Study Design and Cohort Comparability in a Study of Major Cardiovascular Events in New Users of Prucalopride Versus Polyethylene Glycol 3350

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Electronic Supplementary Material

Electronic Supplementary Material 1: Data Sources and Measurement

United Kingdom

In the UK, nearly all residents are registered in a general medical practice that uses electronic medical records. Those records are available for research purposes in two main data sources: the CPRD (formerly the General Practice Research Database) and THIN. These two data sources have similar information recorded by GPs; there is an overlap of general medical practices and patients between the CPRD and THIN, and combining the CPRD and THIN data after deduplicating the data sources increases the size relative to the CPRD alone by approximately 27% [1]. The ISD Scotland data are drawn from routinely collected national administrative data on death certification data, hospital diagnoses and dispensed prescriptions; study-specific additional clinical information can be requested.

CPRD

The CPRD (https://www.cprd.com/intro.asp) contains diagnostic and prescribing information recorded by GPs as part of their routine clinical practice in the UK. The CPRD has information on 4.4 million individuals (active contributors), which represents approximately 6.9% of the UK population [2]. These data are linkable, at least partially, with other health care data sets (e.g., hospitalization and national mortality data). Updated, valid and linked data are available through the CPRD Division of the UK Medicines and Health Care Products Regulatory Agency.

Detailed information on prescriptions written by the GPs, including prescribed dose and duration, is automatically recorded in the database. Read codes are used for recording clinical diagnoses by GPs. Additional diagnostic and treatment information can be found in free-text fields, letters from specialists and hospitals, and other sources. Information on specialist visits and hospitalizations are routinely forwarded to the GP, who enters that information into the medical record. The CPRD also includes information recorded by GPs on patient demographics and lifestyle factors (although not complete for all patients).

Approximately 65% of the English practices have consented to have their patient information linked to other health care data sets, such as the HES and the national death register at the ONS, via the patient's National Health Service number, sex, date of birth, and postal code. English practices represent approximately 75% of all practices contributing to the CPRD; therefore, approximately half of the total CPRD practices have this link. Linkage to HES enables access to the hospitalization data, i.e., admission date, discharge diagnosis, and procedure codes. Linkage to the national death register at ONS can be used to ascertain death and causes of death and to validate the mentions of death in the GP records. Death rates by age group and various causes of death, including ischemic heart disease, are comparable between linked CPRD data and official rates for England and Wales, and the subset of linked CPRD practices seems to be a representative sample of the general population [3]. Data in HES and ONS are updated every 6 months, but the lag time can be more than 1 year. Questionnaires may be sent to GPs to validate outcomes identified in the electronic medical record. Most practices are eligible to receive questionnaires, and the response rate is approximately 50% depending on the type of outcome being queried.

Research at the CPRD requires approval from the CPRD Independent Scientific Advisory Committee, which was obtained for this study.

THIN

Data from THIN, formerly available through IMS Health, are now available through IQVIA (https://www.iqvia.com/en/locations/uk-and-ireland/thin). Established in 2002, THIN includes electronic medical records for more than 17 million patients in the UK, of whom 3.1 million are registered with a practice that is actively contributing to THIN. THIN records information on all services provided by the GP. As with the CPRD, information on specialist visits and hospitalizations are routinely forwarded to the GP, who enters that information into the medical record.

All practices record information received on hospital admissions, discharge diagnoses, medications, outpatient specialist visits, and fact of death. Linked HES data was not available for THIN. When a drug is prescribed, a computer record is immediately created and added to the data source. Free-text comments written by the physician in the medical record are available to use for validation.

THIN supplies deidentified data for approved drug safety and epidemiological studies. Such research needs to be approved by a Scientific Review Committee (SRC), for this study, the South East Multicentre Research Ethics Committee [4]. Ethics approval was obtained for this study.

ISD Scotland

The Scottish record linkage system (ISD Scotland) contains electronic coded information on all outpatient dispensed prescriptions and all nonpsychiatric hospitalizations in Scotland. The data

source covers 100% of the Scottish population. The following information, among others, is included in the hospitalization data: birth date, age, sex, main condition, reason for admission, other conditions present, investigative procedures and treatments, and admission and discharge dates. Outpatient diagnoses are not available, except by accessing individual GP medical records on an ad hoc basis. Case validation for hospitalizations can be obtained by accessing the original case records. The fact and date of death and ICD-10–coded underlying cause of death are identified by linkage to the national death register.

