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Global Clinical Epidemiology

Non-Interventional Study Protocol

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REDACTED PROTOCOL

Title	Assessing the incidence of ischemic colitis in treated adult hypertensive patients in the United States – a descriptive, retrospective cohort study with secondary use of data from a US health claims database
Protocol version identifier	v0
Date of last version of protocol	26 June 2013
EU PAS register number	Study not registered
Active substance	Aliskiren (C09XA/Renin-inhibitors)
Medicinal product	Rasilez®, Tekturna®
Product reference	EMEA/H/C/000780
Procedure number	Not applicable
Marketing authorization holder(s)	Novartis Europharm Limited Wimblehurst Road Horsham West Sussex RH12 5AB United Kingdom

Joint PASS	No
Research question and objectives	[redacted]
Country (-ies) of study	United States
Author	[redacted]

[redacted]

Marketing authorization holder(s)

Marketing authorization holder(s)	Novartis Europharm Limited Wimblehurst Road Horsham West Sussex RH12 5AB United Kingdom
MAH contact person	[redacted]

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2 List of abbreviations

AB	Alpha Blocker
ACEI	Angiotensin-Converting Enzyme inhibitor
ARB	Angiotensin II Receptor Blocker
BB	Beta Blocker
CCB	Calcium Channel Blocker
CCI	Charlson Comorbidity Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CPT	Current Procedural Terminology
GPI	Generic Product Identification
HMO	Health Maintenance Organization
HCPCS	Healthcare Common Procedure Coding System
IC	Ischemic Colitis
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IQR	Interquartile Range
IR	Incidence Rate
MPR	Medication Possession Ratio
NDC	National Drug Code
PPO	Preferred Provider Organization
PY	Person-Year

3 Responsible parties

Table 3-1 Main responsible parties

Role	Person
Main protocol author	[redacted]
Principal investigator (PI)	[redacted]
MAH contact person	[redacted]

4 Abstract

Title	Assessing the incidence of ischemic colitis in treated adult hypertensive patients in the United States – a descriptive, retrospective cohort study with secondary use of data from a US health claims database
Version and Date	v0 26 June 2013
Name and affiliation of main author	[redacted]
Rationale and background	Aliskiren is the first known representative of a new class of non-peptide orally active direct renin inhibitors (DRIs) that blocks the renin-angiotensin-aldosterone-system (RAAS) at its rate-limiting step. It induces a net reduction in plasma renin activity, angiotensin II and aldosterone levels. Aliskiren is effective in reducing blood pressure and overall is well tolerated. Ischemic colitis (IC) is included in the risk management plan (RMP) as a potential risk for aliskiren based on isolated reports in patients receiving aliskiren. There is also evidence that other antihypertensive drugs may be associated with the development of IC. In a case-control study published in 2010, some evidence was found that use of antihypertensive drugs (specifically calcium channel blockers or ACE inhibitors) was associated with an increased risk of developing IC. Based on that IMS conducted a study for Novartis in 2011 to assess the incidence of probable IC in patients treated with any antihypertensive medication, the results of which were shared with the European Medicines Agency (EMA) by Novartis. The study population included only a small number of patients receiving a direct renin inhibitor (i.e. aliskiren, the only direct renin inhibitor available at the time the study was conducted), on account of the fact that aliskiren had only been on the market for a short period of time when the study was conducted. Therefore, Novartis committed to re-run this analysis as requested by the Committee for Medicinal Products for Human Use (CHMP) focusing on patients using aliskiren as well as making some minor modifications to the previous study's design based on specific comments received from CHMP for the first study run in 2011 (e.g. including a general population sample, stratification of prevalent antihypertensive treatment cohort based on the date of the first antihypertensive drug prescription identified in the pre-index period, time-varying exposure analysis of incidence rates).
Research question and objectives	The objective of this study is to assess the [redacted]
Study design	This will be a descriptive, retrospective cohort study with secondary use of data derived from the United States PharMetrics™ Health Plan Claims Database from 1 July 2005 through 30 June 2012 (or the most recent data available at the time of data extraction).
Population	All adult hypertensive subjects with a prescription for an antihypertensive

	medication between 1 January 2006 and 31 March 2012 will initially be selected for inclusion into the study from the PharMetrics™ claims database. Patients will be selected for analysis if they show evidence of a hypertension diagnosis; have at least 1 prescription for an antihypertensive medication on or after the hypertension diagnosis date OR with days supply (i.e., the number of days that the amount of dispensed medication will last when taken as prescribed) overlapping the diagnosis date; are 18 years of age or older at the time of the index date; and have continuous health plan enrollment for a minimum of 180 days prior to the index date and a minimum of 90 days following the index date. Patients' index date will be defined by the first claim for aliskiren identified during the index window. For patients with no evidence of aliskiren claims during the index window, the date of the first prescription for any other antihypertensive medication will be considered the index date. In addition to hypertensive patients, patients without a diagnosis of hypertension and/or evidence of antihypertensive therapy will be included in the study to represent a general population.
Variables	[redacted]. Incidence of IC will be calculated per 100,000 person-years and presented as incidence rates (IR) with 95% confidence intervals (CI). [redacted] Patients will be stratified into the incident antihypertensive treatment cohort if there is no evidence of antihypertensive prescriptions in the 180 days prior to the index date. Patients with evidence of at least 1 antihypertensive prescription in the 180 days prior to the index date will be stratified into the prevalent antihypertensive treatment cohort. The total number of patients classified as monotherapy, dual combination therapy (fixed-dose and free-dose combinations), and triple-plus combination therapy (fixed-dose and free-dose combinations), at index and prior to the end of follow-up will be provided. Adherence to index antihypertensive drug therapy will be defined using the proxy measure known as the Medication Possession Ratio (MPR). MPR will be calculated as the total number of days covered by the index drugs divided by the total number of follow-up days. Covariates that will also be reported include age, gender, geographic region, health plan type, payer type, available days of follow-up, Charlson comorbidity index, comorbid conditions (e.g. irritable bowel syndrome, peripheral vascular disease, vascular insufficiency of intestine, acute coronary syndrome,), and probable rule-out IC conditions and procedures.
Data sources	Data will be taken from the PharMetrics™ database, which comprises fully adjudicated medical and pharmaceutical claims for over 70 million unique patients from nearly 80 health plans across the U.S. (approximately 16 million covered lives per year) from January 2001 through June 2012. The database includes both inpatient and outpatient diagnoses (in ICD-9-CM format) and procedures (in CPT-4 and HCPCS formats) as well as both retail and mail order prescription records. Available data on prescription records include the National Drug Code (NDC) and the Generic Product Identification (GPI) code, as well as the quantity of the medication dispensed. Additional data elements include demographic variables (age, gender, and geographic region), product type (e.g., HMO, PPO), payer type (e.g., commercial, self-pay), provider specialty, and start and stop dates of health-plan enrollment.
Study size	Because this is an exploratory epidemiologic study and not a hypothesis

