PASS Information

Title	Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort: Final Study Report
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Active substance	Prucalopride (A06AX05); macrogol (A06AD15)
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Product reference	EMEA/H/C/001012
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Joint PASS	No
Research question and objectives	The primary objective of this study was to estimate, in real-world settings, the adjusted incidence rate ratio (IRR) and 95% confidence interval (CI) for major adverse cardiovascular events (MACE)—defined as the composite of hospitalization for acute myocardial infarction (AMI), hospitalization for stroke, and in-hospital cardiovascular death—in initiators of prucalopride versus initiators of polyethylene glycol 3350 (PEG), both indicated for chronic constipation, adjusting for cardiovascular risk factors and other potential confounders.
Country(-ies) of study	United Kingdom, Germany, Sweden
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1 Abstract

Title: Cohort Study of the Relative Incidence of Major Cardiovascular Events Among Patients Initiating Prucalopride Versus a Matched Comparator Cohort: Final Study Report

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Keywords: chronic constipation, prucalopride, cardiovascular safety, pharmacoepidemiology, multidatabase

Rationale and background: Prucalopride, a 5-hydroxytryptamine receptor type 4 (5-HT_4) agonist, was first approved in Europe in October 2009 for the treatment of chronic constipation in adult patients in whom laxatives have been ineffective. Prucalopride is currently approved in 82 countries. No signal for increased risk of adverse cardiovascular (CV) events has been observed for prucalopride during extensive nonclinical and clinical CV investigations or as a result of safety monitoring during the entire clinical development program and 9 years of postmarketing experience.

However, given the prior experience with other 5-HT_4 receptor agonists, the United States Food and Drug Administration (FDA) expressed interest in having additional information about CV safety for any members of this drug class, including prucalopride. The results of this study will be used as part of the FDA's assessment of the New Drug Application for prucalopride in the United States.

Research question and objectives: The primary objective of the study was to estimate, in real-world settings, the adjusted incidence rate ratio (IRR) and 95% confidence interval (CI) for major adverse CV events (MACE)—defined as the composite of hospitalization for acute myocardial infarction, hospitalization for stroke, and in-hospital CV death—in initiators of prucalopride versus initiators of polyethylene glycol 3350 (PEG), two treatments indicated for chronic constipation. The adjusted analyses accounted for CV risk factors and other potential confounders.

Secondary objectives of the study were as follows:

- Estimate incidence rates for MACE and its individual components in the prucalopride and PEG cohorts
- Estimate adjusted IRRs for the individual components of MACE for the prucalopride cohort compared with the PEG cohort

Study design: This was an observational (noninterventional) population-based cohort study of patients initiating prucalopride or PEG from three European member states (United Kingdom [UK], Sweden, and Germany). The incidence rate of MACE for prucalopride and PEG users and the adjusted incidence rate ratios (IRRs) and incidence rate differences (IRDs) of MACE comparing prucalopride to PEG use were calculated individually for each data source and after pooling the aggregated results from UK and Sweden. Data from Germany was excluded from the pooled analyses, as the patient population was markedly different compared to the other countries in terms of comorbidities because of differences in prescribing and reimbursement practices between prucalopride and PEG.

Setting: This study was implemented in five administrative health care data sources in three European member states: in the UK, two data sources derived from electronic medical records from general practices—the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN)—and the Information Services Division (ISD) of Scotland, an administrative health care data source; in Sweden, the Swedish National Registers (SNR) including health data from the National Patient Register, the Prescribed Drug Register, the National Cancer Register, the Cause-of-Death Register, and information from the Total Population Register; and in Germany, the German Pharmacoepidemiological Research Database (GePaRD), constructed from claims of statutory health insurance agencies. Patients and practices that could potentially be included in multiple UK data sources were retained in only one data source.

Subjects and study size, including dropouts: The prucalopride cohort consisted of adult patients who had a dispensing (for claims data sources) or prescription (as recorded in electronic medical record data sources) for prucalopride within the study period with at least 12 months of data coverage in the data source before this first dispensing or prescription, no evidence in the data source of prior use of prucalopride, and no evidence of short use of PEG (i.e., < 5 days) within 12 months before this first prucalopride prescription/dispensing. The first prescription of prucalopride was the index prescription, which determined the index date.

The PEG cohort consisted of patients who had a dispensing or prescription for PEG of at least 5 days within the study period, who had at least 12 months of data coverage in the data source before this first dispensing or prescription, and who had no evidence of prior use of PEG for chronic constipation in the data source. The first prescription for PEG was the index prescription, prescribed or dispensed on the index date. Up to five PEG initiators were selected for each prucalopride initiator, matched by age, sex, and calendar year of first prescription of prucalopride or PEG. (The SNR also matched patients by recent hospitalization and specialty of the prescribing physician to increase comparability between PEG and prucalopride users). At the time of study initiation, PEG was the most commonly prescribed reimbursable medication for chronic constipation in Europe.