Prescriptions issued by the GP and dispensed by pharmacies are contained in the prescription database. They are entered into the system by the GP, pulled down by the pharmacist from the cloud computing system, and then dispensed; if the prescription is handwritten or the practice is not yet set up to use the cloud computing system, then the pharmacist enters it into the prescription database. All prescriptions are centrally scanned. In Scotland, all community prescribing is done by GPs; this may be done on the advice of a specialist [5]. Each record contains a date of prescribing, dispensing, or reimbursement; the drug name; strength; number dispensed; and dosage directions (complete for > 90% of prescriptions). Due to privacy restrictions, the ISD Scotland cannot release cell counts with fewer than five individuals. Approval to access the anonymized patient record for the purposes of this study was granted by the Public Benefit and Privacy Panel for Health and Social Care.

Sweden: SNR

In Sweden, the national health care system provides universal coverage to all residents—10 million inhabitants. Health care coverage includes visits to GPs and specialists, hospital admissions, and hospital outpatient visits; drug costs are either partially or completely covered.

A centralized civil registration system has been in place for many years, enabling personal identification of each person in the entire population and linkage to all national registers containing civil registration numbers, e.g., patient register, cancer register, prescribed drug register, register of causes of death, and population registers.

The following registers in Sweden were used for this study:

- Swedish Prescribed Drug Register

- National Patient Register

- Swedish Cancer Register

- Cause of Death Register

- The Total Population Register of Statistics Sweden

These registers are linked by the personal registration number, a unique identifier assigned to all Swedish residents at birth or upon immigration, and kept unchanged throughout life. All linkage among data sources occurs within the Swedish National Board of Health and Welfare, and anonymized patient-level data are delivered to the Centre for Pharmacoepidemiology at the Karolinska Institutet. All registers are updated yearly.

Swedish Prescribed Drug Register

The Prescribed Drug Register has been functioning since July 2005 and contains data with unique patient identifiers for all filled prescriptions for the whole population of Sweden (10 million inhabitants in 2016) [6, 7]. The register is complete for the entire Swedish population (patient identity data are missing for < 0.3% of all items). All drugs are classified according to the Anatomical Therapeutic Chemical classification system. Measurement units for utilization of

prescription medications are prescriptions, DDDs, and expenditures. The register does not include data on over-the-counter medications. The register is also not complete with regard to drugs used in hospitals and nursing homes.

National Patient Register

The National Patient Register contains data from all hospital admissions in Sweden. It covers all public inpatient care since 1987 and outpatient visits since 2001. The medical data include main and secondary diagnoses and surgical procedures from public and private service providers. In a Swedish study, the positive predictive value of an inpatient recorded diagnosis was 85% to 95 %, and the main diagnosis was missing in 1.0% [8].

Swedish Cancer Register

The Swedish Cancer Register covers the total Swedish population. Approximately 50,000 neoplasms are registered each year in Sweden. It is compulsory for every health care provider to report new cases to the register. Reports provide information about every incident cancer diagnosed at clinical, morphological, or other laboratory examinations, as well as cases diagnosed at autopsy. Since 2005, the site and histological type of the cases have been coded according to the *International Classification of Diseases for Oncology, Third Edition* (ICD-O-3). A study on data quality published in 2009 estimated that underreporting was 3.7% [9].

Causes of Death Register

The Causes of Death Register comprises all deaths among Swedish residents, whether occurring in Sweden or abroad [10]. The causes of death are coded according to the international (English) version of the ICD-10. The register is updated yearly. In 1994, the nonreporting rate was 0.45% of all deaths.

The Total Population Register of Statistics Sweden

The Total Population Register of Statistics Sweden hold individual information on region of residency, occupation, emigration, and immigration.