	testing study, power analysis for sample size estimation was not conducted. Sample size will be determined based on the number of patients available in the database, who meet study inclusion criteria.
Data analysis	All analyses will employ SAS version 9.1 (SAS Institute Inc., Cary, NC). All data will be reported for the aggregate population as well as stratified by the incident versus prevalent antihypertensive treatment cohorts. Unless otherwise specified, results for categorical measures will be provided as the frequency and percentage of total study patients observed in each category. For continuous variables, descriptive statistics (mean, standard deviation [SD], range, median, and interquartile range [IQR]) will be presented. When necessary, continuous variables will be categorized into intervals, with the distribution of patients for each interval provided. No statistical analyses will be performed, and all comparisons between cohorts will be descriptive in nature only.
Milestones	Start of data collection: 02 July 2013 End of data collection: 02 August 2013 Registration in the EU PAS register: 01 July 2013 Final report of study results: 30 September 2013

5 Amendments and updates

Not applicable

6 Milestones

Table 6-1 Study milestones

Milestone	Planned date
Start of data collection	02 July 2013
End of data collection	02 August 2013
<Registration in the EU PAS register>	01 July 2013
Final report of study results	30 September 2013

7 Rationale and background

Ischemic colitis

Ischemic colitis (IC) is an acute, self-limited vascular condition of inadequate blood flow in the colon which leads to colonic inflammation, and which can produce significant morbidity and mortality (Higgins et al 2004, Theodoropoulou and Koutroubakis 2008). IC is the most common form of ischemic injury to the gastrointestinal tract, representing more than half of the cases with gastrointestinal ischemic events (Theodoropoulou and Koutroubakis 2008). Colonic blood flow may be compromised by changes in the systemic circulation or by anatomic or functional changes in the local mesenteric vasculature. The original insult precipitating the ischemic event often cannot be established. The event frequently occurs in elderly patients with diffuse disease in small segmental vessels and with various comorbidities. Approximately 90% of cases of IC occur in patients over 60 years of age, although younger patients may also be affected (Theodoropoulou and Koutroubakis 2008).

A variety of conditions may predispose individuals to IC. Specifically, mesenteric artery emboli, thrombosis, or trauma may lead to occlusive vascular disease and impaired colonic perfusion. Furthermore, hypoperfusion states due to congestive heart failure (CHF), transient hypotension in the perioperative period, strenuous physical activities, and shock due to a variety of causes such as hypovolemia or sepsis can result in IC. Infrequently, mechanical colonic obstruction due to tumors, adhesions, volvuli, hernias, diverticulitis. or prolapse also may cause IC (Theodoropoulou and Koutroubakis 2008).

Many classes of medications predispose individuals to IC. Major classes of pharmacologic agents known to be associated with IC include the following: antibiotics, appetite suppressants (phentermine), chemotherapeutic agents (vinca alkaloids and taxanes), constipation-inducing medications, decongestants (pseudoephedrine), cardiac glycosides, diuretics, ergot alkaloids, hormonal therapies, statins, illicit drugs, immunosuppressive agents, laxatives, non-steroidal anti-inflammatory drugs (NSAIDs), psychotropic medications, serotonin agonists/antagonists, and vasopressors (Theodoropoulou and Koutroubakis 2008).

Iatrogenic causes also may result in IC; specifically, IC follows aortic reconstruction with an incidence of 2% to 3% and is higher after abdominal aortic aneurysm repair. Furthermore, IC may be a complication of coronary artery bypass surgery or a rare complication of colonic surgery or colonoscopy (Theodoropoulou and Koutroubakis 2008).

Determining the true incidence of IC poses some difficulties. In two prospective series of patients, all of whom had endoscopy after aortic surgery, only half of those with IC confirmed by histopathology were clinically suspected to have IC by their surgeons. A strict definition of IC would require biopsy confirmation of each diagnosis, although in clinical practice, the criteria used to make a diagnosis of IC are likely to vary. However, even when the diagnosis is clinically suspected and then confirmed by endoscopy and biopsy, finding these cases in an administrative or medical record database depends on appropriate coding for this unusual diagnosis (Higgins et al 2004).

The incidence of IC, as determined by colonoscopy, was evaluated retrospectively from 1992 through 2001 at two large metropolitan hospitals in Indianapolis, Indiana. The annual incidence of IC (per 10,000 admissions) was reported as follows: 1992, 2.12; 1993, 1.20; 1994, 1.81; 1995, 1.90; 1996, 3.74; 1997, 4.10; 1998, 4.46; 1999, 7.49; 2000, 7.83; 2001, 7.49. The rise in incidence from 1992 to 2001 was statistically significant (Elmore and Elliott 2005).