The study size was driven by the number of prucalopride initiators and associated duration of exposure that was available in the selected data sources during the study period. Per the study protocol, it was estimated that 10,950 prucalopride new users would be sufficient to reach, with 80% probability, an upper bound of the two-sided 95% CI of the IRR of less than 3 if the true IRR is 1.0 and the baseline rate of MACE is 2 per 1,000, with assumed average prucalopride treatment duration of 130 days.

Variables and data sources: Prucalopride or PEG exposure was ascertained from general practitioner (GP) prescriptions in the CPRD and THIN data and by outpatient dispensings in the ISD, GePaRD, and SNR data. CV risk factors and other covariates were identified from the available health care utilization codes before the index date.

The primary endpoint, MACE, comprised the first occurrence of any of its individual components during follow-up. The CV endpoints of interest were identified by applying modified versions of existing algorithms of diagnosis codes from published pharmacoepidemiologic studies to data from hospital admissions and discharge diagnoses. In the CPRD and THIN, validation of outcomes was conducted by obtaining, as available, linkage to Hospital Episode Statistics discharge diagnoses and to Office for National Statistics death records (CPRD only), GP questionnaires (CPRD only), and review of free-text comments (THIN only). In the ISD Scotland, validation of outcomes

was conducted through medical chart abstraction. For cases in the UK data sources, an adjudication committee of three clinical experts determined final status. Cases included in Sweden were identified using modifications of electronic algorithms previously validated in the Swedish registers. Cases identified in Germany were manually reviewed for admission diagnosis codes to verify the case status.

Analyses: For each cohort, the prevalence of known risk factors for MACE at baseline was described. Crude and standardized incidence rates of each outcome of interest were calculated for the prucalopride and PEG cohorts by categories of each covariate of interest, and corresponding crude and standardized IRRs and IRDs were estimated.

Within each data source, propensity scores were developed using logistic regression with prucalopride versus PEG as the outcome and included variables shown to be potential confounders, including CV risk factors. To optimize comparability of cohorts, the propensity score distributions of prucalopride and PEG cohorts were evaluated, and individuals below percentile 1 of the prucalopride distribution and above percentile 99 of the PEG distribution were trimmed from the cohorts, which eliminated all patients with nonoverlapping propensity score. Incidence rates, IRRs, and IRDs were standardized against person-years in the prucalopride cohort and stratified by data source and propensity score decile.

For the UK data sources, where validation was conducted, a sensitivity analysis of the primary analysis was performed in which cases classified as "probable" were additionally included as events following review by the adjudication committee. An additional sensitivity analysis was conducted for all data sources to assess the impact of including out-of-hospital CV deaths in the MACE composite endpoint (MACE+). A bias analysis was conducted to determine the potential impact of unmeasured confounding assuming different scenarios of prevalence of the confounders and their association with the outcome.

Post hoc subgroup analyses by sex, age, sex by age, and history of cardiovascular disease were conducted for the primary pooled analysis per FDA request after the planned analyses had been initiated.

Results: The pooled analyses of aggregate data included 35,087 patients with chronic constipation treated with prucalopride (n = 5,715) or PEG (n = 29,372), including 5,120 matched patients from the CPRD, 3,044 from THIN, 6,960 from the ISD, and 19,963 from the SNR. The average duration of cumulative prucalopride and PEG use after the index date was approximately 175 days and 82 days, respectively.

In all data sources, the vast majority of participants were women (i.e., 95% in the CPRD and THIN, 96% in ISD Scotland, and 91% in Sweden), and the proportion of patients aged 55 years and older was roughly similar in the UK data sources (34% in the CPRD, 31% in THIN, and 21% in ISD) and higher in Sweden (53%). In general, prucalopride patients had more baseline GI comorbidities, whereas PEG patients tended to have more baseline cardiovascular diseases in CPRD, THIN, and SNR and more baseline history of cancer in all data sources.

The pooled standardized incidence rates (95% CI) of MACE among patients initiating prucalopride per 1,000 person-years was 6.57 (3.90-10.39) and 10.24 (6.97-14.13) for PEG. The overall pooled adjusted IRR for MACE (i.e., combining the three UK data sources and the SNR) was 0.64 (95% CI, 0.36-1.14). The pooled adjusted IRD for MACE combining the three UK data sources and the SNR was −3.66 per 1,000 person-years (95% CI, −8.27 to 0.95). The pooled adjusted IRRs for individual components of MACE

were 0.95 (95% CI, 0.38-2.39) for hospitalization for nonfatal AMI, 0.54 (95% CI, 0.23-1.29) for hospitalization for nonfatal stroke, and 0.47 (95% CI, 0.13-1.67) for in-hospital CV death.