This study was conducted in collaboration with the Centre for Pharmacoepidemiology at the Karolinska Institutet.
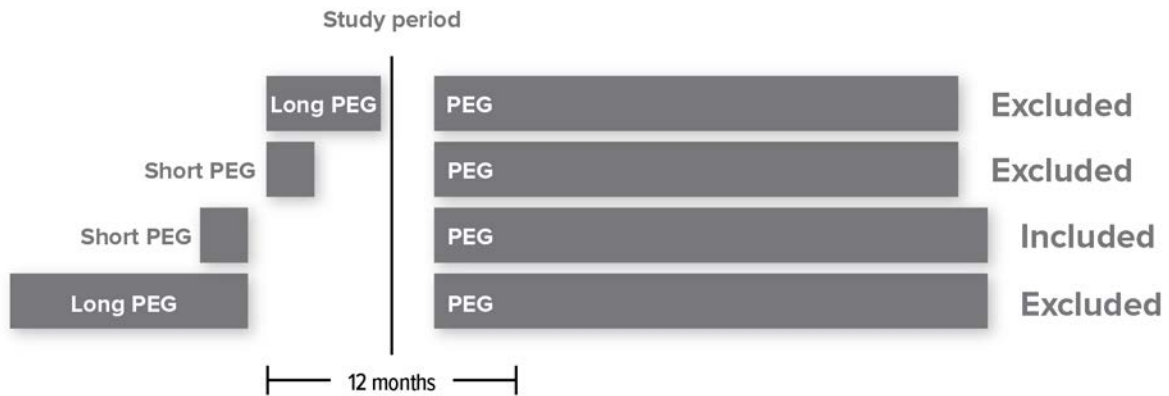
Electronic Supplementary Material 2: Cohort Identification
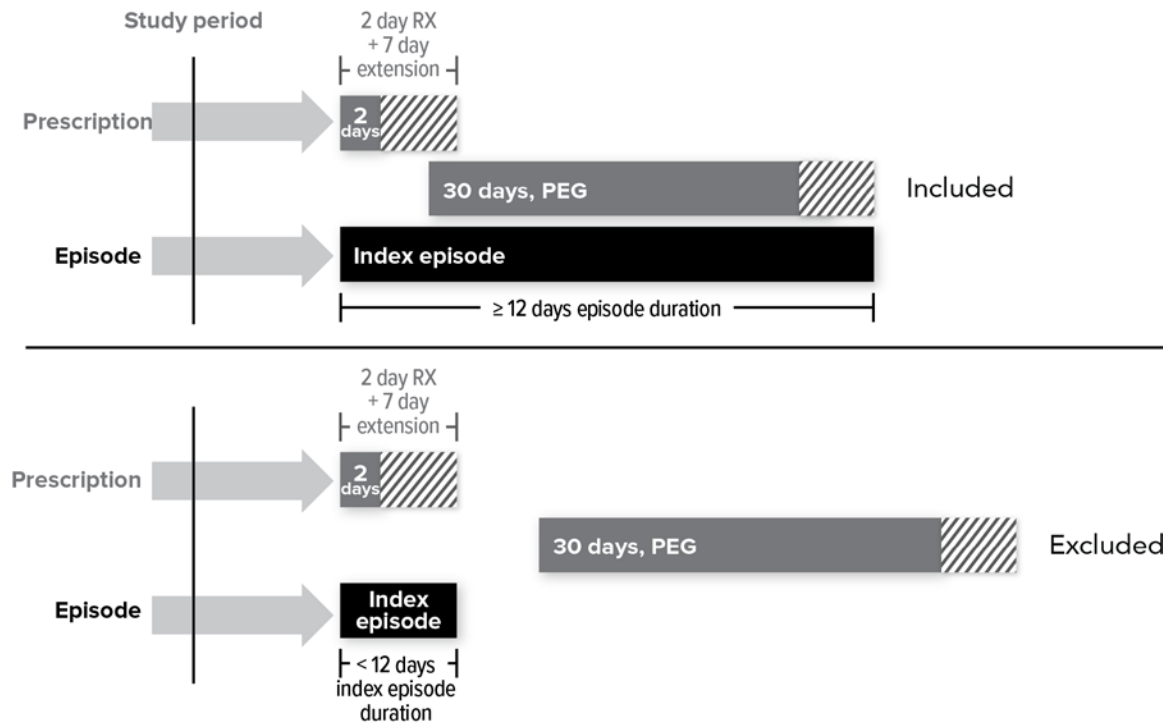
Figure S-1. **Inclusion of Prucalopride Initiators**
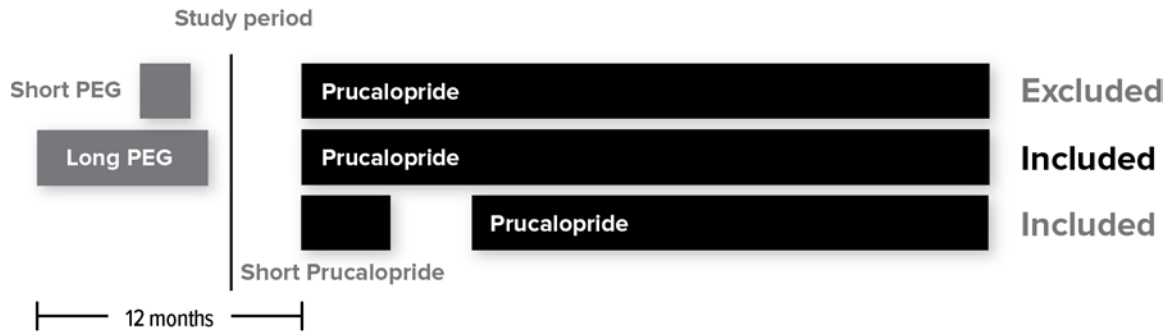
PEG = polyethylene glycol 3350.