Loftus et al (2002) utilized the resources of the Rochester Epidemiology Project to identify all county residents who were diagnosed with IC between January 1, 1976 and December 31, 1998. The Rochester Epidemiology Project is a medical records linkage system encompassing all health care providers in Olmsted County, Minnesota. A total of 173 cases were identified (110 females; 64%). The median age at diagnosis was 70.6 years (range, 23 to 97 years). A diagnosis of IC was made by endoscopy in 57% of cases, by radiography in 9%, by surgery in 23%, and by autopsy in 11%. The overall age-adjusted and sex-adjusted incidence rate was 6.1 cases per 100,000 person-years for definite cases, and 9.9 cases per 100,000 person-years for definite plus probable cases. The overall crude incidence rate (definite plus probable IC) rose from 3.3 cases per 100,000 person-years in 1976 to 1978, to 12.3 per 100,000 person-years in 1994 to 1998. For definite cases, the change was from 2.2 to 8.1 cases per 100,000 person-years. The incidence rate tripled over the course of the study.

Higgins et al (2004) performed a systematic review of the published literature regarding the epidemiology of IC. This review found that relatively few studies have been performed on the subject. The authors found only four general population studies meeting their criteria, none of which had been published in full manuscript form. The incidence of IC in the general population in these studies ranged from 4.5 to 44 cases per 100,000 person-years. Three of the studies were relatively homogeneous in their estimates of the incidence, with a range of 4.5 to 9.9 per 100,000 person-years, whereas the large U.S. Health Maintenance Organization (HMO) study reported estimates 5-fold to 10-fold higher than the other studies.

Ischemic colitis and hypertension

It has been postulated that due to a decrease of the intestinal blood flow, antihypertensive drugs may act as a risk factor for IC (Green and Tendler 2005, Nozawa et al 2007).

Additionally, there are some case reports linking hypertension and/or exposure to antihypertensive drugs to IC (Détry et al 1979).

In addition, there is some evidence from a non-interventional study that certain antihypertensive drug classes may be associated with the development of IC. In a case-control study published in 2010, Cubiella Fernández et al (2010) reported increased odds of developing IC in patients who used calcium channel blockers or ACE inhibitors.

Aliskiren and ischemic colitis

Aliskiren is the first known representative of a new class of non-peptide orally active direct renin inhibitors that blocks the renin-angiotensin-aldosterone-system (RAAS) at its rate-limiting step. It induces a net reduction in plasma renin activity, angiotensin II and aldosterone levels. Aliskiren is effective in reducing blood pressure and overall is well tolerated.

IC is included in the risk management plan (RMP) as a potential risk for aliskiren based on isolated reports in patients receiving aliskiren. There is no mechanistic basis for aliskiren being causative for the development of IC, other than the potential of antihypertensive drugs to decrease intestinal blood flow which may act as a risk factor for IC as discussed above. As outlined above, information on IC in patients diagnosed with hypertension and/or receiving antihypertensive treatment is scarce in the literature. In 2011, IMS conducted a study for Novartis to assess the incidence of IC in patients treated with any antihypertensive medication, the results of which were shared with the European Medicines Agency (EMA) by Novartis. The study was considered as "well designed and the results provided are in line with the expected objective". Findings from this study indicated that the incidence rate of probable IC was higher among the prevalent antihypertensive therapy cohort compared to incident antihypertensive treatment patients. When evaluated by antihypertensive drug classification, patients who used triple-plus combination therapy had a higher IR per 100,000 person-years of probable IC than those on monotherapy and dual-combination therapy. The study population included only a small number of patients receiving a direct renin inhibitor (i.e. aliskiren, the only direct renin inhibitor available at the time the study was conducted), on account of the fact that aliskiren had only been on the market for a short period of time when the study was conducted. Therefore, Novartis committed to re-run this analysis as requested by the Committee for Medicinal Products for Human Use (CHMP) focusing on patients using aliskiren as well as making some minor modifications to the previous study's design based on specific comments received from CHMP for the first study run in 2011 (e.g. including a general population sample, stratification of prevalent antihypertensive treatment cohort based on the date of the first antihypertensive drug prescription identified in the pre-index period, time-varying exposure analysis of incidence rates) and provide a final report until Q3 2013 latest.

8 Research question and objectives

The objective of this study is to assess th [redacted]

[redacted]

9 Research methods

9.1 Study design

This will be a descriptive, retrospective cohort study with secondary use of data from the United States PharMetrics™ Health Plan Claims Database from 1 July 2005 through 30 June 2012 (or the most recent data available at the time of extraction), designed to [redacted]. This design allows for the direct calculation of incidence rates on a large sample of patients, while taking into consideration the temporal sequence of exposure to antihypertensive therapy and the development of IC. The selection of the PharMetrics Health Plan Claims Database was based on its offering of real-world data, longitudinal access to medical and pharmacy claims, and a relatively large sample of patients with exposure to aliskiren (e.g. compared to European data sources).

9.2 Setting

All adult hypertensive subjects with a prescription for an antihypertensive medication between 1 January 2006 and 31 March 2012 will initially be selected for inclusion into the study from the PharMetrics™ claims database. Records in the PharMetrics™ US claims database are generally representative of the national, commercially insured population in terms of age and gender. The data are also longitudinal, with an average duration of member enrollment of two years. Only health plans that submit data for all members are included in the database, ensuring complete data capture and representative samples.

9.2.1 Inclusion criteria

The patient selection criteria were defined in a manner that ensures a confirmed diagnosis of hypertension and adequate representation of patients using aliskiren. Patients will be selected into the study cohort if they meet the following criteria:

- Evidence of a hypertension diagnosis (ICD-9-CM codes 401.xx-405.xx); the date of the first hypertension diagnosis will be considered the diagnosis date;
- At least 1 prescription for an antihypertensive medication (Annex 3.1, Annex 3.2, Annex 3.3) within 180 days of the diagnosis date OR with at least one days supply overlapping the diagnosis date;
- 18 years of age or older at the time of the index date (defined below);
- Continuous health plan enrollment for a minimum of 180 days prior to the index date (pre-index period) and a minimum of 90 days of continuous enrollment following the index date (post-index period).

