole 20 mg (6 m)	- Total: 622 - C: 311 - OD: 311	NR	Due to unwillingness to continue: - C: 13.8% - OD: 6.2% - p=0.001 Due to unwillingness to continue because of AE: - C: 7.4% - OD: 2.3% - p=0.0028 Due to unwillingness to continue because of heartburn: - C: 4.8% - OD: 2.9% - No significant difference Due to unwillingness to continue because of another reason (not specified): - C: 1.3% - OD: 1.0% - No significant difference Due to an AE: - C: 9.6% - OD: 3.2% - No statistical comparison
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS				
Tepeŝ, 2009[46]	Mixed population of endoscopically proven NERD and LA Grade A-B GERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 196 - C: 102 - OD: 94	- C: 83.3% - OD: 88.3% - No statistical comparison	Reasons discontinuation: - Non-cooperation: C: 6.9% / OD: 6.4% - Other disease/pregnancy: C: 2.0% / OD: 2.1% - Withdrawal of consent: C: 3.9% / OD: 1.1% - Unknown: C: 3.9% / OD: 2.1% - AE: C: 0% / OD: 0% - No statistical comparison

Keys: AE = adverse event, C = continuous therapy, GERD = gastroesophageal reflux disease, m = months, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, UK = United Kingdom

Table 73: Health-related quality of life (comparison studies different PPI and/or dosage)

Reference Country	Study population PPI	Sample size	QOLRAD	PAGI-QoL	Reflux-Qual	Visual analogue scale*
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS						
Cibor, 2006[45]	Endoscopically proven NERD Lansoprazole 15 mg or 30 mg (11 m)	- Total: 60 - C: 20 - OD: 20	NR	NR	NR	NR
Tepeŝ, 2009[46]	Endoscopically proven NERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 56 - C: 25 - OD: 23	NR	NR	NR	NR
Tsai, 2004[18]	Endoscopically proven NERD Lansoprazole 15 mg or esomeprazole 20 mg (6 m)	- Total: 622 - C: 311 - OD: 311	NR	NR	NR	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS						
Tepeŝ, 2009[46]	Mixed population of Endo-scopically proven NERD and LA Grade A-B GERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 196 - C: 102 - OD: 94	NR	NR	NR	Mean at end of follow-up: - C: 9.7 - OD: 9.4 - No significant difference

Keys: C = continuous therapy, GERD = gastroesophageal reflux disease, m = months, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, PAGI-QoL = Patient Assessment of upper Gastrointestinal disorders - Quality of Life, QOLRAD = Quality of Life in Reflux and Dyspepsia, UK = United Kingdom
* Visual analogue scale from 1 to 10 (1 worst; 10 best, not affected by GERD symptoms)

Table 74: General symptom relief (comparison studies different PPI and/or dosage)

Reference Country	Study population PPI	Sample size	Definition symptom relief	Overall symptom relief	Definition relapse	% relapse	Mean (SD) perceived daily symptom load
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Cibor, 2006[45]	Endoscopically proven NERD Lansoprazole 15 mg or 30 mg (11 m)	- Total: 60 - C: 20 - OD: 20	-	NR	-	NR	NR
Tepeŝ, 2009[46]	Endoscopically proven NERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 56 - C: 25 - OD: 23	% cumulative remission	At 3 months - ITT / PP: - C: 92.0% / 92.0% - OD: 80.7% / 80.7% At 6 months - ITT / PP: - C: 80.0% / 90.9% - OD: 61.3% / 67.9% At 9 months - ITT / PP: - C: 76.0% / 90.5% - OD: 58.1% / 66.7% At 12 months - ITT / PP: - C: 76.0% (95% CI 59.2-92.7) / 90.5% (95% CI 77.9-100) - OD: 48.4% (95% CI 30.8-66.0) / 57.7% (95% CI 38.7-76.8) - p<0.05 PP and ITT; no statistical comparisons at 3, 6 and 9 months	- >3 reflux episodes of more than 5 minutes duration in 1 hour and occurring on more than 1 day in a week, or reflux problems lasting for more than 1 hour per day and occurring on more than 1 day in a week - % ≥1 relapse	At 3 months - ITT: - C: 8.0% - OD: 19.4% At 6 months - ITT: - C: 8.0% - OD: 29.0% At 9 months - ITT: - C: 8.0% - OD: 29.0% At 12 months - ITT: - C: 8.0% - OD: 35.5% - No statistical comparison	NR
Tsai, 2004[18]	Endoscopically proven NERD Lansoprazole 15 mg or esomeprazole 20 mg (6 m)	- Total: 622 - C: 311 - OD: 311	-	NR	-	NR	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS							
Tepeŝ, 2009[46]	Mixed population of endoscopically proven NERD and LA Grade A-B GERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 196 - C: 102 - OD: 94	% cumulative remission	At 3 months - ITT: - C: 92.2% - OD: 81.9% At 6 months - ITT: - C: 86.3% - OD: 71.3% At 9 months - ITT: - C: 79.4% - OD: 64.9% At 12 months - ITT: - C: 70.6% - OD: 57.5% - No statistical comparison	- Relapse in NERD: >3 reflux episodes of more than 5 minutes duration in 1 hour and occurring on more than 1 day in a week, or reflux problems lasting for more than 1 hour per day and occurring on more than 1 day in a week - Relapse in ERD: a positive endoscopic finding, in addition to a positive history - % ≥1 relapse	At 12 months - ITT: - C: 15.3% (95% CI 7.6-22.9) - OD: 34.9% (95% CI 24.6-45.2) - p<0.05	NR

Keys: C = continuous therapy, GERD = gastroesophageal reflux disease, m = months, ITT = intention-to-treat analysis, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, PP = per-protocol analysis, UK = United Kingdom

Table 75: Heartburn (comparison studies different PPI and/or dosage)

Reference Country	Study population PPI	Sample size	% no heart-burn at study end	% heart-burn-free days	% weeks with ≤2 days/week heartburn	Mean (SD) nr heartburn episodes	Mean (SD) days heart-burn episodes
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Cibor, 2006[45]	Endoscopically proven NERD Lansoprazole 15 mg or 30 mg (11 m)	- Total: 60 - C: 20 - OD: 20	NR	NR	NR	NR	NR
Tepeŝ, 2009[46]	Endoscopically proven NERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 56 - C: 25 - OD: 23	NR	NR	NR	NR	NR
Tsai, 2004[18]	Endoscopically proven NERD Lansoprazole 15 mg or esomepra-zole 20 mg (6 m)	- Total: 622 - C: 311 - OD: 311	NR	NR	NR	NR	Mean nr of days with heartburn symptoms in previous 7 days: At 1 month: - C: 0.9 - OD: 2.0 - No statistical com-parison At 3 months: - C: 0.6 - OD: 1.6 - No statistical com-parison At 6 months: - C: 0.9 - OD: 1.6 - No statistical com-parison
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS							
Tepeŝ, 2009[46]	Mixed population of Endoscopically proven NERD and LA Grade A-B GERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 196 - C: 102 - OD: 94	NR	NR	NR	NR	NR

Keys: C = continuous therapy, GERD = gastroesophageal reflux disease, m = months, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, UK = United Kingdom

Table 76: Other specific symptoms/outcomes (comparison studies different PPI and/or dosage)

Reference Country	Study population PPI	Sample size	% no regurgi-tation at study end	% no epigastric pain at study end	Mean (SD) nr of reflux days	% mucosal breaks at study end	% reflux esophagitis at study end
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Cibor, 2006[45]	Endoscopically proven NERD Lansoprazole 15 mg or 30 mg (11 m)	- Total: 60 - C: 20 - OD: 20	NR	NR	NR	NR	NR
Tepeŝ, 2009[46]	Endoscopically proven NERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 56 - C: 25 - OD: 23	NR	NR	NR	NR	NR
Tsai, 2004[18]	Endoscopically proven NERD Lansoprazole 15 mg or esomepra-zole 20 mg (6 m)	- Total: 622 - C: 311 - OD: 311	NR	NR	NR	NR	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS							
Tepeŝ, 2009[46]	Mixed population of endoscopically proven NERD and LA Grade A-B GERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 196 - C: 102 - OD: 94	NR	NR	NR	NR	NR

Keys: C = continuous therapy, GERD = gastroesophageal reflux disease, m = months, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, UK = United Kingdom

Table 77: Treatment satisfaction at end of treatment* (comparison studies different PPI and/or dosage)

Reference Country	Study population PPI	Sample size	Definition satisfaction	General	% satisfied with treatment of heartburn	% satisfied with way taking treatment
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS						
Cibor, 2006[45]	Endoscopically proven NERD Lansoprazole 15 mg or 30 mg (11 m)	- Total: 60 - C: 20 - OD: 20	Verbal rating scale (0 completely dissatisfied, 1 rather dissatisfied, 2 rather satisfied, 3 completely satisfied)	% completely satisfied: - After 2 months: C: 100% / OD: 90% - After 5 months: C: 95% / OD: 90% - After 11 months: C: 95% / OD: 90% - No significant difference between treatment groups at any time point Mean (SD) satisfaction score: - After 2 months: C: 3 (0) / OD: 2.85 (0.48) - After 5 months: C: 2.95 (0.22) / OD: 2.9 (0.3) - After 11 months: C: 2.95 (0.22) / OD: 2.9 (0.3) - No significant difference between treatment groups at any time point	NR	NR
Tepeŝ, 2009[46]	Endoscopically proven NERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 56 - C: 25 - OD: 23	-	NR	NR	NR
Tsai, 2004[18]	Endoscopically proven NERD Lansoprazole 15 mg or esomeprazole 20 mg (6 m)	- Total: 622 - C: 311 - OD: 311	Treatment Satisfaction Questionnaire, how satisfied with way heartburn is treated, 7 answer options, lowest score = most satisfied; satisfied = lower 4 answer options	NR	% satisfied with way heartburn is treated: At 1 month: - C: 87.8% - OD: 93.2% - p=0.02 At 3 months: - C: 88.1% - OD: 92.6% - No significant difference At 6 months: - C: 89.1% - OD: 91.6% - No significant difference	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS						
Tepeŝ, 2009[46]	Mixed population of endoscopically proven NERD and LA Grade A-B GERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 196 - C: 102 - OD: 94	-	NR	NR	NR

Keys: C = continuous therapy, GERD = gastroesophageal reflux disease, m = months, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, UK = United Kingdom
* Satisfaction assessed by patient

Table 78: Short-term safety (comparison studies different PPI and/or dosage)

Reference Country	Study population PPI	Sample size	% AEs	% SAEs	% patients with endoscopy during treatment
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS					
Cibor, 2006[45]	Endoscopically proven NERD Lansoprazole 15 mg or 30 mg (11 m)	- Total: 60 - C: 20 - OD: 20	NR	NR	NR
Tepeŝ, 2009[46]	Endoscopically proven NERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 56 - C: 25 - OD: 23	NR	NR	NR
Tsai, 2004[18]	Endoscopically proven NERD Lansoprazole 15 mg or esomeprazole 20 mg (6 m)	- Total: 622 - C: 311 - OD: 311	Diarrhoea: - C: 14% - OD: 5% - p<0.001 - Other AEs no significant difference	- C: 1.6% - OD: 2.9% - No statistical comparison	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS					
Tepeŝ, 2009[46]	Mixed population of endoscopically proven NERD and LA Grade A-B GERD Omeprazole 10 mg or 20 mg (12 m)	- Total: 196 - C: 102 - OD: 94	- C: 13.7% - OD: 0% - No statistical comparison	- C: 0% - OD: 0% - No statistical comparison	NR

Keys: AE = adverse event, C = continuous therapy, GERD = gastroesophageal reflux disease, m = months, NERD = non-erosive reflux disease, NR = not reported, OD = on-demand therapy, SAE = severe adverse event, UK = United Kingdom

15.3.3 Summary tables non-comparison studies on continuous PPI therapy

Table 79: Treatment use (non-comparison continuous studies)

Reference Country	Study population PPI	Sample size	Definition compli-ance	Mean (SD) pills/day	Mean (SD) total nr of pills	% days PPI intake during study	Compliance
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Dabholkar, 2011[48] USA	Endoscopically proven NERD Continuous dexlanso-prazole 60 or 90 mg once daily (12 months)*	153	Difference between the total number of capsules dispensed and returned / total number of days re-ceiving study drug	NR	NR	NR	97%
Kusano, 2014[51] Japan	Endoscopically proven NERD Continuous omepra-zole 10-20 mg/day, lansoprazole 15-30 mg/day, or rabepra-zole 10 mg/day (≥1 year)	46	NA	NR	NR	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS							
Brusselaers, 2018[49] Sweden	GERD patients (using ICD codes) Continuous any PPI at defined daily dose (at least 6 months)	201744	NA	NR	NR	NR	NR
Kaplan-Machlis, 2000[47] USA	Symptomatic GERD Continuous omepra-zole sodium 20 mg once daily (24 weeks)	130	NA	NR	NR	NR	NR
Talley, 2002[50] Australia	Symptomatic GERD Continuous pantopra-zole 20 mg once daily and placebo twice daily (12 months)	154	Consumption of 80-120% of expected number of tablets	NR	NR	NR	90%

Keys: GERD = gastroesophageal reflux disease, ICD = International Classification of Diseases, NA = not applicable, NERD = non-erosive reflux disease, NR = not reported, SD = standard deviation, USA = United States of America
* NERD continuation of initial treatment, GERD 90 mg group only

Table 80: Health-related quality of life (non-comparison continuous studies)

Reference Country	Study population PPI	Sample size	PAGI-QoL	PGWB	SF-36
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS					
Dabholkar, 2011[48] USA	Endoscopically proven NERD Continuous dexlansoprazole 60 or 90 mg once daily (12 months)[a]	153	Statistically significant improvements from baseline to each time point in each subscale and the total score for both treatment groups (all $p < 0.05$)	NR	NR
Kusano, 2014[51] Japan	Endoscopically proven NERD Continuous omeprazole 10-20 mg/day, lansoprazole 15-30 mg/day, or rabeprazole 10 mg/day (≥1 year)	46	NR	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS					
Brusselaers, 2018[49] Sweden	GERD patients (using ICD codes) Continuous any PPI at defined daily dose (at least 6 months)	201744	NR	NR	NR
Kaplan-Machlis, 2000[47] USA	Symptomatic GERD Continuous omeprazole sodium 20 mg once daily (24 weeks)	130	NR	NR	NR
Talley, 2002[50] Australia	Symptomatic GERD Continuous pantoprazole 20 mg once daily and placebo twice daily (12 months)	154	NR	NR	NR

Keys: GERD = gastroesophageal reflux disease, MCS = Mental Component Summary, NERD = non-erosive reflux disease, NR = not reported, PAGI-QoL = Patient Assessment of upper Gastrointestinal disorders - Quality of Life, PCS = Physical Component Summary, PGWB = Psychological General Well-Being, SF-36 = short Form-36, USA = United States of America

Table 81: Symptom relief (non-comparison continuous studies)

Reference Country	Study population PPI	Sample size	% no heartburn at study end	% heartburn control at study end	% no regur-gitation	Perception of flow of gastric content into oesophagus
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS						
Dabholkar, 2011[48] USA	Endoscopically proven NERD Continuous dexlanso-prazole 60 or 90 mg once daily (12 months)[a]	153	NR	NR	NR	NR
Kusano, 2014[51] Japan	Endoscopically proven NERD Continuous omepra-zole 10-20 mg/day, lansoprazole 15-30 mg/day, or rabepra-zole 10 mg/day (≥1 year)	46	NR	NR	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS						
Brusselaers, 2018[49] Sweden	GERD patients (using ICD codes) Continuous any PPI at defined daily dose (at least 6 months)	201744	NR	NR	NR	NR
Kaplan-Machlis, 2000[47] USA	Symptomatic GERD Continuous omepra-zole sodium 20 mg once daily (24 weeks)	130	Only in Figure (~32.0) Treatment effect not statistically expressed	NR	NR	NR
Talley, 2002[50] Australia	Symptomatic GERD Continuous pantopra-zole 20 mg once daily and placebo twice daily (12 months)	154	NR	- Complete control: 77 - Sufficient control: 86 - Treatment effect not statistically expressed	NR	NR

Keys: GERD = gastroesophageal reflux disease, NERD = non-erosive reflux disease, NR = not reported, USA = United States of America

Table 82: Treatment satisfaction at end of treatment* (non-comparison continuous studies)

Reference Country	Study population PPI	Sample size	Definition satisfaction	General	% willingness to change therapy
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS					
Dabholkar, 2011[48] USA	Endoscopically proven NERD Continuous dexlansoprazole 60 or 90 mg once daily (12 months)[a]	153	NA	NR	NR
Kusano, 2014[51] Japan	Endoscopically proven NERD Continuous omeprazole 10-20 mg/day, lansoprazole 15-30 mg/day, or rabeprazole 10 mg/day (≥1 year)	46	Satisfied: upper 2 of 5 answer options Totally satisfied: upper 1 of 5 answer options	- Satisfied: 80.4% - Totally satisfied: 50.0%	- Yes: 13.0 - Maybe: 8.7 - Increase PPI dosage: 13.0 - Satisfied with current PPI: 65.2
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS					
Brusselaers, 2018[49] Sweden	GERD patients (using ICD codes) Continuous any PPI at defined daily dose (at least 6 months)	201744	NA	NR	NR
Kaplan-Machlis, 2000[47] USA	Symptomatic GERD Continuous omeprazole sodium 20 mg once daily (24 weeks)	130	NA	NR	NR
Talley, 2002[50] Australia	Symptomatic GERD Continuous pantoprazole 20 mg once daily and placebo twice daily (12 months)	154	NA	NR	NR

Keys: GERD = gastroesophageal reflux disease, NA = not applicable, NERD = non-erosive reflux disease, NR = not reported, USA = United States of America
* Satisfaction assessed by patient

Table 83: Short-term safety (non-comparison continuous studies)

Reference Country	Study population PPI	Sample size	% AEs	% SAEs	% patients with endoscopy during treatment
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS					
Dabholkar, 2011[48] USA	Endoscopically proven NERD Continuous dexlansoprazole 60 or 90 mg once daily (12 months)[a]	153	- Treatment-emergent: 71.2 - Treatment-related: 25.5 - AE leading to discontinuation: 11.1	- Treatment-emergent: 5.9 - Treatment-related: 4.6	NR
Kusano, 2014[51] Japan	Endoscopically proven NERD Continuous omeprazole 10-20 mg/day, lansoprazole 15-30 mg/day, or rabeprazole 10 mg/day (≥1 year)	46	NR	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS					
Brusselaers, 2018[49] Sweden	GERD patients (using ICD codes) Continuous any PPI at defined daily dose (at least 6 months)	201744	NR	NR	NR
Kaplan-Machlis, 2000[47] USA	Symptomatic GERD Continuous omeprazole sodium 20 mg once daily (24 weeks)	130	NR	NR	NR
Talley, 2002[50] Australia	Symptomatic GERD Continuous pantoprazole 20 mg once daily and placebo twice daily (12 months)	154	≥1 AE: 56 AE leading to discontinuation: 12.3 - Related to medication: 7.1 - Not related to medication: 5.2	No SAEs related to misdiagnosis or treatment	NR

Keys: AE = adverse event, GERD = gastroesophageal reflux disease, NERD = non-erosive reflux disease, NR = not reported, SAE = severe adverse event, USA = United States of America

Table 84: Long-term safety (non-comparison continuous studies)

Reference Country	Study population PPI	Sample size	% AEs	% death
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS				
Dabholkar, 2011[48] USA	Endoscopically proven NERD Continuous dexlansoprazole 60 or 90 mg once daily (12 months)[a]	153	NR	Death after completing or prematurely discontinuing the study: 1.3 - None treatment-related
Kusano, 2014[51] Japan	Endoscopically proven NERD Continuous omeprazole 10-20 mg/day, lansoprazole 15-30 mg/day, or rabeprazole 10 mg/day (≥1 year)	46	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS				
Brusselaers, 2018[49] Sweden	GERD patients (using ICD codes) Continuous any PPI at defined daily dose (at least 6 months)	201744	Adenocarcinoma: 0.16 - SIR (95% CI): 6.87 (6.13-7.67) Squamous cell carcinoma: 0.06 - SIR (95% CI): 3.35 (2.76-4.03)	NR
Kaplan-Machlis, 2000[47] USA	Symptomatic GERD Continuous omeprazole sodium 20 mg once daily (24 weeks)	130	NR	NR
Talley, 2002[50] Australia	Symptomatic GERD Continuous pantoprazole 20 mg once daily and placebo twice daily (12 months)	154	NR	NR

Keys: AE = adverse event, GERD = gastroesophageal reflux disease, NERD = non-erosive reflux disease, NR = not reported, SIR = standardised incidence ratio (relative to the entire Swedish background population of same age, sex and calendar period), USA = United States of America

15.3.4 Summary tables non-comparison studies on on-demand PPI therapy

Table 85: Treatment use (non-comparison on-demand studies)

Reference Country	Study population PPI	Sample size	Definition compliance	Mean (SD) pills/day	Mean (SD) total nr of pills	% days PPI intake during study	Compliance
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Bytzer, 2004[19] 14 European countries	Endoscopically proven NERD On-demand rabeprazole 10 mg max once daily (6 months)	279	NA	NR	NR	NR	NR
Juul-Hansen, 2009[54] Norway	Endoscopically proven NERD On-demand lansoprazole max 60 mg daily (15 mg capsules; 6 months)	32	NA	Median (95% CI): 1.2 (1.0-1.6) No significant change in tablet requirements from 1 month to another	NR	NR	NR
Ponce, 2004[53] Spain	Endoscopically proven NERD On-demand rabeprazole 20 mg max once daily (6 months)	17	NA	0.27 (0.18)	NR	NR	NR
Talley, 2001[55] Denmark, Finland, Norway, Sweden	Endoscopically proven NERD On-demand esomeprazole 20 mg max once daily (6 months)	170	NA	0.34 (NR)	NR	NR	NR
Talley, 2002 Talley, 2002[50] UK, Ireland, Canada	Endoscopically proven NERD On-demand esomeprazole 40 or 20 mg max once daily (6 months)	- Total: 575 - Group I: 293 - Group II: 282	NA	- Group I: 0.29 (NR) - Group II: 0.33 (NR)	NR	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS							
Bigard, 2005[57] France	Endoscopically uninvestigated GERD On-demand lansoprazole 15 mg max once daily (6 months)	84	NA	0.30 (0.31)	40.0 (37.0)	26	NR
Meineche-Schmidt, 2004 Meineche-Schmidt, 2004[52] Denmark	Endoscopically uninvestigated GERD On-demand esomeprazole 20 mg max once daily (26 weeks)	453	NA	NR	NR	NR	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS							
Kaspari, 2005[58] Germany, Lithuania	Mixed population of endoscopically proven NERD and Grade I GERD (Savary-Miller) On-demand pantoprazole 20 mg max once daily (6 months)	213	NA	0.34 (NR)	51.9 (NR)	NR	NR

Reference Country	Study population PPI	Sample size	Definition compliance	Mean (SD) pills/day	Mean (SD) total nr of pills	% days PPI intake during study	Compliance
Ponce, 2004[53] Spain	Mixed population of endoscopically proven NERD and LA Grade A or B GERD On-demand rabeprazole 20 mg max once daily (6 months)	55	NA	0.30 (0.19)	NR	NR	NR
Scholten (Digestion), 2005[59] Austria, the Netherlands, Germany	Mixed population of endoscopically proven NERD and mild GERD (grade 0-1 Savary-Miller) On-demand pantoprazole 40 or 20 mg max once daily (24 weeks)	- Total: 435 - Group I: 218 - Group II: 217	NA	- Group I: 0.40 (NR) - Group II: 0.41 (NR)	- Group I: 67.5 (NR) - Group II: 67.1 (NR)	NR	NR
Scholten (Clin Drug Invest), 2005[60] Germany	Mixed population of endoscopically proven NERD and mild GERD (grade 0-1 Savary-Miller) On-demand pantoprazole 20 mg max once daily (24 weeks)	234	NA	0.44 (NR)	79.2 (NR)	NR	NR
Scholten, 2007[61] Germany	Mixed population of endoscopically proven NERD and LA Grade A or B GERD On-demand pantoprazole or esomeprazole 20 mg max once daily (6 months)	- Total: 199 - Group I: 99 - Group II: 100	NA	- Group I: 0.31 (NR) - Group II: 0.36 (NR)	- Group I: 52.6 (NR) - Group II: 59.9 (NR)	NR	NR

Keys: GERD = gastroesophageal reflux disease, ICD = International Classification of Diseases, NA = not applicable, NERD = non-erosive reflux disease, NR = not reported, SD = standard deviation, UK = United Kingdom

Table 86: Health-related quality of life (non-comparison on-demand studies)

Reference Country	Study population PPI	Sample size	PAGI-QoL	PGWB	SF-36
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS					
Bytzer, 2004[19] 14 European countries	Endoscopically proven NERD On-demand rabeprazole 10 mg max once daily (6 months)	279	NR	Mean score: 72.8 (normal population level) Decrease PGWB score in patients who discontinued treatment: -7.4 (p>0.25)	NR
Juul-Hansen, 2009[54] Norway	Endoscopically proven NERD On-demand lansoprazole max 60 mg daily (15 mg capsules; 6 months)	32	NR	NR	NR
Ponce, 2004[53] Spain	Endoscopically proven NERD On-demand rabeprazole 20 mg max once daily (6 months)	17	NR	NR	NR
Talley, 2001[55] Denmark, Finland, Norway, Sweden	Endoscopically proven NERD On-demand esomeprazole 20 mg max once daily (6 months)	170	NR	NR	NR
Talley, 2002[50] UK, Ireland, Canada	Endoscopically proven NERD On-demand esomeprazole 40 or 20 mg max once daily (6 months)	- Total: 575 - Group I: 293 - Group II: 282	NR	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS					
Bigard, 2005[57] France	Endoscopically uninvestigated GERD On-demand lansoprazole 15 mg max once daily (6 months)	84	NR	NR	NR
Meineche-Schmidt, 2004[52] Denmark	Endoscopically uninvestigated GERD On-demand esomeprazole 20 mg max once daily (26 weeks)	453	NR	NR	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS					
Kaspari, 2005[58] Germany, Lithuania	Mixed population of endoscopically proven NERD and Grade I GERD (Savary-Miller) On-demand pantoprazole 20 mg max once daily (6 months)	213	NR	NR	NR
Ponce, 2004[53] Spain	Mixed population of endoscopically proven NERD and LA Grade A or B GERD On-demand rabeprazole 20 mg max once daily (6 months)	55	NR	NR	NR
Scholten (Digestion), 2005[59] Austria, the Netherlands, Germany	Mixed population of endoscopically proven NERD and mild GERD (grade 0-1 Savary-Miller) On-demand pantoprazole 40 or 20 mg max once daily (24 weeks)	- Total: 435 - Group I: 218 - Group II: 217	NR	NR	NR

Reference Country	Study population PPI	Sample size	PAGI-QoL	PGWB	SF-36
Scholten (Clin Drug Invest), 2005[60] Germany	Mixed population of endoscopically proven NERD and mild GERD (grade 0-1 Savary-Miller) On-demand pantoprazole 20 mg max once daily (24 weeks)	234	NR	NR	NR
Scholten, 2007[61] Germany	Mixed population of endoscopically proven NERD and LA Grade A or B GERD On-demand pantoprazole or esomeprazole 20 mg max once daily (6 months)	- Total: 199 - Group I: 99 - Group II: 100	NR	NR	NR

Keys: GERD = gastroesophageal reflux disease, MCS = Mental Component Summary, NERD = non-erosive reflux disease, NR = not reported, PAGI-QoL = Patient Assessment of upper Gastrointestinal disorders - Quality of Life, PCS = Physical Component Summary, PGWB = Psychological General Well-Being, SF-36 = Short Form-36, UK = United Kingdom

Table 87: Symptom relief (non-comparison on-demand studies)

Reference Country	Study population PPI	Sample size	% moderate-severe heartburn at study end	% heartburn control at study end	% heartburn duration at study end	% moderate-severe regurgitation at study end	Perception of flow of gastric content into oesophagus
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS							
Bytzer, 2004[19] 14 European countries	Endoscopically proven NERD On-demand rabeprazole 10 mg max once daily (6 months)	279	NR	Sufficient control: 86.4* Complete 24h control - After 1-2 days of treatment: 30 - After ≤4 days of treatment: 59	NR	NR	NR
Juul-Hansen, 2009[54] Norway	Endoscopically proven NERD On-demand lansoprazole max 60 mg daily (15 mg capsules; 6 months)	32	NR	NR	NR	NR	NR
Ponce, 2004[53] Spain	Endoscopically proven NERD On-demand rabeprazole 20 mg max once daily (6 months)	17	NR	NR	≥2 days/week: 6.2	NR	NR
Talley, 2001[55] Denmark, Finland, Norway, Sweden	Endoscopically proven NERD On-demand esomeprazole 20 mg max once daily (6 months)	170	13	NR	≤1 day/week: 50	NR	NR
Talley, 2002[50] UK, Ireland, Canada	Endoscopically proven NERD On-demand esomeprazole 40 or 20 mg max once daily (6 months)	- Total: 575 - Group I: 293 - Group II: 282	NR	NR	NR	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS							
Bigard, 2005[57] France	Endoscopically uninvestigated GERD On-demand lansoprazole 15 mg max once daily (6 months)	84	NR	NR	NR	NR	NR
Meineche-Schmidt, 2004[52] Denmark	Endoscopically uninvestigated GERD On-demand esomeprazole 20 mg max once daily (26 weeks)	453	NR	NR	NR	NR	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS							
Kaspari, 2005[58] Germany, Lithuania	Mixed population of endoscopically proven NERD and Grade I GERD (Savary-Miller) On-demand pantoprazole 20 mg max once daily (6 months)	213	NR	NR	NR	NR	NR

Reference Country	Study population PPI	Sample size	% moderate-severe heart-burn at study end	% heartburn con-trol at study end	% heartburn duration at study end	% moderate-severe regur-gitation at study end	Perception of flow of gastric content into oe-sophagus
Ponce, 2004[53] Spain	Mixed population of endoscopically proven NERD and LA Grade A or B GERD On-demand rabepra-zole 20 mg max once daily (6 months)	55	NR	NR	≥2 days/week: 12.8	NR	NR
Scholten (Digestion), 2005[59] Austria, the Nether-lands, Ger-many	Mixed population of endoscopically proven NERD and mild GERD (grade 0-1 Savary-Miller) On-demand panto-prazole 40 or 20 mg max once daily (24 weeks)	- Total: 435 - Group I: 218 - Group II: 217	NR	NR	NR	NR	NR
Scholten (Clin Drug Invest), 2005[60] Germany	Mixed population of endoscopically proven NERD and mild GERD (grade 0-1 Savary-Miller) On-demand panto-prazole 20 mg max once daily (24 weeks)	234	4.3	NR	NR	2.3	NR
Scholten, 2007[61] Germany	Mixed population of endoscopically proven NERD and LA Grade A or B GERD On-demand panto-prazole or esomepra-zole 20 mg max once daily (6 months)	- Total: 199 - Group I: 99 - Group II: 100	NR†	NR	NR	NR‡	NR

Keys: GERD = Gastroesophageal reflux disease, NERD = non-erosive reflux disease, NR = not reported, UK = United Kingdom
* Mean change heartburn severity: 0.7 (assessed using 5-point Likert scale: 0=none, 4=very severe); † Mean heartburn intensity during the treatment period - ITT population: Group 1: 1.12, Group 2: 1.32, - PP population: Group 1: 1.10, Group 2: 1.33 (intensity assessed as 0=no, 1=mild, 2=moderate, 3=severe); ‡ Mean regurgitation intensity during the treatment period - ITT population: Group 1: 0.99, Group 2: 1.11, - PP population: Group 1: 1.00, Group 2: 1.12 (intensity assessed as 0=no, 1=mild, 2=moderate, 3=severe)

Table 88: Treatment satisfaction at end of treatment* (non-comparison on-demand studies)

Reference Country	Study population PPI	Sample size	Definition satisfac-tion	General	% willingness to change therapy
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS					
Bytzer, 2004[19] 14 European countries	Endoscopically proven NERD On-demand rabeprazole 10 mg max once daily (6 months)	279	NA	NR	NR
Juul-Hansen, 2009[54] Norway	Endoscopically proven NERD On-demand lansoprazole max 60 mg daily (15 mg capsules; 6 months)	32	NA	NR	NR
Ponce, 2004[53] Spain	Endoscopically proven NERD On-demand rabeprazole 20 mg max once daily (6 months)	17	Verbal rating scale (0 totally unsatis-fied, 100 maximum satisfaction)	Median (range): 97 (50-100)	NR
Talley, 2001[55] Denmark, Fin-land, Norway, Sweden	Endoscopically proven NERD On-demand esomeprazole 20 mg max once daily (6 months)	170	NA	NR	NR
Talley, 2002[50] UK, Ireland, Canada	Endoscopically proven NERD On-demand esomeprazole 40 or 20 mg max once daily (6 months)	- Total: 575 - Group I: 293 - Group II: 282	NA	NR	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS					
Bigard, 2005[57] France	Endoscopically uninvestigated GERD On-demand lansoprazole 15 mg max once daily (6 months)	84	NA	NR	NR
Meineche-Schmidt, 2004[52] Denmark	Endoscopically uninvestigated GERD On-demand esomeprazole 20 mg max once daily (26 weeks)	453	Satisfied: upper 4 of 7 answer options Very satisfied: up-per 2 of 7 answer options	- Satisfied: 96% - Very satisfied: 80%	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS					
Kaspari, 2005[58] Germany, Lithu-ania	Mixed population of endoscopi-cally proven NERD and Grade I GERD (Savary-Miller) On-demand pantoprazole 20 mg max once daily (6 months)	213	NA	NR	NR
Ponce, 2004[53] Spain	Mixed population of endoscopi-cally proven NERD and LA Grade A or B GERD On-demand rabeprazole 20 mg max once daily (6 months)	55	Verbal rating scale (0 totally unsatis-fied, 100 maximum satisfaction)	Median (range): 90 (10-100)	NR
Scholten (Di-gestion), 2005[59] Austria, the Netherlands, Germany	Mixed population of endoscopi-cally proven NERD and mild GERD (grade 0-1 Savary-Miller) On-demand pantoprazole 40 or 20 mg max once daily (24 weeks)	- Total: 435 - Group I: 218 - Group II: 217	NA	NR	NR

Reference Country	Study population PPI	Sample size	Definition satisfac-tion	General	% willingness to change therapy
Scholten (Clin Drug Invest), 2005[60] Germany	Mixed population of endoscopi-cally proven NERD and mild GERD (grade 0-1 Savary-Miller) On-demand pantoprazole 20 mg max once daily (24 weeks)	234	NA	NR	NR
Scholten, 2007[61] Germany	Mixed population of endoscopi-cally proven NERD and LA Grade A or B GERD On-demand pantoprazole or esomeprazole 20 mg max once daily (6 months)	- Total: 199 - Group I: 99 - Group II: 100	NA	NR	NR

Keys: GERD = Gastroesophageal reflux disease, NA = not applicable, NERD = non-erosive reflux disease, NR = not reported, UK = United Kingdom
* Satisfaction assessed by patient

Table 89: Short-term safety* (non-comparison on-demand studies)

Reference Country	Study population PPI	Sample size	% AEs	% SAEs	% patients with endoscopy during treatment
POPULATION OF ENDOSCOPICALLY PROVEN NERD PATIENTS					
Bytzer, 2004[19] 14 European countries	Endoscopically proven NERD On-demand rabeprazole 10 mg max once daily (6 months)	279	≥1 AE: 40.5 (<1% probably related to study medication) AE leading to discontinuation: 1.4	NR	NR
Juul-Hansen, 2009[54] Norway	Endoscopically proven NERD On-demand lansoprazole max 60 mg daily (15 mg capsules; 6 months)	32	AE leading to discontinuation: 12.5	NR	NR
Ponce, 2004[53] Spain	Endoscopically proven NERD On-demand rabeprazole 20 mg max once daily (6 months)	17	NR	NR	NR
Talley, 2001[55] Denmark, Finland, Norway, Sweden	Endoscopically proven NERD On-demand esomeprazole 20 mg max once daily (6 months)	170	≥1 AE: 42.9 AE leading to discontinuation: 0.6	2.9 All unlikely to be related to study drug	NR
Talley, 2002[50] UK, Ireland, Canada	Endoscopically proven NERD On-demand esomeprazole 40 or 20 mg max once daily (6 months)	- Total: 575 - Group I: 293 - Group II: 282	≥1 AE: - Group 1: 73.7 - Group 2: 67.0 AE leading to discontinuation: - Group 1: 4.4 - Group 2: 4.6	- Group 1: 1.4 (all unlikely to be related to study drug) - Group 2: 2.5 (14.3% possibly, rest unlikely to be related to study drug)	NR
POPULATION OF ENDOSCOPICALLY UNINVESTIGATED GERD PATIENTS					
Bigard, 2005[57] France	Endoscopically uninvestigated GERD On-demand lansoprazole 15 mg max once daily (6 months)	84	≥1 AE: 54.8 AE related to study drug: 10.7 AE leading to discontinuation: 6.0 (mainly GI disorders, 80% of these related to study drug)	0	NR
Meineche-Schmidt, 2004[52] Denmark	Endoscopically uninvestigated GERD On-demand esomeprazole 20 mg max once daily (26 weeks)	453	NR	NR	NR
MIXED POPULATION OF ENDOSCOPICALLY PROVEN NERD AND LOW GRADE GERD PATIENTS					
Kaspari, 2005[58] Germany, Lithuania	Mixed population of endoscopically proven NERD and Grade I GERD (Savary-Miller) On-demand pantoprazole 20 mg max once daily (6 months)	213	≥1 AE: 35.7 AE related to study medication: 2.8	NR	NR
Ponce, 2004[53] Spain	Mixed population of endoscopically proven NERD and LA Grade A or B GERD On-demand rabeprazole 20 mg max once daily (6 months)	55	NR	NR	NR

Reference Country	Study population PPI	Sample size	% AEs	% SAEs	% patients with endoscopy during treatment
Scholten (Digestion), 2005[59] Austria, the Netherlands, Germany	Mixed population of endoscopically proven NERD and mild GERD (grade 0-1 Savary-Miller) On-demand pantoprazole 40 or 20 mg max once daily (24 weeks)	- Total: 435 - Group I: 218 - Group II: 217	≥1 AE: - Group 1: 30 - Group 2: 31	NR	NR
Scholten (Clin Drug Invest), 2005[60] Germany	Mixed population of endoscopically proven NERD and mild GERD (grade 0-1 Savary-Miller) On-demand pantoprazole 20 mg max once daily (24 weeks)	234	≥1 AE: 33.8 AE leading to discontinuation: 0.9 Likely or definitely related to study drug: 0	2.6 Likely or definitely related to study drug: 0	NR
Scholten, 2007[61] Germany	Mixed population of endoscopically proven NERD and LA Grade A or B GERD On-demand pantoprazole or esomeprazole 20 mg max once daily (6 months)	- Total: 199 - Group I: 99 - Group II: 100	≥1 AE: - Group 1: 21.0 - Group 2: 23.0 AE likely to be related to study drug: - Group 1: 1.0 - Group 2: 4.0 - None of the AEs was considered definitely related to each of the study drugs	SAE: - Group 1: 2.0 - Group 2: 3.0	NR

Keys: AE = adverse event, GERD = gastroesophageal reflux disease, NERD = non-erosive reflux disease, NR = not reported, SAE = severe adverse event, UK = United Kingdom
* No studies reported long-term safety outcomes

15.4 Inputs for cost-effectiveness model

Table 90: List of model inputs used for the transition probabilities

Monthly relapse probabilities[40 75 78]			
Input parameter	**Base-case parameter**	**PSA value sampled from**	**Assumptions**
continuous PPI relapse	0.0102	Beta(55,858)	Observed relapse numbers in 6 months in Szucs et al. [40]
on-demand PPI relapse	0.0104	Beta(60,931)	
relapse off-treatment	0.0110	Mixture of beta distributions	Relapse probabilities (given endoscopy outcome) from rates in Nocon et al. [75] The endoscopy outcome probabilities from Zagari et al. [78]
relapse on usual care treatment	0.0137	Mixture of beta distributions	Relapse probabilities (given endoscopy outcome & GERD medication) and GERD medication probability given endoscopy outcome are from Nocon et al. [75] The endoscopy outcome probabilities from Zagari et al. [78]
Monthly direct (pre-relapse) endoscopy probabilities[40 75 78]			
Input parameter	**Base-case parameter**	**PSA value sampled from**	**Assumptions**
continuous endoscopy	0.0022	Beta(12,901)	Direct endoscopy numbers estimated from observed endoscopy and relapse numbers in 6 months in Szucs et al. [40]
on-demand endoscopy	0.0019	Beta(11,980)	Direct endoscopy numbers estimated from observed endoscopy and

			relapse numbers in 6 months in Szucs et al. [40]
usual care endoscopy	0.0021	Mixture of beta distributions	Direct endoscopy probability given GERD medication is from Szucs et al. (it is assumed that endoscopy probability under other GERD medication is average of those under on-demand and continuous PPI therapy) [40] GERD medication probability given endoscopy outcome are from Nocon et al. [75] The endoscopy outcome probabilities from Zagari et al. [78]
Monthly drug-remission (i.e. going off-treatment) probabilities[75] [78]			
Input parameter	**Base-case parameter**	**PSA value sampled from**	**Assumptions**
Drug-remission on-demand	0.0063	Mixture of beta distributions	Remission probability under on-demand PPI treatment given endoscopy outcome from Nocon et al. [75] the endoscopy outcome probabilities from Zagari et al. [78]
Drug-remission continuous	0.0037	Mixture of beta distributions	Remission probability under continuous PPI treatment given endoscopy outcome from Nocon et al. [75] The endoscopy outcome probabilities from Zagari et al. [78]
Drug-remission usual care	0.0055	Mixture of beta distributions	Remission probability given GERD medication from Nocon et al. (it is assumed that remission

			probability under other GERD medication is average of those under on-demand and continuous PPI therapy) [75] GERD medication probability given endoscopy outcome are from Nocon et al. [75] the endoscopy outcome probabilities from Zagari et al. [78]
Post-endoscopy monthly transition probabilities[76]			
Input parameter	**Base-case parameter**	**PSA value sampled from**	**Assumptions**
NERD/HERD→NERD/HERD in 1 month (year<2)	0.9752	Dirichlet distribution	The number of transitions between the post-endoscopy states observed before year 2 and after year 2 observed in Malfertheiner et al. study are used to calculate the 2-year and 3-year transition probabilities, which are transformed to monthly transition probabilities using eigenvalue decomposition (using R script). [76]
NERD/HERD→MERD in 1 month (year<2)	0.0247		
NERD/HERD→SERD in 1 month (year<2)	9.8763E-05		
MERD→NERD/HERD in 1 month (year<2)	0.0568		
MERD→MERD in 1 month (year<2)	0.9388		
MERD→SERD in 1 month (year<2)	0.0044		
SERD→NERD/HERD in 1 month (year<2)	0.0099		
SERD→MERD in 1 month (year<2)	0.0840		
SERD→SERD in 1 month (year<2)	0.9060		
NERD/HERD→NERD/HERD in 1 month (after year 2)	0.9860		
NERD/HERD→MERD in 1 month (after year 2)	0.0138		
NERD/HERD→SERD in 1 month (after year 2)	0.0001		
MERD→NERD/HERD in 1 month (after year 2)	0.0243		
MERD→MERD in 1 month (after year 2)	0.9741		
MERD→SERD in 1 month (after year 2)	0.0016		

SERD→NERD/HERD in 1 month (after year 2)	0.0048		
SERD→MERD in 1 month (after year 2)	0.0359		
SERD→SERD in 1 month (after year 2)	0.9593		
Probability of BE incidence in upcoming years[76]			
Input parameter	**Base-case parameter**	**PSA value sampled from**	**Assumptions**
NERD/HERD	0.0595	Beta(138,2186)	The probabilities are obtained from model calibration, using the 5-year BE incidences observed in Malfertheiner et al. study. [76]
MERD	0.1137	Beta(233,1820)	
SERD	0.1438	Beta(334,1990)	
Probability of endoscopy outcomes[78]			
Input parameter	**Base-case parameter**	**PSA value sampled from**	**Assumptions**
NERD/HERD	0.7592	Dirichlet	In Zagari et al. study, among the 245 subjects with reflux symptoms, 186 had negative endoscopic findings. Also in the same study, the ratio of the number of patients with grade I esophagitis to the number of patients with higher grade esophagitis is 101/20. [78]
MERD	0.2		
SERD	0.0408		
Probability of no GERD among NERD[79]			
Input parameter	**Base-case parameter**	**PSA value sampled from**	**Assumptions**
% No GERD among NERD	27%	Beta(54,146)	In the Savarino et al. study 54 patients out of 200 endoscopically negative patients with reflux symptoms were not acid reflux. [79]
Probability of high dose drug response[77]			

Input parameter	Base-case parameter	PSA value sampled from	Assumptions
% response after high-dose drug therapy	71.19%	Beta(1344,544)	1344 out of 1888 patients responded to high-dose therapy in Heading et al. [77]
Percentage of treatment patterns under NERD/HERD[75]			
Input parameter	**Base-case parameter**	**PSA value sampled from**	**Assumptions**
PPI continuous	30.57%	Dirichlet distribution	Weighted average of the year-specific GERD medication intake percentages from Nocon et al. [75]
PPI on-demand	23.24%		
Other medication (e.g. H2RA and antacids)	14.37%		
No medication	31.82%		
Percentage of treatment patterns under MERD[75]			
Input parameter	**Base-case parameter**	**PSA value sampled from**	**Assumptions**
PPI continuous	43.20%	Dirichlet distribution	Weighted average of the year-specific GERD medication intake percentages from Nocon et al. [75]
PPI on-demand	21.72%		
Other medication (e.g. H2RA and antacids)	10.37%		
No medication	24.72%		
Percentage of treatment patterns under SERD[75]			
Input parameter	**Base-case parameter**	**PSA value sampled from**	**Assumptions**
PPI continuous	59.25%	Dirichlet distribution	Weighted average of the year-specific GERD medication intake percentages from Nocon et al. [75]
PPI on-demand	16.45%		
Other medication (e.g. H2RA and antacids)	7.07%		
No medication	17.23%		
Mortality[40 77]			
Input parameter	**Base-case**	**PSA value**	**Assumptions**

	parameter	sampled from	
Mortality	General population mortality adjusted based on the age and sex characteristics according to the baseline of the Szucs et al.	Not sampled	It is assumed no disease specific mortality for GERD

Table 91: Overall and per formulation per pill drug acquisition costs and market shares for PPIs[29]

Formulation	market share*	price per pill (CHF)
Dexlansoprazolum 30 mg	0.54%	1.06
Dexlansoprazolum 60 mg	0.65%	1.34
Esomeprazolum 20 mg	7.09%	0.65
Esomeprazolum 40 mg	12.73%	0.75
Lansoprazolum 15 mg	0.91%	0.55
Lansoprazolum 30 mg	1.56%	0.90
Omeprazolum 10 mg	0.49%	0.48
Omeprazolum 20 mg	6.42%	0.73
Omeprazolum 40 mg	4.00%	0.98
Pantoprazolum 20 mg	24.41%	0.45
Pantoprazolum 40 mg	40.46%	0.68
Rabeprazolum 10 mg	0.15%	0.84
Rabeprazolum 20 mg	0.59%	1.24
overall PPI per pill cost	0.66	

*Market shares were based on the 2018 data. In the PSA, costs were sampled using gamma distribution, assuming standard error is 20% of the mean. The parameters of the gamma distribution were found using fitting of the first two moments

Table 92: Overall and per formulation per pill drug acquisition costs and market shares for high-dose drug therapy[29]

Formulation	market share*	price per pill in CHF
Dexlansoprazolum 60 mg	1.09%	1.34
Esomeprazolum 40 mg	21.22%	0.75
Lansoprazolum 30 mg	2.60%	0.90
Omeprazolum 40 mg	6.67%	0.98
Pantoprazolum 40 mg	67.44%	0.68
Rabeprazolum 20 mg	0.99%	1.24
overall PPI per pill cost	0.74	

*Market shares were based on the 2018 data. In the PSA, costs were sampled using gamma distribution, assuming standard error is 20% of the mean. The parameters of the gamma distribution were found using fitting of the first two moments

Table 93: Overall and per formulation per pill drug acquisition costs and market shares for H2RAs[29]

Formulation	market share*	price per pill in CHF
Ranitidin 150 mg	49.85%	0.38
Ranitidin 300 mg	50.15%	0.65
overall H2RA per pill cost	0.52	

*Market shares were based on the 2018 data. In the PSA, costs were sampled using gamma distribution, assuming standard error is 20% of the mean. The parameters of the gamma distribution were found using fitting of the first two moments

Table 94: Overall and per formulation per pill drug acquisition costs and market shares for antacids[29]

Formulation	market share	price per pill in CHF
Alucol	20.7%	0.28
Andursil	5.6%	0.28
Riopan	73.7%	0.29
overall antacid per pill cost	0.29	

*Market shares were based on the 2018 data. In the PSA, costs were sampled using gamma distribution, assuming standard error is 20% of the mean. The parameters of the gamma distribution were found using fitting of the first two moments

Table 95: Distribution of the patients in the continuous and on-demand PPI therapy across per day tablet use levels[40]

number (%) of patients receiving continuous PPI therapy*	number (%) of patients in on-demand PPI therapy*	average number of tablets received per day
6 (0.65%)	40 (4.14%)	0 - 0.1
5 (0.54%)	51 (5.27%)	0.1 - 0.2
4 (0.43%)	71 (7.34%)	0.2 - 0.3
7 (0.76%)	77 (7.97%)	0.3 - 0.4
20 (2.18%)	130 (13.45%)	0.4 - 0.5
18 (1.96%)	118 (12.21%)	0.5 - 0.6
30 (3.27%)	85 (8.79%)	0.6 - 0.7
47 (5.13%)	66 (6.83%)	0.7 - 0.8
138 (15.06%)	72 (7.45%)	0.8 - 0.9
335 (36.57%)	84 (8.69%)	0.9 - 1
188 (20.52%)	96 (9.93%)	1 - 1.1
37 (4.03%)	25 (2.58%)	1.1 - 1.2
32 (3.49%)	19 (1.96%)	1.2 - 1.3
11 (1.2%)	4 (0.41%)	1.3 - 1.4
7 (0.76%)	6 (0.62%)	1.4 - 1.5
6 (0.65%)	3 (0.31%)	1.5 - 1.6
7 (0.76%)	2 (0.2%)	1.6 - 1.7
3 (0.32%)	3 (0.31%)	1.7 - 1.8
4 (0.43%)	5 (0.51%)	1.8 - 1.9
3 (0.32%)	3 (0.31%)	1.9 - 2
5 (0.54%)	3 (0.31%)	2 - 2.1
3 (0.32%)	3 (0.31%)	2.1 - 2.2

* These numbers were extracted from the corresponding figure from Szucs et al. study. In the PSA, these numbers were varied using bootstrapping technique. In OWSA, the uncertainty of the tablet use volume is reflected in average monthly treatment costs.

Table 96: The HCRU costs in CHF associated with the post-endoscopy states[75]

HCRU type	NERD/HERD (standard error)	MERD (standard error)	SERD (standard error)	Additional BE related costs (standard error)
Hospital related costs	8.42 (2.10)	10.06 (1.99)	10.06 (1.99)	10.46 (9.17)
Doctor visit costs	3.40 (0.12)	3.67 (0.11)	3.67 (0.11)	1.49 (0.54)
Indirect costs (not used in the base-case)	5.98 (1.54)	5.03 (1.09)	5.03 (1.09)	1.15 (3.74)

* These costs were derived from the yearly figures from Nocon et al. study. All figures were translated to 2018 CHF values using purchasing power parity adjusted exchange/inflation rates. In the PSA, costs were sampled using gamma distribution. The parameters of the gamma distribution were found using fitting of the first two moments.

Table 97: PSA details on monthly resource use frequencies

Resource use type	PSA value sampled from (for frequency in 6 month for on-demand PPI	PSA value sampled from (for frequency in 6 month for continuous PPI)
Clinician visit	Beta(431,560)	Beta(381,532)
Telephone	Beta(136,855)	Beta(133,780)
Specialist visit	Beta(24,967)	Beta(17,896)
Hospital admission (all types)	Beta(3,988)	Beta(2,911)
Helicobacter Pylori test	Beta(22,969)	Beta(18,895)

List of assumptions

- It was assumed that the change in reimbursement restriction would have no impact on the medication use and clinical effectiveness for the on-demand patients.
- In the base-case, it was also assumed that the reimbursement restriction level was applicable to the on-demand PPI therapy patients, in all endoscopically uninvestigated states (patients receiving on-demand PPI therapy both before their first relapse as well as after their first relapse, when

they receive on-demand PPI therapy as part of the usual care). Additionally, the reimbursement restriction affected the patients receiving on-demand PPI therapy in the endoscopically investigated NERD state.

- Under both on-demand and continuous PPI therapy, controlled symptoms could deteriorate. Then a patient can either be referred to the endoscopy or a high-dose therapy can be initiated.
- No additional disease specific mortality was assumed.
- After six month, if the patient has not relapsed, then s/he is considered to be post-6 month maintenance state.
- After the high dose therapy, if the patient does not respond, the patient is referred to the endoscopy. Otherwise, the dose is readjusted to the minimum, which the patient can control his/her symptoms
- After the first relapse, when the patients are not yet referred to the endoscopy, the wide range of the treatments patients are receiving are modelled as a “treatment basket”, which includes on-demand PPI, continuous PPI and other GERD medications. The weighs of different therapy types are the same in both continuous and on-demand arm.
- In the pre-endoscopy states, patients can stop their treatment and be off-treatment.
- After endoscopy, patients enter post-endoscopy states (NERD/HERD, MERD, SERD, BE), and they remain moving in between the post-endoscopy states.
- Some of the suspected NERD patients can be later identified as not GERD
- The general population utilities were assumed, only utility decrements for endoscopy and symptom relapse events were considered.

15.5 PSA results with different discounting rates

Figure 11 Cost-effectiveness Scatter Plot - Discount rate 3%

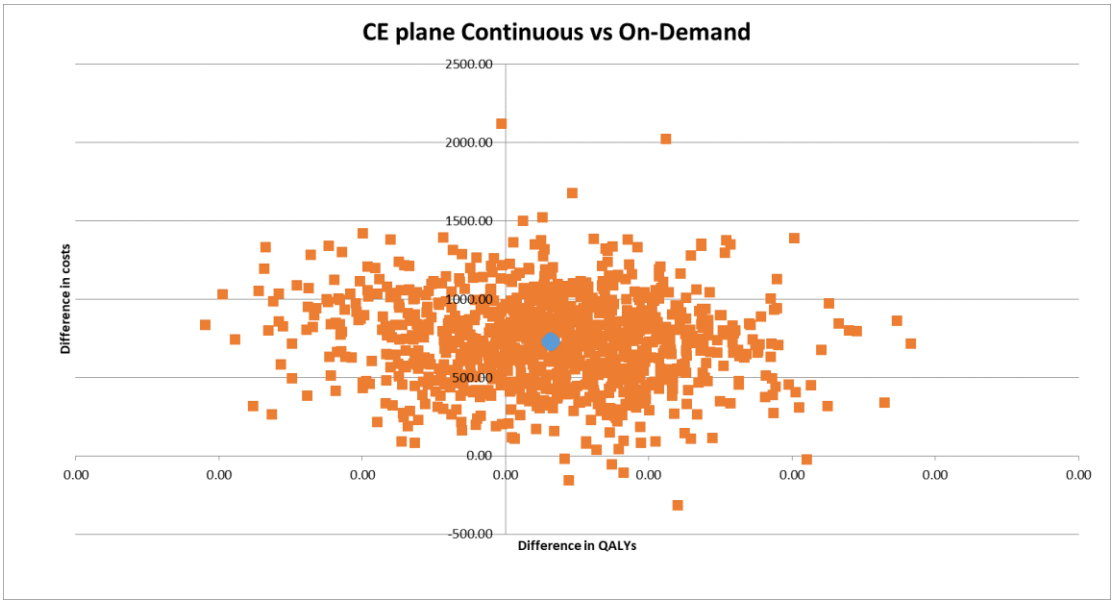
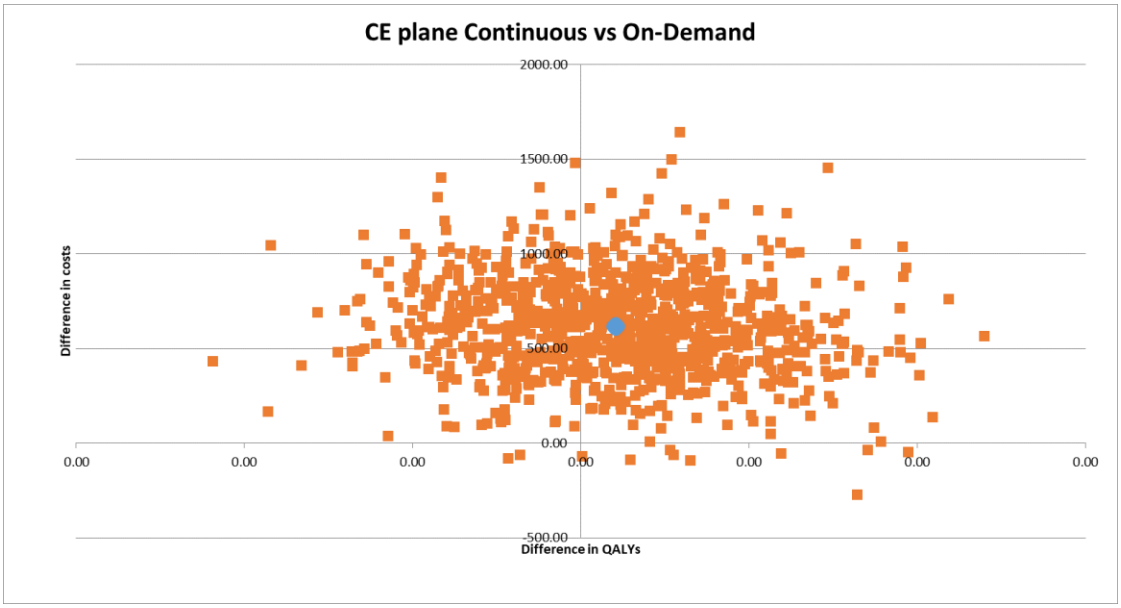


Figure 12 Cost-effectiveness Scatter Plot - Discount rate 6%



15.6 R code for cost-effectiveness model

R code to transform 2-year and 3-year post-endoscopy state transition probabilities to monthly transition probabilities

```
install.packages("expm")

install.packages("matlib")

library("expm")

library("matlib")


rr <- t(matrix(c(0.787096774,        0.277617675, 0.007684918,

0.487874465, 0.492154066, 0.019971469,

0.31372549,   0.450980392, 0.235294118),nrow=3,ncol=3))

vv<-eigen(rr)$vectors

dd= t(matrix(c(1.0469929,     0,     0,

            0,      0.2853714,     0,

            0,      0,     0.1821806),nrow=3,ncol=3))


ddm<-t(matrix(c(1.0469929^(1/36),      0,     0,

              0,    0.2853714^(1/36),  0,

              0,    0,     0.1821806^(1/36)),nrow=3,ncol=3))

vv %*% ddm %*% inv(vv)


r <- t(matrix(c(0.731988473,  0.258405379, 0.009606148,

0.594771242, 0.383442266, 0.021786492,

0.462765957, 0.425531915, 0.111702128),nrow=3,ncol=3))

v<-eigen(r)$vectors

d= t(matrix(c(1,       0,     0,
```

```
        0,      0.16011995,   0,
        0,      0,     0.06701292),nrow=3,ncol=3))

dm<-t(matrix(c(1,   0,     0,
        0,     0.16011995^(1/24),       0,
        0,     0,     0.06701292^(1/24)),nrow=3,ncol=3))
v %*% dm %*% inv(v)
```

15.7 Verification tests conducted on the cost-effectiveness model

Pre-analysis calculations	
Does the technology (drug/device, etc.) acquisition costs increase with higher prices?	Yes
Event-state calculations	
Calculate the sum of the number of patients at each health state	Added up to the cohort size
Check if all probabilities and number of patients in a state are greater than or equal to zero	Yes
Check if all probabilities are smaller than or equal to one	Yes
Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods?	larger
In case of lifetime horizon, check if all patients are dead at the end of the time horizon	Yes
Set all utilities to one Set all utilities to zero	The QALYs accumulated at a given time would be the same as the life years accumulated at that time No utilities will be accumulated in the model

Decrease all state utilities simultaneously (but keep event based utility decrements constant)	Lower utilities will be accumulated each time
Set all costs to zero	No costs will be accumulated in the model at any time
Put mortality rates to 0	Patients never die
Put mortality rate extremely high	Patients die in the first few cycles
Change around the effectiveness, utility and safety related model inputs between two treatment options	Accumulated life years and QALYs in the model at any time should be also reversed
Check if the number of alive patients estimate at any cycle is in line with general population life table statistics	At any given age, the % alive should be lower or equal in comparison to the general population estimate
Check if the QALY estimate at any cycle is in line with general population utility estimates	At any given age, the utility assigned in the model should be lower or equal in comparison to the general population estimate
Set the inflation rate of the previous year higher	The costs (which are based on a reference from previous years) assigned at each time will be higher
Result calculations	
Check the incremental life years and QALYs gained results. Are they in line with the comparative	If a treatment is more effective, it generally results in positive

clinical effectiveness evidence of the treatments involved?	incremental LYs and QALYs in comparison with the less effective treatments
Check the incremental cost results. Are they in line with the treatment costs?	If a treatment is more expensive, and if it does not have much effect on other costs, it generally results in positive incremental costs.
Total life years > total quality adjusted life years	Yes
Undiscounted results > discounted results	Yes
Divide undiscounted total QALYs by undiscounted life years.	This value should be within the outer ranges (maximum and minimum) of the all utility value inputs.
Does the total life years, QALYs and costs decrease if a shorter time horizon is selected?	Yes
Is the reporting and contextualization of the incremental results correct?	The use of the terms such as: “dominant”/ “dominated”/ “extendedly dominated”/ “cost-effective” etc. should be in line with the results. In the incremental analysis table involving multiple treatments, ICERs should be calculated against the next non-dominated treatment.

If disentangled results are presented, do they sum up to the total results? (e.g. different cost types sum up to the total costs estimate)	Yes
Check the discounted value of costs/qalys after 2 years	Discounted value=undiscounted/$(1+r)^2$
Set discount rates to zero	The discounted and undiscounted results should be the same
Set mortality rate to zero	The undiscounted total life years per patient should be equal to the length of the time horizon
Put the consequence of adverse event/discontinuation to zero. (zero costs and zero mortality/utility decrements)	The results would be the same as the results when AE rate is set to zero.
Uncertainty analysis calculations	
Are the upper and lower bounds used in the one-way sensitivity analysis used confidence intervals based on the statistical distribution assumed for that parameter? Are the resulting ICER, incremental costs/QALYs with upper and lower bound of a parameter plausible and in line with a priori expectations?	Yes Yes
Check that all parameters used in the sensitivity analysis have an appropriate associated distributions - upper and lower bounds should surround the deterministic value (i.e. Upper bound ≥ mean ≥ Lower	Yes

bound) - standard error and not standard deviation used in sampling - Lognormal / gamma distribution for hazard ratios and costs/ resource use - Beta for utilities and proportions/probabilities - Dirichlet for multinomial - Multivariate normal for correlated inputs (e.g. survival curve or regression parameters) - Normal for other variables as long as samples don't violate requirement to remain positive when appropriate	
Check PSA output mean costs, QALYs and ICER compared to the deterministic results. Is there a large discrepancy?	No
If you take new PSA runs from the excel model do you get similar results?	Yes
Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	Yes
Does the PSA cloud demonstrate a strange behavior or has a strange shape?	No
Are the scenario analysis results plausible and in line with a priori expectations?	Yes