The IRR and IRD results were robust to the alternative definitions of the MACE endpoints that added out-of-hospital cardiovascular death and probable cases to the definition of MACE (and possible in-hospital cardiovascular deaths), as well as to bias analyses that considered the hypothetical impact of unmeasured confounding in different scenarios of confounder prevalence and association with the outcomes. The results were also consistent across all subgroups; however, for the post hoc subgroup analyses of men older than 55 years, an IRR of 2.57 (95% CI, 0.71-9.26) was observed based on 4 events in the prucalopride cohort and 11 events in the PEG cohort.

Although Germany was not included in the main analyses, results are included for transparency. In Germany, after trimming, 30,714 matched patients from GePaRD (88% female and 66% aged 55 years and older) were identified. In general, fewer prucalopride patients had history of comorbid conditions at baseline compared to PEG patients. The standardized incidence rate of MACE per 1,000 person-years was 11.05 (95% CI, 8.03-14.69) for prucalopride and 21.53 (95% CI, 18.52-24.78) for PEG. The adjusted IRR for MACE was 0.51 (95% CI, 0.37-0.71), and the adjusted IRD for MACE was −10.48 (95% CI, −14.99 to −5.98).

Discussion: The primary objective of this study was to estimate, in real-world settings, the IRR and 95% CI for MACE in initiators of prucalopride compared with initiators of PEG, adjusting for potential confounders. More specifically, the study aimed to investigate whether the upper bound of the two-sided 95% CI for the adjusted IRR was less than 3.00. The pooled point estimate of the IRR was 0.64 (95% CI, 0.36-1.14), with a 95% CI that included the null value and an upper limit below 3.00. Thus, the results indicate no evidence of an increased risk of MACE overall among patients with chronic constipation using prucalopride. Differences in baseline comorbidities between the prucalopride and PEG cohorts were minimized after standardization by propensity score decile and data source for data sources included in the final pooled analyses. In the post hoc subgroup analysis for men over the age of 55 years, an IRR of 2.57 (95% CI, 0.71-9.26) was observed. This observation should be interpreted with caution given the small sample size (as expected, given most use of prucalopride is in women) and the lack of power to draw conclusive evidence for this subgroup.

The study was designed as a multidatabase study in which the primary aggregated results would be pooled across the participating data sources. It was originally intended to include GePaRD data from Germany; however, because of the reimbursement policies in Germany, the disparate clinical profile of German patients compared to other countries, particularly in users of PEG, precluded combining the study population of GePaRD with those from the UK and Sweden. Nevertheless, inclusion of data from Sweden compensated for the German data in achieving a sufficient study size.

In the sensitivity analyses using alternative definitions of the MACE study endpoint, the results were consistent with those from the main, pooled analysis. The main results were also robust to potential unmeasured confounders.

Limitations: Determining exposure duration accurately is challenging when using secondary health care data, and exposure misclassification is possible. Also, no direct measure of patient adherence was available, and it was assumed that patients were administered the product as prescribed. Efforts were made to harmonize the definitions

of exposure periods, key study variables, including endpoints and key covariates, across data sources. Still, nuances were allowed for endpoint definitions, such as the definition of sudden cardiac death in the SNR, to adapt the core definitions to the local coding practices and thus avoid outcome misclassification. Similarly, minor adaptations were also allowed for some covariates included in the analyses.

Regarding validation of the study endpoints, validation via medical record review was not performed in the SNR for this study since the endpoints used in the Swedish analysis have previously been validated on a register level. Also, in the CPRD, THIN, and the ISD, disparate sources of information were used to adjudicate cases. Moreover, some clinical information was incomplete for several potential cases. This may have limited the ability of clinical reviewers to adjudicate the study events, particularly regarding death events, for which the information included in the patient profiles/medical records often was limited.

Conclusion: In this study of patients with chronic constipation using prucalopride or PEG (> 90% women), the pooled IRR of MACE comparing prucalopride use with PEG use was 0.64 (95% CI, 0.36-1.14). Moreover, the upper limit of the 95% CI for this estimate was below the prespecified threshold of 3.00. These results were robust to the use of alternative definitions of the study endpoint (i.e., including out-of-hospital CV death and probable MACE cases—and possible in-hospital cardiovascular deaths—after validation) and to bias analyses for hypothetical unmeasured confounders. In the post hoc analyses, results were also consistent, except for the small subgroup of men older than 55 years of age, where additional analyses are warranted. The overall pooled analyses were consistent with the finding of no evidence of an increased risk of MACE in patients with chronic constipation using prucalopride as compared with PEG.

Marketing Authorization Holder(s): Shire Pharmaceuticals

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