For the general population cohort, patients will be selected into the study if they meet the following criteria:

- 18 years of age or older at the time of the index date;

- Continuous health plan enrollment for a minimum of 180 days prior to the index date (i.e., the pre-index period) and a minimum of 90 days of continuous enrollment following the index date (i.e., the post-index period).

9.2.2 Exclusion criteria

Patients will be excluded from the study cohort if they meet the following criteria:

- A diagnosis of probable IC during the 180-day pre-index period or first 30 days following the index date;
- A gap in enrollment ≥30 days at any time during the post-index period until the end of the patient's observation period or data availability;
- ≥65 years and not enrolled in Medicare Risk (complete claims histories may not be available for individuals aged 65 years or older whose insurance coverage is not Medicare Risk due to issues of coordination of benefits with traditional Medicare or another payer);
- Payer type of Medicare Cost (complete claims histories may not be available);
- Invalid days supply on the index antihypertensive medication claim;
- Other data validity issues (such as invalid or missing year of birth, gender, or enrollment date).

Pharmacy claims for all patients within the PharMetrics™ database will be examined starting on 1 January 2006 and continuing through the end of the index window (31 March 2012) to identify any claims for aliskiren (Annex 3.1). Patients with at least 1 prescription for aliskiren at any time during the index window, regardless of evidence of any other antihypertensive medication use prior to the aliskiren claim, will be considered index aliskiren patients, and the first aliskiren claim identified during the index window will be considered the index date. Because aliskiren patients will be given preferential selection and it is possible that the first aliskiren claim identified within the index window can occur beyond 180 days of the hypertension diagnosis, the diagnosis date for these patients will be the first hypertension diagnosis seen within 180 days of the aliskiren prescription. For all other patients with no evidence of any aliskiren claims during the index window, the date of the first prescription for an antihypertensive medication (other than aliskiren) (Annex 3.1, Annex 3.2, Annex 3.3) within 180 days of the diagnosis date will be considered the index date. This is summarized in the table below.

Table 9-1 Definitions 'index window' and 'index date'

Term	Definition, timing
Index Window	1 January 2006 – 31 March 2012
Index Date (aliskiren)	Date of first aliskiren claim that is within the index window
Index Date (all other antihypertensive medications)	Date of first prescription for antihypertensive medication
New index date	The index date created for stratifications for the prevalent hypertension cohort, defined as the date of the first antihypertensive drug prescription identified in the 180 days prior to the initial index date (see Section 9.7)

In addition to hypertensive patients, patients without a diagnosis of hypertension and/or evidence of antihypertensive therapy will be included in the study to represent a general

population. General population patients will be included in the study during the same selection window as the hypertensive cohort. A random date within the selection window will be chosen to represent the index date for the general population patients, and general population patients will be followed for the same period as the hypertensive cohort.

9.3 Variables

9.3.1 [redacted] – endpoint of interest

[redacted]

9.3.2 Exposure

[redacted]:

- [redacted];
- [redacted]

Patients will be classified as monotherapy initiators, dual combination initiators, or triple-plus combination initiators based on their index antihypertensive drug use and separately, on antihypertensive drug use within the 30 day period before the end of follow-up.

Patients will be classified according to their antihypertensive therapy use into the following groups (classification of individual antihypertensive drugs/drug classes):

- Monotherapy Initiators (Annex 3.1):
  a. Aliskiren
  b. Angiotensin-converting enzyme inhibitor (ACEI) initiators (e.g., captopril, enalapril, lisinopril)
  c. Angiotensin II receptor blocker (ARB) initiators (e.g., valsartan, candesartan, losartan)
  d. Alpha blocker (AB) initiators (e.g., prazosin, terazosin, phentolamine)
  e. Beta blocker (BB) initiators (e.g., atenolol, metoprolol, carvedilol)
  f. Calcium channel blocker (CCB) initiators (e.g., amlodipine, diltiazem, verapamil)
  g. Diuretic initiators (including thiazides such as hydrochlorothiazide and chlorthalidone; loop diuretics such as furosemide, torasemide, and bumetanide; and potassium-sparing diuretics such as amiloride, spironolactone, and triamterene)
  h. Other antihypertensive drug monotherapy initiators (e.g., vasodilators, selective aldosterone receptor antagonists, centrally acting alpha agonists)
- Dual Combination Initiators (fixed-dose (Annex 3.2) and free dose combinations; note that these are mutually exclusive categories):

a. Dual combination initiators including aliskiren
b. Dual combination initiators including an ACEI but not aliskiren
c. Dual combination initiators including neither an ACEI nor aliskiren

- Triple-plus Combination Initiators (fixed-dose (Annex 3.3) and free dose combinations; note that these are mutually exclusive categories):
  a. Triple-plus combination initiators including aliskiren
  b. Triple-plus combination initiators including an ACEI but not aliskiren
  c. Triple-plus combination initiators including neither an ACEI nor aliskiren

To be classified into a dual or triple-plus free-agent combination therapy cohort, patients will have to have each of the drugs that qualify the patient for that cohort within the first 30 days after the index date (including the index date) **and** at least one additional prescription for each of those drugs within days supply + 30 days of the first prescription of those drugs.

Patients will be classified as monotherapy, dual combination initiators, or triple-plus combination initiators, as detailed above, based on the index antihypertensive therapies identified.