Figure S-2. **Inclusion of PEG Initiators**

PEG = polyethylene glycol 3350.

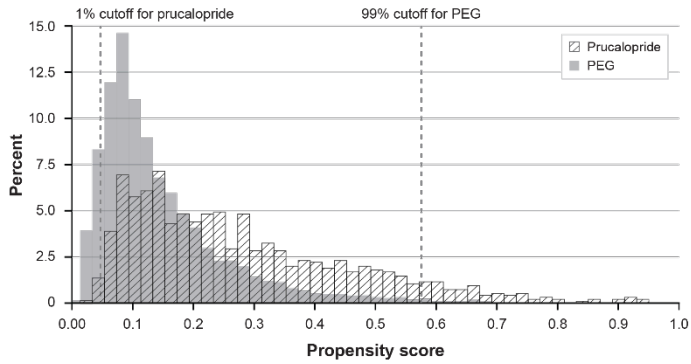**Figure S-3.   Inclusion of PEG Initiators Regarding Duration of First Episode**

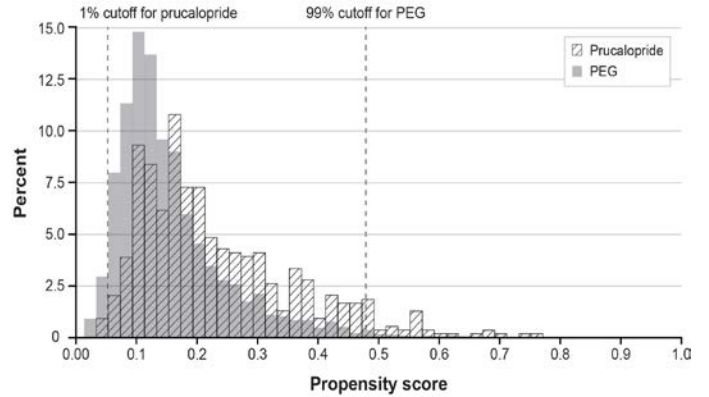PEG = polyethylene glycol 3350; RX = prescription/dispensing.

Electronic Supplementary Material 3: Modelling Propensity to Receive Prucalopride

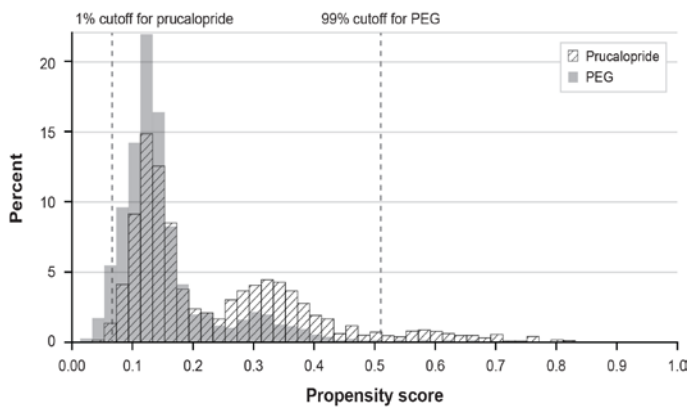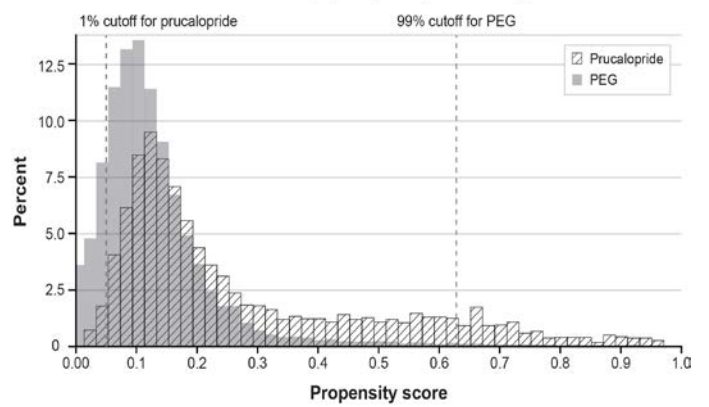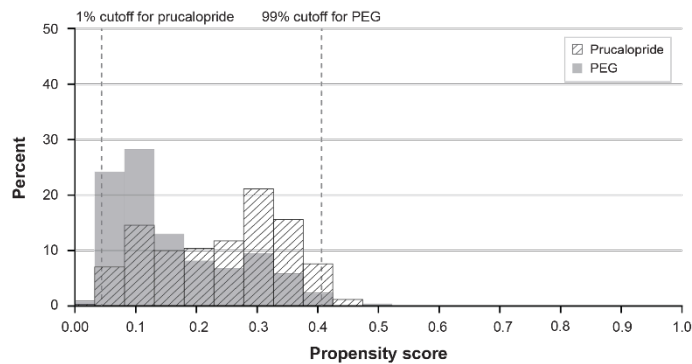## Distribution of Propensity Scores (Before Trimming)

CPRD

THIN

ISD

SNR

GePaRD

Table S-1.   Variables Included in the Propensity Score Models of Each Data Source

Variables	CPRD	THIN	ISD	SNR	GePaRD
Age at index	Yes	Yes	Yes	Yes	Yes
Alcohol use	Yes	No	NA	NA	Yes (through alcohol-related disorders)
Anticoagulants	Yes	Yes	Yes	Yes	Yes
Antidiabetics	Yes	Yes	Yes	Yes	Yes
Antihypertensives	Yes	Yes	Yes	Yes	Yes
Antipsychotics	No	No	No	No	Yes
Aspirin and other antiplatelets	Yes	Yes	Yes	Yes	Yes
Asthma diagnosis (without any COPD diagnosis)	Yes	Yes	No	Yes	Yes
At least one cardiovascular risk factor	No	No	No	No	Yes
Atrial fibrillation or flutter	No	No	No	No	Yes
Calendar period	Yes	Yes	Yes	No	Yes
Cancer	Yes	Yes	Yes	Yes	Yes
Cerebrovascular revascularization	Yes	No	No	No	Yes
Chronic opioid use	Yes	Yes	Yes	Yes	Yes
Chronic renal disease	Yes	No	No	Yes	Yes
Colonoscopy or similar procedure during the first 21 days of follow-up	Yes	No	No	No	No
Constipation diagnosis	No	No	No	Yes	No
COPD	Yes	Yes	Yes	Yes	Yes
Coronary revascularization	Yes	No	Yes	Yes	Yes
Country	Yes	No	—	—	—
Diabetes	Yes	Yes	Yes	Yes	Yes

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Variables	CPRD	THIN	ISD	SNR	GePaRD
History of hospitalization for acute myocardial infarction	Yes	No	Yes	Yes	Yes
History of hospitalization for cardiovascular disease	No	Yes	No	No	Yes
History of hospitalization for ischemic heart disease (including MI)	Yes	No	Yes	Yes	Yes
History of hospitalization for peripheral vascular disease	Yes	No	Yes	Yes	Yes
History of hospitalization for stroke	Yes	No	Yes	Yes	Yes
History of hospitalization for transient ischemic attack	Yes	No	Yes	Yes	Yes
Hyperlipidemia	Yes	No	Yes	Yes	Yes
Hypertension	Yes	Yes	Yes	Yes	Yes
IBS diagnosis	Yes	Yes	Yes	Yes	No
Non-steroidal anti-inflammatory drugs	No	No	No	No	Yes
Number of medical visits	Yes	No	No	Yes	No
Other gastrointestinal-related diagnoses	Yes	No	Yes	Yes	No
Obesity diagnosis	Yes	Yes	No	Yes	No
Prescription or dispensing for opioid medications	Yes	Yes	Yes	Yes	Yes
Peripheral revascularization	Yes	No	Yes	Yes	Yes
Recent hospitalization	Yes	Yes	Yes	Yes	Yes
Sex	Yes	Yes	Yes	Yes	Yes
Smoking	Yes	Yes	NA	NA	NA
Socioeconomic level	Yes	Yes	Yes	Yes	NA
Statins	Yes	Yes	Yes	Yes	Yes
Thrombolytics	No	No	No	No	Yes
Interaction term between chronic opioid use and cancer	No	No	No	No	Yes

Variables	CPRD	THIN	ISD	SNR	GePaRD
Interaction term between opioid medication and recent hospitalization	No	No	No	No	Yes
Interaction term between recent hospitalization and sex	No	No	No	No	Yes
Interaction term between index year, sex and age	No	No	No	Yes	No

— = not applicable to the data source; COPD = chronic obstructive pulmonary disease; CPRD = Clinical Practice Research Datalink; GePaRD = German Pharmacoepidemiological Research Database; IBS = irritable bowel syndrome; ISD = Information Services Division; MI = myocardial infarction; NA = variable not available in the data source; no = variable available in the data source but not included in the propensity score model; SNR = Swedish National Registers; THIN = The Health Improvement Network; yes = variable included in the propensity score model.

Electronic Supplementary Material 4: Rules for Reimbursement of Study Drugs in Germany, Sweden, and the United Kingdom

In the United Kingdom (UK), patients with chronic constipation are most commonly diagnosed by general practitioners (GPs). Patients are referred to specialist gastroenterologists if malignancy or other serious diseases are suspected; further testing is required to clarify disease etiology if patients do not respond to diet changes, lifestyle advice, and laxatives. Elderly patients may also be diagnosed by and/or referred to geriatricians. Common therapies include lactulose, Dulcolax (bisacodyl), Fybogel (ispaghula husk), Senokot (senna), and Movicol (polyethylene glycol 3350 [PEG]); the latter is the most common reimbursed prescription medication for constipation in the UK. Prescriptions are free for certain groups in England (e.g., patients aged 60 years and older and those with a specified medical condition and a valid medical exemption certificate) but otherwise require a fixed co-payment [11]. The National Institute for Health and Care Excellence (NICE) guidance recommends prucalopride as an option for the treatment of chronic constipation only in patients who have had treatment with at least two laxatives from different classes at the highest tolerated recommended doses for at least 6 months, have not received adequate relief, and for whom alternative treatments for constipation are under consideration. Although NICE recommends that prucalopride should only be prescribed by a clinician with experience of treating chronic constipation, after careful review of the patient's previous courses of laxative treatments, most prucalopride repeat prescriptions are followed up in primary care.

In Scotland, all prescriptions for all medications are free of charge to patients. The Scottish Medicines Consortium have advised that prucalopride is not recommended for use within the National Health Service (NHS) Scotland for the symptomatic treatment of chronic constipation; despite this, it is still used in primary care where it would be initiated by clinical specialists via changes to patients' prescribing by GPs.

In Sweden, all residents are covered by a national pharmaceutical benefits scheme that subsidizes most prescription drugs. All purchases of prescription drugs are registered in the prescription database regardless of the drug's subsidy status. Prucalopride has been available and reimbursed since 2012 for treatment of chronic constipation. It is a second- and third-line treatment to be used when conventional laxatives are not sufficient. Both specialists and GPs may prescribe prucalopride for treating constipation. PEG has been available for a longer time and is used in a more diverse group of patients and prescribers than prucalopride. PEG is also routinely used as preventive treatment during short- or long-term treatment with opioids after surgery.

In Germany, patients with chronic constipation are most commonly diagnosed by primary care practitioners and internal medicine physicians. Patients are referred to specialist gastroenterologists if they are nonresponsive to diet changes, lifestyle advice, and laxatives, and if malignancy is suspected or further testing is required to clarify etiology. German reimbursement authorities classify prucalopride similar to laxatives, resulting in restricted reimbursement—that is, no reimbursement and thus no prescription if used to treat any idiopathic chronic constipation and limited reimbursement for selected cases in patients with secondary chronic constipation. As German Pharmacoepidemiological Research Database (GePaRD) is based on claims data, only reimbursed dispensings can be identified. In Germany, reimbursable prescribed drugs are reimbursed by the health insurance provider with a co-payment up to €10

[12]. Prucalopride prescribing is predominantly initiated by specialists, with repeat prescriptions written in primary care. On the other hand, German reimbursement policies generally classify PEG as a medical device [13], which makes it subject to stricter prescribing regulations, i.e., it can only be prescribed to patients with serious comorbidities and poorer health (e.g., cancer, mucoviscidosis, end-of-life care).

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