Patients will also be classified according to the antihypertensive drugs they are taking within the 30 day period before the end of the follow-up period. Note that "taking" a medication will be defined as having at least 1 day of drug coverage within this period, and it will not necessarily be linked to having an actual prescription fill date during this period. Patients with only one type of drug (irrespective of the number of fills) during these 30 days will be identified as monotherapy users, while those with prescriptions for two or three different antihypertensive medications will be classified as dual combination users or triple-plus combination users, respectively, as detailed above. For patients who do not have evidence of any antihypertensive drug use within the last 30 days of their follow-up, we will check for the antihypertensive drugs used within the last 60 days to classify them into one of the cohorts described. Similarly, for patients who do not have evidence of any antihypertensive drug use within the last 60 days of their follow-up, we will check for the antihypertensive drugs used within the last 90 days. If a patient does not have any antihypertensive medications within the last 90 days of their follow-up, he will be classified into a "no antihypertensives" cohort.

9.3.3 Follow-up

The follow-up period for a patient will begin on the index date and end on the earliest of one of the following:

1. Recorded diagnosis of probable IC;
2. Recorded claim for one of the rule-out conditions such as acute pancreatitis, acute cholecystitis, or diverticulitis (for full list, see Annex 3.4) or rule-out procedures such as gall bladder surgery, hysterectomy, or stomach surgery (for full list, see Annex 3.5) for a probable IC diagnosis;
3. End of enrollment in the database;
4. End of the study period (June 30, 2012 [or latest available update]).

The total number of patients classified as monotherapy, dual combination therapy, and triple-plus combination therapy at index, by specific drug categories, will be provided. Similarly,

the total number of patients classified as monotherapy, dual combination therapy, and triple-plus combination therapy prior to end of follow-up, by specific drug categories, as well as those classified as having received no antihypertensive medication prior to end of follow-up, will be reported.

Adherence to index antihypertensive drug therapy will be defined using the proxy measure known as the Medication Possession Ratio (MPR). MPR will be calculated as the total number of days covered by the index drugs divided by the total number of follow-up days. Patients will be followed from the index date through the end of their follow-up period. On each day, the antihypertensive drugs on-hand will be identified (either by fill date or by the days supply from last drug). If the drugs identified on-hand are exactly the same as those of the index antihypertensive drug therapy, patients will be considered adherent on that day; if not (e.g., patients added, dropped, or changed therapies), patients will be considered non-adherent on that day. Thus, for patients who index on dual combination or triple-plus combination therapy, the numerator will comprise the number of days they remain adherent to that drug regimen and **not** just to any of the component drugs. Multiple drugs on the same day will count as one day of coverage. Adherence to index antihypertensive drug therapy will be calculated only on that subset of patients who have ≥2 prescriptions for each antihypertensive drug in their index drug regimen during their follow-up period.

Adherence to any antihypertensive drug therapy also will be defined by means of MPR, in a method similar to the one described above. MPR will be calculated as the total number of days covered by any antihypertensive drug in the post-index follow-up period divided by the total number of days in the follow-up period. Patients will be followed from the index date through the end of their follow-up period. On each day, the antihypertensive drugs on-hand will be identified (either by fill date or by the days supply from last drug). If any antihypertensive drug is identified on-hand, regardless of the index antihypertensive therapy, patients will be considered adherent on that day; if not, patients will be considered non-adherent on that day. Multiple drugs on the same day will be counted as one day of coverage. Adherence to any antihypertensive therapy will be calculated only on the subset of patients with ≥2 prescriptions for antihypertensive medications.

9.3.4 Other variables

Data will also be gathered on the following demographic and clinical variables:

- Age and age group (18-29, 30-39, 40-49, 50-59, 60-69, ≥70 years)
- Gender (male, female)
- Geographic region (Northeast, Midwest, South, West)
- Health plan type (consumer-directed healthcare product, HMO, indemnity, point-of-service [POS], preferred provider organization [PPO], unknown)
- Payer type (commercial, Medicaid, Medicare Risk, self-insured, unknown)
- Available days of follow-up (post-index)
- Charlson Comorbidity Index (CCI) score, Dartmouth-Manitoba adaptation (Roos et al 1997)
- Co-morbid conditions (irritable bowel syndrome, ischemic bowel disease, chronic diarrhea, chronic constipation, peripheral vascular disease, vascular insufficiency of intestine, acute

coronary syndrome, coronary heart disease or angina [including acute coronary syndrome], heart failure, stroke or transient ischemic attack), pre-index and post-index (Annex 3.6)

- Probable IC rule-out conditions (Annex 3.4) and IC rule-out procedures (Annex 3.5)

9.4 Data sources

Data will be taken from the PharMetrics™ database, which comprises fully adjudicated medical and pharmaceutical claims for over 70 million unique patients from nearly 80 health plans across the U.S. (approximately 16 million covered lives per year) from January 2001 through June 2012. The database includes both inpatient and outpatient diagnoses (in ICD-9-CM format) and procedures (in CPT-4 and HCPCS formats) as well as both retail and mail order prescription records. Available data on prescription records include the National Drug Code (NDC) and the Generic Product Identification (GPI) code, as well as the quantity of the medication dispensed. Amounts charged by providers and amounts allowed and paid by health plans are available for all services rendered, as well as dates of service for all claims. Allowed amounts will be used in this study. Additional data elements include demographic variables (age, gender, and geographic region), product type (e.g., HMO, PPO), payer type (e.g., commercial, self-pay), provider specialty, and start and stop dates of health-plan enrollment.

Records in the PharMetrics™ US claims database are generally representative of the national, commercially insured population in terms of age and gender. The data are also longitudinal, with an average duration of member enrollment of two years. Only health plans that submit data for all members are included in the database, ensuring complete data capture and representative samples. Data contributions are also subjected to a series of quality checks to ensure a standardized format and to minimize error rates.

9.5 Study size

Because this is an exploratory epidemiologic study and not a hypothesis testing study, power analysis for sample size estimation was not conducted. Sample size will be determined based on the number of patients available in the database, and who meet study inclusion criteria.

9.6 Data management

All analyses will employ SAS version 9.1 (SAS Institute Inc., Cary, NC).

9.7 Data analysis

All analyses will be performed by IMS.

All data will be reported for the aggregate population, as well as stratified by the incident versus prevalent antihypertensive treatment cohorts.

Additional stratifications will be made on the prevalent antihypertensive treatment cohort based on the date of the first antihypertensive drug prescription identified in the 180 day pre-index period. We will use the date of the first antihypertensive drug prescription identified in the 180 days period prior to the initial index date as the ‘new index date’ assuming that this exposure correlates with underlying hypertension (but without a corresponding claim for hypertension at that time). We will stratify these patients according to the time period the

index date was shifted backwards, e.g. in a sub-group of patients with the index date shifted by 1-60, 61-120, and 121-180 days.

Incidence of IC will be calculated per 100,000 person-years (PYs) and presented as incidence rates (IRs) with 95% confidence intervals (CIs). These rates will be reported by age group and gender as well as by index antihypertensive drug cohort (stratified by age group and gender), antihypertensive drug cohort prior to the end of follow-up (stratified by age and gender), and by adherence (using medication possession ratio or MPR, defined later in this document) to the index antihypertensive therapy and to any antihypertensive therapy. Additional IRs that take into account patients' varying exposure to antihypertensive medications will be calculated per person-time contributed to each drug classification. Patients' exposure time to the drug classifications will be defined by the total number of days a patient is on therapy for each drug. For combination initiators, therapy days will be defined as the total number of days that the antihypertensive drug is on-hand for all drugs in the regimen. A treatment gap of 60 days will be allowed, so as to capture those patients who may be on combination therapy but may experience a gap in days supply of one or more drugs in the regimen. Thus, a patient will be considered on therapy if they have days supply of all of the drugs in the regimen within 60 days of the end of supply of the previous fill. Finally, the incidence rate of probable IC will also be calculated for a sample (approximately the same number of patients that qualify for the treated hypertension cohort) of the general population (patients from the PharMetrics database without a diagnosis of hypertension or antihypertensive use).

Unless otherwise specified, results for categorical measures will be provided as the frequency (number of cases) and percentage of total study patients observed in each category. For continuous variables, descriptive statistics (mean, standard deviation [SD], range, median, and interquartile range [IQR]) will be presented. When necessary, continuous variables will be categorized into intervals, with the distribution of patients (n, %) for each interval provided. No statistical analyses will be performed, and all comparisons between cohorts will be descriptive in nature only. All analyses will be on observed, not projected, data.

9.8 Quality control

Data contributions from the PharMetrics™ claims database are subjected to a series of quality checks to ensure a standardized format and to minimize error rates. Only health plans that submit data for all members are included in the database, ensuring complete data capture and representative samples. All statistical codes will be quality checked by a separate programmer prior to closing out the study. At the end of each project, all project related programming code, tables, and documents are archived and stored on a server where they can be retrieved when needed in the future. A password is required to log into the system where all data are stored.

9.9 Limitations of the research methods

This study is limited by the following factors. If an incorrect diagnosis was listed in the medical record, or the medical record was incomplete, then patients might have been misclassified, resulting in selection bias. Bias may also be introduced by the preferential selection of aliskiren patients; however a greater representation of aliskiren patients than that observed in the first study was desired for the current research objectives. The correspondence between pharmacy submission of claims and patients' receipt and consumption of the

medication is assumed and not directly measured. However, prior work suggests that medication exposure measures can be accurately derived from pharmacy claims. The study also assumes that all information needed for case classification is present and not differential across the cohorts of interest.

The claims dataset does not include uninsured patients and those covered only by Medicare (Part D), and the source population consists primarily of commercially insured patients in the US; therefore, the results are most generalizable to similar commercially insured patients and may not be generalizable to other populations if they differ in their accessibility to physician services or prescriptions. The database does not provide information on systemic factors that could affect care, including plan limits on medication use. Due to the large and diverse nature of the plans in the database, however, these factors should not have an impact on the study results.

Finally, the primary outcome of interest, [redacted]; no chart reviews will be performed to verify this diagnosis.

9.10 Other aspects

Not applicable.

10 Protection of human subjects

As a non-interventional study, by definition no interventions will be made to patients under study.

In compliance with the Health Insurance Portability and Accountability Act (HIPAA), patient data included in the analysis are de-identified; therefore, this study will be exempt from Institutional Review Board (IRB) review.

11 Management and reporting of adverse events/adverse reactions

As this is a non-interventional study with secondary use of data form a US health claims database, safety monitoring and safety reporting on an individual case level is not applicable. In studies based on secondary data sources with a safety relevant result, only aggregated safety results, i.e. the overall association between an exposure and an outcome, should be reported and be included in the periodic aggregated regulatory reports submitted to Health Authorities.

12 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, manuscripts describing this work will be submitted for publication in peer-review journals. Findings may also be submitted for presentation at scientific conferences.

13 References (available upon request)

Cubiella Fernández J, Núñez Calvo L, González Vázquez L, et al (2010) Risk factors associated with the development of ischemic colitis. World J Gastroenterol; 16(36):4564-9.

Détry R, Devroede G, Madarnas P, et al (1979) Ischemic colitis associated with hypertension. Can J Surg; 22(3):256-7.

Elmore MF and Elliott RN (2005) Dramatic rise in the incidence of ischemic colitis in two metropolitan hospitals over a 10 year period. Am J Gastroenterol; 100(Suppl 9):S144-64.

Green BT and Tendler DA (2005) Ischemic colitis: a clinical review. South Med J; 98(2):217-22.

Higgins PD, Davis KJ, Laine L (2004) Systematic review: the epidemiology of ischaemic colitis. Aliment Pharmacol Ther; 19(7):729-38.

Loftus EV, Sandborn WJ, Tremaine WJ, et al (2002) Incidence of ischemic colitis in Olmsted County, Minnesota. 1976-1998. Am J Gastroenterol; 97(Suppl 11):S121-2.

Nozawa H, Akiyama Y, Sunaga S, et al (2007) Ischemic colitis following colonoscopy in an elderly patient on cardiovascular medication. Endoscopy; 39(Suppl 1):E344-5.

Roos LL, Stranc L, James RC, et al (1997) Complications, comorbidities, and mortality: improving classification and prediction. Health Serv Res; 32(2):229-38.

Theodoropoulou A and Koutroubakis IE (2008) Ischemic colitis: clinical practice in diagnosis and treatment. World J Gastroenterol; 14(48):7302-8.

Annex 1 – List of stand-alone documents

Annex 1-Table 1-1 List of stand-alone documents

Number	Document reference number	Date	Title
1	--	15 May 2013	Novartis IC Table Shells

Annex 2 – ENCePP checklist for study protocols

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document

and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Assessing the incidence of ischemic colitis in treated adult hypertensive patients in the United States – a descriptive, retrospective cohort study with secondary use of data from a US health claims database

Study reference number: CSPP100A2416

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection [1]	☒	☐	☐	10, 11
1.1.2 End of data collection [2]	☒	☐	☐	10, 11
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	10, 11
1.1.6 Final report of study results.	☒	☐	☐	10, 11

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8, 13, 14
2.1.2 The objective(s) of the study?	☒	☐	☐	8, 13, 14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8, 9, 14, 15
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

No hypothesis testing study, only descriptive

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	8, 14
3.2Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	9, 16
3.3Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9, 20

Comments:

No secondary endpoints to be assessed

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1Is the source population described?	☒	☐	☐	19
4.2Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	14
4.2.2 Age and sex?	☒	☐	☐	18
4.2.3 Country of origin?	☒	☐	☐	8, 14, 19
4.2.4 Disease/indication?	☒	☐	☐	8, 14
4.2.5 Co-morbidity?	☒	☐	☐	9, 18, 19
4.2.6 Seasonality?	☐	☒	☐	
4.3Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	14, 15

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	16, 17
5.2Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	
5.4Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	16
6.2Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	20

Comments:

Some discussion within the 'limitations' section

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	18, 19
7.2Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	18, 19

Comments:

Information is captured on specific co-morbidties possibly associated with ischemic colitis which may possibly act as confounder or effect modifier; however, since only incidence rates will be assessed (not relative risks) analyses will not be adjusted/controlled for confounders/effect modifiers

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	15-17, 19
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	16, 19
8.1.3 Covariates?	☒	☐	☐	18, 19
8.2Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	15-17, 19
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	16, 19
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	18, 19
8.3Is a coding system described for:				

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	16, 32-34
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	16
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	16, 17, 31, 32
8.4Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☐	☒	☐	

Comments:

No hypothesis testing, only descriptive

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	19, 20
10.4 Are stratified analyses included?	☒	☐	☐	19, 20
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Only descriptive analyses, no analytical analyses with relative risk assessment

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☒	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.3 Are methods of quality assurance described?	☒	☐	☐	20
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	20, 21
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐ ☐	☒ ☒	☐ ☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	20, 21

Comments:

Descriptive study

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☒	21
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	21

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	11

Comments:

Section 5 ‘Amendments and updates’; however, currently there are no amendments or updates

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	22
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	22

Comments:

[redacted]

Annex 3 – Additional information

Annex 3.1 - Antihypertensive drugs – Single agents

Annex 3-Table 3-1 Antihypertensive drugs – Single agents

Drug class	Generic names (examples)	GPI codes/HCPC codes
Direct Renin Inhibitor	aliskiren	3617*
Angiotensin-converting Enzyme Inhibitors (ACEI)	captopril, enalapril, lisinopril	3610*, 369985*
Angiotensin II Receptor Blockers (ARB)	valsartan, candesartan, losartan	3615*
Alpha Blockers (AB)	prazosin, terazosin, doxazosin	362020*, (excluding 36202010*, 36202020*), 56852025*
Beta Blockers (BB)	atenolol, metoprolol, carvedilol	33*, 369988*
Calcium Channel Blockers (CCB)	amlodipine, diltiazem, verapamil	34*, 409925* / C9248
Diuretics	thiazides (hydrochlorothiazide, chlorthalidone); loop diuretics (furosemide, torasemide, bumetanide); or potassium-sparing diuretics (amiloride, spironolactone, triamterene)	369980022*, 3720*, 3750*, 3760*, 379900* / S0171, J1940, J3265, J1205
Vasodilators	hydralazine, diazoxide, minoxidil	3640*
Selective Aldosterone Receptor Antagonists	eplerenone	36250030*
Centrally Acting Alpha Agonists	clonidine, guanabenz, guanfacine, methyldopa, alseroxylon, deserpidine, rauwolfia (serpentina), reserpine, guanadrel, guanethidine, rescinnamine	362010*, 362030*, 36202010*, 36202020*

Annex 3.2 - Antihypertensive drugs - Dual fixed combinations

Annex 3-Table 3-2 Antihypertensive drugs - Dual fixed combinations

Drug classes	GPI codes
AB + Diuretic	369955027*
ACEI + CCB	369915*
ACEI + Diuretic	369918*
ARB + CCB	369930*
ARB + Diuretic	369940*
BB + Diuretic	369920*
Centrally Acting Alpha Agonist + Diuretic	369910*, 369950*, 369955023* (excluding 369910022*, 36991003*)
Centrally Acting Alpha Agonist + Vasodilator	369910022*
Direct Renin Inhibitor + ARB	369965*
Direct Renin Inhibitor + CCB	369967*
Direct Renin Inhibitor + Diuretic	369960*

Drug classes	GPI codes
Vasodilator + Diuretic	369990*

AB = Alpha Blocker; ACEI = Angiotensin-Converting Enzyme inhibitor; ARB = Angiotensin II Receptor Blocker; BB = Beta Blocker; CCB = Calcium Channel Blocker

Annex 3.3 - Antihypertensive drugs - Triple-plus fixed combinations

Annex 3-Table 3-3 Antihypertensive drugs - Triple-plus fixed combinations

Drug classes	GPI codes
ARB + CCB + Diuretic	369945*
Centrally Acting Alpha Agonist + Vasodilator + Thiazide Diuretic	36991003*

ARB = Angiotensin II Receptor Blocker; CCB = Calcium Channel Blocker

Annex 3.4 - IC rule-out conditions

Annex 3-Table 3-4 IC rule-out conditions

Criterion	Condition	ICD-9-CM diagnosis code
Diagnosis Within +/- 42 Days (6 Weeks) of an IC Diagnosis	acute pancreatitis	577.xx
	acute cholecystitis	575.xx
	diverticulitis	562.xx
	appendicitis	540.xx-543.xx
	peritonitis and retroperitoneal infections	567.xx
	regional enteritis (includes Crohn's disease and granulomatous enteritis)	555.xx
	ulcerative colitis	556.xx
Diagnosis on a Physician Visit Claim Within +/- 14 Days (2 Weeks) of an IC Diagnosis	infectious gastroenteritis	001.xx-009.xx

IC = ischemic colitis; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification

Annex 3.5 - IC rule-out procedures

Annex 3-Table 3-5 IC rule-out procedures

Criterion	Procedure	CPT-4 procedure codes
Procedure During a Hospitalization Where an IC Diagnosis was Made	gall bladder surgery	47600-47620, 47562-47564
	lysis adhesion	44005, 44180, 44200, 56310
	hysterectomy / gynecologic surgery	56405-58960, 58999
	stomach surgery	43500-43999, S2085, S2082
	small bowel surgery	44010, 44015, 44020, 44021, 44110-44137, 44201-44203, 44227, 44300-44316, 44360-44386, 44602, 44603, 44615, 44620, 44625, 44640-44680, 44700, 44238, 44799

Criterion	Procedure	CPT-4 procedure codes
	pancreatic surgery	48000-48999
	spleen surgery	38100-38102, 38115, 38120, 38129, 38200
	liver surgery	47000-47399
	genitourinary surgery	50010-55980
	neurosurgery	61000-64999
	orthopedic surgery	20000-29999
	thoracic or cardiothoracic surgery	32000-33999, 92973, 92980-92998, 93501-93581
	cancer surgery	17304-17310, 19120, 19260, 19271, 19272, 21181, 27075-27079, 27615, 31300, 31540, 31541, 31640, 31641, 31785, 31786, 32661, 32662, 33050, 33120, 33130, 39220, 42420, 42425, 42426, 43216, 43217, 43228, 43250, 43251, 43258, 43272, 43610, 43611, 44364, 44365, 44369, 44392-44394, 45160, 45170, 45190, 45308, 45309 45315, 45320, 45333, 45338, 45339, 46610, 46611-46615, 46937, 46938, 47711, 47712, 49200, 49201, 49215, 51530, 52234, 52235, 52240, 52339, 54530, 54535, 57135, 58140, 58145, 60545, 60600, 60605, 61500, 61510, 61518-61530, 61546-61548, 61563, 61564, 61624-61626, 67208, 67210, 67218, 68500, 68505, 68540, 68550, 69550, 69552, 69554, 69970, 77295, 88307, 88309, 88358

IC = ischemic colitis; CPT = Current Procedural Terminology

Annex 3.6 - Comorbid conditions

Annex 3-Table 3-6 Comorbid conditions

Condition	ICD-9-CM diagnosis codes
Irritable Bowel Syndrome	564.1
Peripheral Vascular Disease	440, 440.0–440.2, 440.20–440.24, 440.29, 440.3, 440.30–440.32, 440.8, 440.9, 443, 443.0–443.2, 443.21–443.24, 443.29, 443.8, 443.81, 443.89, 443.9, 445.0, 445.01, 445.02, 445.81, 445.89, 447.8, 447.9, 459.30–459.33, 459.39, 459.8, 459.81
Vascular Insufficiency of Intestine (Including Ischemic Bowel Disease)	557.x
Chronic Constipation	564.0x
Chronic Diarrhea	564.5
Acute Coronary Syndrome	411.1, 411.8, 411.81, 411.89
Coronary Heart Disease and Angina (Including Acute Coronary Syndrome)	410–410.92, 411–411.89, 412, 413–413.9, 414–414.9

Condition	ICD-9-CM diagnosis codes
Heart Failure	428.xx, 402.x1, 404.x1, 404.x3
Stroke or Transient Ischemic Attack	325, 430–432, 432.0, 432.1, 432.9, 433, 433.0, 433.00, 433.01, 433.1, 433.10, 433.11, 433.2, 433.20, 433.21, 433.3, 433.30, 433.31, 433.8, 433.80, 433.81, 433.9, 433.90, 433.91, 434, 434.0, 434.00, 434.01, 434.1, 434.10, 434.11, 434.9, 434.90, 434.91, 435, 435.0, 435.1, 435.2, 435.3, 435.8, 435.9, 436, 437, 437.0, 437.1, 437.3–437.9, 438, 438.0, 438.1, 438.10–438.12, 438.19, 438.2, 438.20–438.22, 438.3, 438.30–438.32, 438.4, 438.40, 438.41, 438.42, 438.5, 438.50–438.53, 438.6–438.8, 438.81–438.85, 438.89, 438.9, 852.01, 852.02, 852.03, 852.04, 852.05, 852.06, 852.1, 852.10

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification