Real-World Axitinib Use in the United States: A Retrospective Study Using Linked Datasets

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ABSTRACT

BACKGROUND: Axitinib is approved by the FDA for the treatment of advanced renal cell carcinoma (RCC) after failure of 1 previous systemic therapy and is distributed primarily through specialty pharmacies. Although the efficacy and safety of axitinib have been established in clinical trials, information from real-world populations will help to elucidate patients' clinical profiles and utilization patterns. Prescription records alone provide limited information on patient characteristics and other treatment experiences. Expansion of these data with information from medical claims databases should yield observational real-world data that may help to optimize therapy for patients with advanced RCC.

OBJECTIVE: To link information from a specialty pharmacy database with information from medical and pharmacy claims databases to characterize real-world treatment patterns of axitinib as subsequent systemic therapy in patients with RCC in the United States.

METHODS: This retrospective, observational, cohort study linked de-identified patient-level data from 22 specialty pharmacies that dispense axitinib with databases of longitudinal medical and pharmacy claims. Eligible patients had a diagnosis of RCC (≥1 claim for RCC defined as ICD-9-CM code 189.0), previously received ≥1 systemic therapy, had the first prescription for axitinib dispensed between May 2012 and April 2013 (index), and had consistent claims reporting by pharmacies and physicians. All treatment data were used to calculate cycle, line of therapy, and duration of therapy; prescription data were used to determine axitinib dose modifications. Multivariate and logistic regression analyses were conducted to assess the effect of patient/prescriber characteristics on duration of axitinib therapy and dose modifications, respectively.

RESULTS: In all, 1,175 patients met the study inclusion criteria and had data present in specialty pharmacy and claims databases. Most patients (74%) were male, and 68% were aged 55-74 years. Mean (SD) Charlson Comorbidity Index score was 2.7 (±1.1); the most common comorbidity was hypertension (in 199 patients, 17%). Based on Rx-Risk-V, the most frequent concomitant conditions were pain (40%) and ischemic heart disease/hypertension (30%); the most frequent concomitant medications were antihypertensive medications (46%) and opiates (40%). Most prescribers (63%) were affiliated with an academic center, and all U.S. geographic regions were represented. In all, 847 patients (72%) had commercial insurance. Axitinib was prescribed as second-line therapy in 659 patients (56%), as third-line therapy in 326 patients (28%), and as fourth-line or later therapy in 190 patients (16%). In the overall population, mean (SD) duration of axitinib therapy was 168.6 (±148.4) days. Axitinib treatment duration was 21 days longer in males than females (P=0.013); 28 days longer in patients in the Northeast than in the Midwest or West (P=0.010 and P=0.016, respectively); and 26 days longer in patients receiving baseline hypothyroidism treatment (P=0.004). In patients receiving second-line axitinib, the most common first-line therapy was sunitinib (56%), followed by pazopanib (16%) and everolimus (12%). Mean (SD) duration of second-line axitinib treatment was 172.3 (±150.6) days and ranged from 127 days in patients who previously received temsirolimus to 196 days in those who previously received sorafenib. Of 1,025 patients who initiated axitinib at the standard 5 mg twice daily starting dose, 70% remained at this dose throughout treatment, whereas 10% had a dose increase. Younger age and gender (male) were associated with dose increases (OR=0.958, 95% CI=0.941-0.975 and OR=0.573, 95% CI=0.364-0.903, respectively). Baseline hypothyroidism treatment was associated with dose decreases and increases (OR=1.662, 95% CI=1.088-2.539 and OR=2.149, 95% CI=1.353-3.413, respectively).

CONCLUSIONS: This analysis demonstrates the feasibility and utility of linking specialty pharmacy data to other longitudinal databases to better understand patient, provider, and reimbursement characteristics. These data provide insight into routine clinical use of axitinib as subsequent RCC therapy in the United States in the period following FDA approval, as well as additional information on sequencing of targeted agents in patients with advanced RCC.

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What is already known about this subject

- Axitinib is approved in the United States for the treatment of advanced renal cell carcinoma (RCC) after failure of 1 previous systemic treatment.
- The standard starting dose of axitinib is 5 mg orally twice daily (BID); dose adjustments below or above the starting dose (to a maximum 10 mg BID) may be made based on individual safety and tolerability and are supported by retrospective and prospective studies.
- Many patients with advanced RCC have disease progression or become resistant to targeted agents; however, few observational studies have examined treatment patterns beyond first-line systemic therapy.

What this study adds

- Given the increasing distribution of oncology drugs through specialty pharmacies in the United States and the limited information in prescription records, this observational study demonstrates the feasibility and utility of linking de-identified specialty pharmacy data to other longitudinal databases to enrich our understanding of patient and provider characteristics.

What this study adds *(continued)*

- Treatment patterns among patients who received axitinib as subsequent therapy indicate that axitinib was initiated most commonly in the second-line setting following first-line treatment with sunitinib; pazopanib and everolimus were also prescribed as first-line therapy.
- Most patients initiated axitinib at the recommended 5 mg BID starting dose and remained on this dose throughout treatment; dose modifications were less frequent than in the pivotal phase III AXIS trial of axitinib versus sorafenib.

An estimated 62,700 individuals will be diagnosed with kidney or renal pelvis cancer in the United States in 2016, and 14,240 deaths because of this disease are predicted.[1] Renal cell carcinoma (RCC) accounts for approximately 90% of renal tumors.[2] The median age at diagnosis is approximately 64 years, and RCC occurs more commonly in males.[1] Approximately 25%-30% of patients with RCC present with metastatic disease (mRCC) at diagnosis, and 20%-30% of patients with localized disease experience relapse with metastases following resection.[2,3] In the United States during the years 2004-2010, the 5-year relative survival rates were 91.8% for localized disease, 64.6% for regional disease, and 12.1% for distant disease.[4]

Since their introduction in 2005, targeted agents acting on the vascular endothelial growth factor (VEGF) pathway or the mammalian target of rapamycin (mTOR) pathway have revolutionized the treatment of mRCC and improved clinical outcomes compared with cytokine-based regimens,[5] which were historically used to treat this disease. Presently, there are 7 targeted agents approved in the United States for clear-cell mRCC: VEGF receptor tyrosine kinase inhibitors (TKIs; i.e., sunitinib, sorafenib, pazopanib, and axitinib); monoclonal antibody to VEGF (i.e., bevacizumab); and mTOR inhibitors (i.e., everolimus and temsirolimus). Based on high-level evidence, the National Comprehensive Cancer Network (NCCN) issued category 1 recommendations for sunitinib, pazopanib, or bevacizumab (combined with interferon-α) as first-line therapy in patients with mRCC, as well as temsirolimus, specifically for those with poor prognosis.[2] However, patients with mRCC may not respond to first-line treatment or may develop resistance to these drugs and require subsequent therapies to control their disease.[6,7] Consequently, optimizing treatment sequences in patients with mRCC is an important area of investigation.[7]

Axitinib (Inlyta) was approved by the U.S. Food and Drug Administration (FDA) in 2012 for the treatment of advanced RCC after failure of 1 previous systemic therapy.[8] In the pivotal phase III AXIS trial, axitinib significantly prolonged progression-free survival versus sorafenib and was well tolerated in previously treated patients with advanced RCC.[9] As a result, axitinib has NCCN category 1 designation as subsequent therapy for advanced RCC after previous treatment with a TKI or cytokines.[2] Axitinib dosing recommendations permit titration below or above the starting dose of 5 mg twice daily (BID) based on patient tolerability and clinician judgment. Patients who tolerate the axitinib 5 mg BID dose for ≥2 consecutive weeks with no adverse reactions above grade 2 (according to Common Toxicity Criteria for Adverse Events), and who are normotensive and not receiving antihypertension medication, may have their dose increased stepwise to 7 mg BID and then to a maximum of 10 mg BID.[8] This dose-titration strategy has been supported by retrospective analyses and a phase II clinical trial.[10,11]

Although positive outcomes with targeted agents in phase III clinical trials have transformed the care of patients with mRCC worldwide, the strict patient eligibility criteria and short-term follow-up in these studies may limit the applicability of these clinical findings to routine patient care. Assessment of real-world use of targeted agents, including sequencing of therapies, may help to optimize treatment of patients with mRCC. The objective of this study was to link information from specialty pharmacy databases with information from databases of medical and pharmacy claims to characterize real-world treatment patterns of axitinib as subsequent systemic therapy in patients with RCC in the United States.

Methods

Study Design and Data Sources

This retrospective observational cohort study utilized the Specialty Pharmacy Data Mart, an IMS-managed database containing data from a limited distribution network of 22 specialty pharmacies (regional and national) that dispense axitinib. Data from the specialty pharmacy database were linked to information in the IMS Health medical and pharmacy claims databases via IMS de-identified unique patient identifiers. These identifiers enable IMS to track patients anonymously and longitudinally over time and between datasets and are not dependent on insurance carrier, pharmacy, or employer. The IMS Health pharmacy claims database includes claims (National Council for Prescription Drug Programs, version 5.2) submitted for patients receiving a prescription via retail and specialty pharmacies (> 1.8 billion prescriptions dispensed annually). The medical claims database includes more than 1 billion annual claims that contain diagnosis and visit information and represents activity of more than 870,000 practitioners per month. The data available in these databases represent patients regardless of age, gender, or insurance type from all 50 states and comply with the Health Insurance Portability and Accountability Act (HIPAA).

This study was conducted in accordance with legal and regulatory requirements and research practices and standards

established by the International Society for Pharmacoepidemiology, International Society for Pharmacoeconomics and Outcomes Research, and Pharmaceutical Research and Manufacturers Association. This study was exempt from institutional review board approval because it was retrospective, noninterventional, and used anonymized data.

Study Sample Selection

This study evaluated linked claims data between April 2009 and February 2014. Patients with a claim for their first axitinib prescription (index) between May 2012 and April 2013 were included. Treatment histories were assessed using data from April 2009 through April 2012 (3-year look back period). Discontinuation or maintenance of axitinib treatment was determined based on data through December 2013 and confirmed using data from January and February 2014 (washout period).

Patients included in this analysis were required to have a diagnosis of RCC (defined as ≥ 1 claim, *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 189.0) or receipt of previous treatment for RCC (Appendix A, available in online article). In addition, patients were required to have ≥ 1 prescription for axitinib (first prescription received between May 2012 and April 2013), ≥ 1 previous systemic therapy, care from an end-treating physician, and consistent reporting of prescription data by pharmacies (reporting ≥ 50% of all claims for that pharmacy per month) and all medical claims (office-based claims) by providers, respectively, during the study period. Patients who paid in cash for oncology services or participated in a clinical trial were excluded, since these data are not collected as part of the medical claims dataset.

Claims 2 and 4 years before the index date were examined to ensure that patients had office visits or prescriptions. Those patients with missing data from the 3-month period beginning 2 or 4 years before the index date were excluded to ensure that patients had treatment/visits in the look back period.

Study Measures

The primary objective of this study was to describe characteristics of axitinib-treated patients and axitinib-prescribing providers using linked datasets. Patient characteristics included age, gender, Charlson Comorbidity Index (CCI) score and groups,[12,13] Rx-Risk-V score and categories,[14] and payer type. The CCI score is calculated by identifying comorbidities in the 12 months before the index prescription. Weights are assigned to the 17 CCI comorbidity categories and the CCI score is calculated.[12,13] Metastatic cancer was not included in the calculation of CCI scores because all patients had metastatic disease. The Rx-Risk-V score was calculated by identifying specific concomitant prescription categories for the patients in the 60 to 120 days before the axitinib index prescription. Each category was summed for the total patient score.[14] Provider characteristics included geographic region per U.S. census and affiliation. Provider affiliations were determined using the IMS Healthcare Organization Services; providers with designations for both academic centers and community practices were counted only as affiliated with the academic center.

TABLE 1 Study Measure Definitions and Calculations

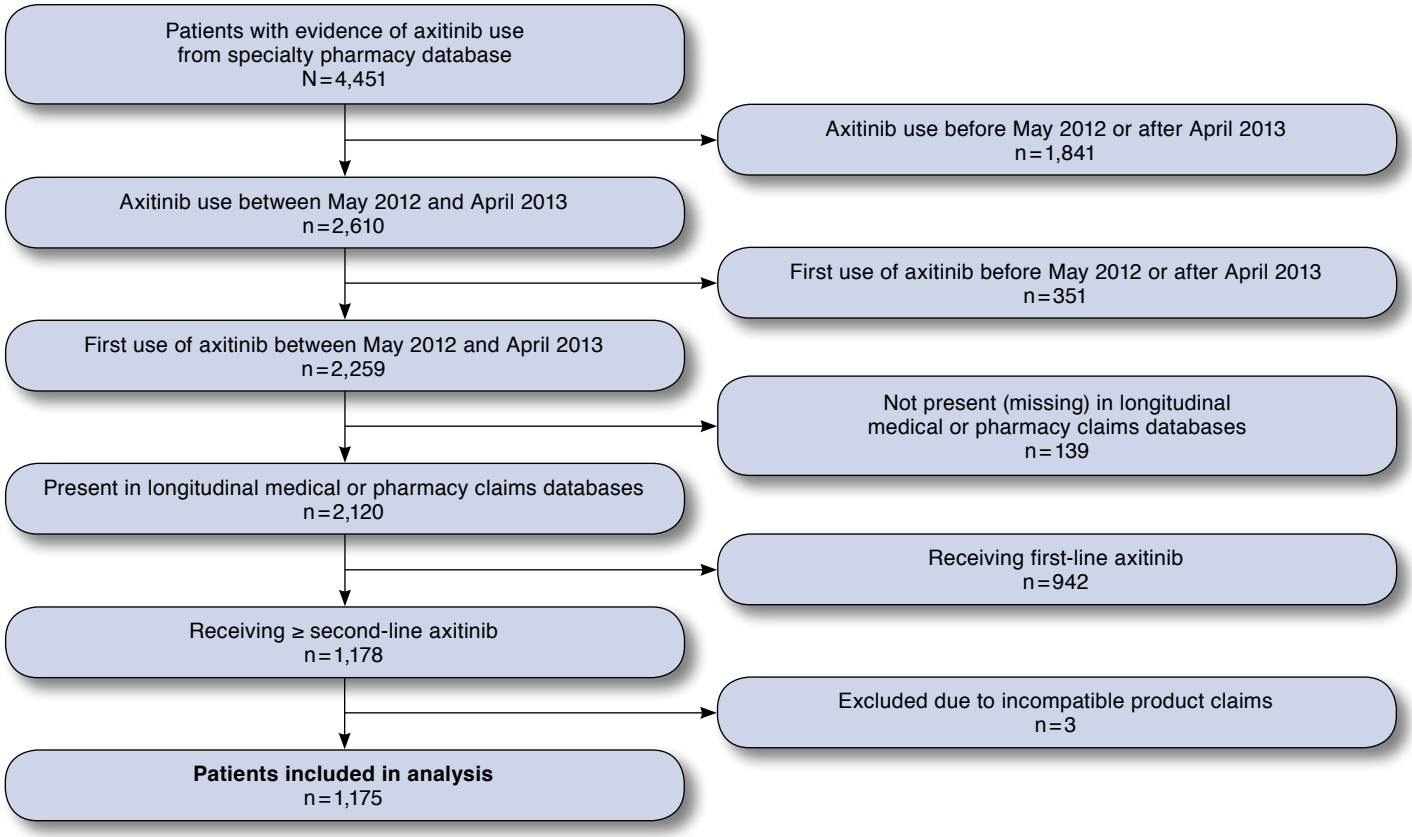
Cycles of therapy	• Drug administrations within a 4- , 21- , or 28-day gap (depending on the regimen) were considered part of the same cycle (range = 7-28 days). • The next drug administration date, within the line of therapy and beyond the 4- , 21- , or 28-day gap, was considered a new cycle. • For oral drugs, each prescription of the same product started a new cycle.
Lines of therapy	• Addition of a new drug after the first 28 days of a line of therapy, or a > 42 day-gap between cycles of a line of therapy, was considered a new line of therapy. • For oral drugs, addition of a new drug incompatible (a drug unlikely to be administered concomitantly) with the current drug was considered a new line of therapy, even if it was added within the first 28 days of a line of therapy.
Duration of therapy	• Calculated for each line of therapy by: *(last fill date + days supply) – (start date + 1 day)* • Elapsed days were also calculated for axitinib as the total number of days supply for axitinib within each line.
Axitinib dose modifications	• Determined based on drug, mg per day, form, strength, days supply, and proximity of prescription fill dates. • Categorized as no change, dose increase, dose decrease, or dose increase then decrease. o A dose increase was determined if the subsequent prescription overlapped the current prescription, and there were ≥ 5 overlapping days supply; then the daily dose was summed. o Otherwise, the daily dose from the new prescription, if different, was considered the dose change. o Due to small sample sizes, dose decrease and dose decrease then increase were classified as dose decrease. o Dose modifications were validated for clinical reasonability of titration pattern and, in some cases, manually reviewed and adjusted.

The secondary objectives were to describe and evaluate treatment patterns, dosing, treatment line, and duration of therapy. Dispensed drugs were identified using National Drug Code numbers and Healthcare Common Procedure Coding System J codes (Appendix B, available in online article), and systemic therapies before axitinib prescription were ascertained from the 3-year look back period; these data were used to calculate cycle, line, duration of therapy, and axitinib dose modifications (defined in Table 1).

Statistical Analysis

Patient and provider characteristics, as well as treatment and dosing patterns are summarized descriptively. Numeric values and percentages are presented for categorical data; means,

FIGURE 1 Selection of Study Patients



standard deviations (SDs), medians, and ranges are presented for continuous data. For some results, continuous variables were categorized into intervals and reported as numeric values and percentages. Inferential statistical tests were not performed to evaluate differences between the axitinib line of therapy subgroups.

The effect of patient/prescriber characteristics on duration of axitinib therapy and dose modifications were evaluated by multivariate and logistic regression analyses, respectively. Covariates included age, gender, prescriber geographic region, payer type, CCI score, prior treatment regimen, affiliation and specialty of axitinib-prescribing physician, concomitant medication classes (based on Rx-Risk-V categories), and line of axitinib therapy. Results were summarized by coefficient estimates for multivariate regression analyses and odds ratios (ORs) with Wald 95% confidence intervals (CIs) for logistic regression analyses. All statistical analyses were performed with 2-sided tests at the 5% significance level using SAS, version 9.3 (SAS Institute, Cary, NC).

Results

Patient and Provider Characteristics

This study included 1,175 patients (Figure 1). Most patients (74%) were male, and mean (SD) age was 63.6 (± 10.1) years (Table 2). Mean (SD) CCI score was 2.7 (± 1.1); the largest proportion of patients (64%) had a score of 2; and the most common comorbidity was hypertension (n = 199, 17%). The most frequently observed Rx-Risk-V categories were pain (40%) and ischemic heart disease/hypertension (30%). The most common concomitant medications were antihypertensive medications (46%) and opiates (40%). Most prescribers (63%) were affiliated with an academic center; 48% were hematology/oncology specialists; all U.S. geographic regions were represented; and 847 (72%) patients had commercial insurance.

In total, 659 (56%) patients received axitinib as second-line therapy; 326 (28%) patients received it as third-line therapy; and 190 (16%) patients received it as fourth-line or later therapy (Table 2). Demographics and clinical characteristics did not appear to differ by line of therapy; however, inferential statistical test were not performed. Patient characteristics, including comorbidity profiles, appeared to be similar between those

TABLE 2 Patient Demographics and Clinical Characteristics

Characteristic	Total (N = 1,175)	Second Line (n = 659)	Third Line (n = 326)	≥ Fourth Line (n = 190)
Age, years				
Mean (SD)	63.6 (± 10.1)	63.6 (± 10.0)	62.9 (± 10.0)	64.5 (± 10.3)
Median (range)	64 (23-85)	64 (29-85)	63 (23-85)	65 (28-85)
Age group, years, n (%)				
< 45	35 (3)	18 (3)	11 (3)	6 (3)
45-54	170 (14)	98 (15)	50 (15)	22 (12)
55-64	424 (36)	240 (36)	116 (36)	68 (36)
65-74	371 (32)	205 (31)	110 (34)	56 (29)
≥ 75	175 (15)	98 (15)	39 (12)	38 (20)
Gender, n (%)				
Male	865 (74)	487 (74)	244 (75)	134 (71)
Female	310 (26)	172 (26)	82 (25)	56 (29)
Charlson Comorbidity Index[a]				
Mean (SD)	2.7 (± 1.1)	2.7 (± 1.0)	2.7 (± 1.1)	2.7 (± 1.1)
Median (range)	2 (2-9)	2 (2-7)	2 (2-9)	2 (2-6)
Score, n (%)				
2	749 (64)	424 (64)	203 (62)	122 (64)
3	194 (17)	105 (16)	55 (17)	34 (18)
4	129 (11)	76 (12)	38 (12)	15 (8)
5-8	103 (9)	54 (8)	30 (9)	19 (10)
Comorbid groups,[b] n (%)				
No comorbidity	418 (36)	252 (38)	99 (30)	67 (35)
Hypertension	199 (17)	115 (17)	58 (18)	26 (14)
Diabetes ± acute complications	171 (15)	103 (16)	49 (15)	19 (10)
Renal disease	162 (14)	88 (13)	46 (14)	28 (15)
Moderate/severe chronic kidney disease	108 (9)	62 (9)	32 (10)	14 (7)
Chronic pulmonary disease	81 (7)	42 (6)	24 (7)	15 (8)
Cardiovascular disease	65 (6)	37 (6)	21 (6)	7 (4)
Congestive heart failure	60 (5)	32 (5)	17 (5)	11 (6)
Rx-Risk-V Index				
Score, n (%)				
0	361 (31)	211 (32)	98 (30)	52 (27)
1	109 (9)	66 (10)	23 (7)	20 (11)
Score, n (%) continued				
2-3	239 (20)	133 (20)	71 (22)	35 (18)
4-5	221 (19)	133 (20)	57 (17)	31 (16)
6-9	228 (19)	107 (16)	73 (22)	48 (25)
10+	17 (1)	9 (1)	4 (1)	4 (2)
Rx-Risk-V categories, n (%)				
No Rx-Risk-V categories	361 (31)	211 (32)	98 (30)	52 (27)
Pain	474 (40)	263 (40)	138 (42)	73 (38)
Ischemic heart disease/ hypertension	348 (30)	182 (28)	102 (31)	64 (34)
Congestive heart failure/ hypertension	285 (24)	153 (23)	84 (26)	48 (25)
Gastric acid disorder	275 (23)	154 (23)	81 (25)	40 (21)
Hyperlipidemia	250 (21)	125 (19)	78 (24)	47 (25)
Hypothyroidism	247 (21)	129 (20)	67 (21)	51 (27)
Hypertension	198 (17)	102 (15)	53 (16)	43 (23)
Anxiety and tension	189 (16)	92 (14)	63 (19)	34 (18)
Depression	187 (16)	99 (15)	56 (17)	32 (17)
All others	573 (49)	304 (46)	170 (52)	99 (52)
Prescriber geographic region, n (%)				
South	420 (36)	234 (36)	114 (35)	72 (38)
Midwest	285 (24)	162 (25)	83 (25)	40 (21)
Northeast	245 (21)	153 (23)	64 (20)	28 (15)
West	224 (19)	109 (17)	65 (20)	50 (26)
Unknown	1 (< 1)	1 (<1)	0	0
Prescriber affiliation, n (%)				
Academic center	743 (63)	419 (64)	211 (65)	113 (59)
Community practice	227 (19)	124 (19)	62 (19)	41 (22)
Unknown	205 (17)	116 (18)	53 (16)	36 (19)
Payer type,[c] n (%)				
Commercial[d]	847 (72)	474 (72)	236 (72)	137 (72)
Medicare	252 (21)	138 (21)	72 (22)	42 (22)
Medicaid	24 (2)	17 (3)	5 (2)	2 (1)
Other	52 (4)	30 (5)	13 (4)	9 (5)

[a]*Metastatic diagnosis excluded from Charlson Comorbidity Index.*
[b]*Includes conditions occurring in ≥ 5% of patients.*
[c]*Based on index prescription.*
[d]*Includes Medicare Advantage.*
SD = standard deviation.

treated by prescribers affiliated with academic centers versus community practices (data not shown).

Treatment Patterns

Sunitinib (38%) was the systemic therapy most frequently prescribed directly before axitinib was initiated in any line of therapy, followed by everolimus (22%) and pazopanib (21%; Table 3). In the overall population, mean (SD) duration of axitinib therapy was 168.6 (± 148.4) days, and 937 (80%) patients discontinued axitinib treatment as of December 2013. Mean and median duration of therapy did not appear to differ substantially between lines of therapy (Table 3).

For the 659 patients prescribed second-line axitinib, mean (SD) duration of axitinib treatment was 172.3 (± 150.6) days and

TABLE 3 Treatment Patterns and Axitinib Dosing Patterns

Characteristic	Total (N = 1,175)	Second Line (n = 659)	Third Line (n = 326)	≥ Fourth Line (n = 190)
Duration of axitinib therapy, days				
Mean (SD)	168.6 (±148.4)	172.3 (±150.6)	169.2 (±146.9)	154.6 (±142.8)
Median (range)	115 (7-688)	114 (8-688)	122 (7-644)	111(10-642)
Therapy received directly before axitinib, n (%)				
Sunitinib	446 (38)	368 (56)	51 (16)	27 (14)
Everolimus	259 (22)	78 (12)	142 (44)	39 (21)
Pazopanib	244 (21)	106 (16)	65 (20)	73 (38)
Temsirolimus	83 (7)	56 (8)	17 (5)	10 (5)
Sorafenib	44 (4)	19 (3)	15 (5)	10 (5)
Bevacizumab	31 (3)	12 (2)	13 (4)	6 (3)
Other	68 (6)	20 (3)	23 (7)	25 (13)
Axitinib daily dose,[a] mg				
Mean (SD)	10.3 (3)	10.3 (3)	10.5 (3)	10.2 (3)
Median (range)	10.0 (2.0-31.5)	10.0 (2.0-31.5)	10.0 (3.5-21.4)	10.0 (2.0-20.0)
Axitinib dose modifications,[a] n (%)				
No change	789 (67)	445 (68)	213 (66)	131 (69)
Decrease	161 (14)	90 (14)	43 (13)	28 (15)
Increase	141 (12)	79 (12)	44 (14)	18 (10)
Increase then decrease	83 (7)	45 (7)	25 (8)	13 (7)

[a] *A total of 1,174 patients were evaluated for axitinib dosing patterns; 1 patient whose titration patterns could not be determined and did not follow expected clinical patterns was excluded.*

SD = standard deviation.

ranged from 127 days in patients previously administered temsirolimus to 196 days in those previously prescribed sorafenib (Table 3 and Figure 2A). The most common first-line treatments in these patients were sunitinib (56%), pazopanib (16%), and everolimus (12%), after which mean (SD) duration of second-line axitinib treatment was 184 (±156), 154 (±125), and 189 (±180) days, respectively. In all, 80% of patients completed second-line axitinib treatment as of December 2013. In patients who received first-line sunitinib or pazopanib, baseline patient and prescriber characteristics were generally similar (data not shown), although a higher proportion of patients prescribed first-line pazopanib had no Rx-Risk-V categories (40% vs. 28%, respectively); statistical significance is unknown.

For the 326 patients prescribed third-line axitinib, mean (SD) duration of axitinib treatment was 169.2 (±146.9) days, ranging from 131 days in patients who received first- and second-line pazopanib to 205 days in patients who received first-line everolimus and second-line pazopanib (Table 3 and Figure 2B). The most common (32%) prior treatment sequence was sunitinib followed by everolimus; mean (SD) duration of axitinib treatment in these patients was 196 (±165) days. In all, 79% of patients completed third-line axitinib treatment as of December 2013.

Multivariate regression analysis revealed several patient characteristics associated with duration of axitinib therapy (Appendix C, available in online article). Longer axitinib treatment duration was observed in males versus females (21 days longer, $P = 0.013$); in patients in the Northeast (28 days longer) versus the Midwest or West ($P = 0.010$ and $P = 0.016$, respectively); and in patients receiving baseline hypothyroidism treatment (26 days longer, $P = 0.004$). Compared with sunitinib, prior bevacizumab and prior temsirolimus were associated with shorter treatment duration (50 days and 31 days shorter, $P = 0.028$ and $P = 0.034$, respectively). Neither the line of axitinib therapy nor the prescriber's affiliation was associated with duration of axitinib treatment (Table 3 and data not shown).

Axitinib Dosing Patterns

In the overall population, 67% of patients remained on the same axitinib dose during the entire course of therapy, whereas 14% had dose decreases; 12% had increases; and 7% had increases followed by decreases (Table 3). A total of 1,025 (87%) patients initiated axitinib at the standard 5 mg BID starting dose. Of these, 715 (70%) patients remained on 5 mg BID throughout treatment, whereas 138 (14%) had dose decreases; 107 (10%) had increases; and 65 (6%) had increases followed by decreases. Axitinib dose modifications did not appear to vary by line of therapy (Table 3).

Baseline hypothyroidism treatment was associated with dose increases (OR = 2.149, 95% CI = 1.353-3.413); dose decreases (OR = 1.662, 95% CI = 1.088-2.539); and dose increases followed by decreases (OR = 2.381, 95% CI = 1.396-4.060).

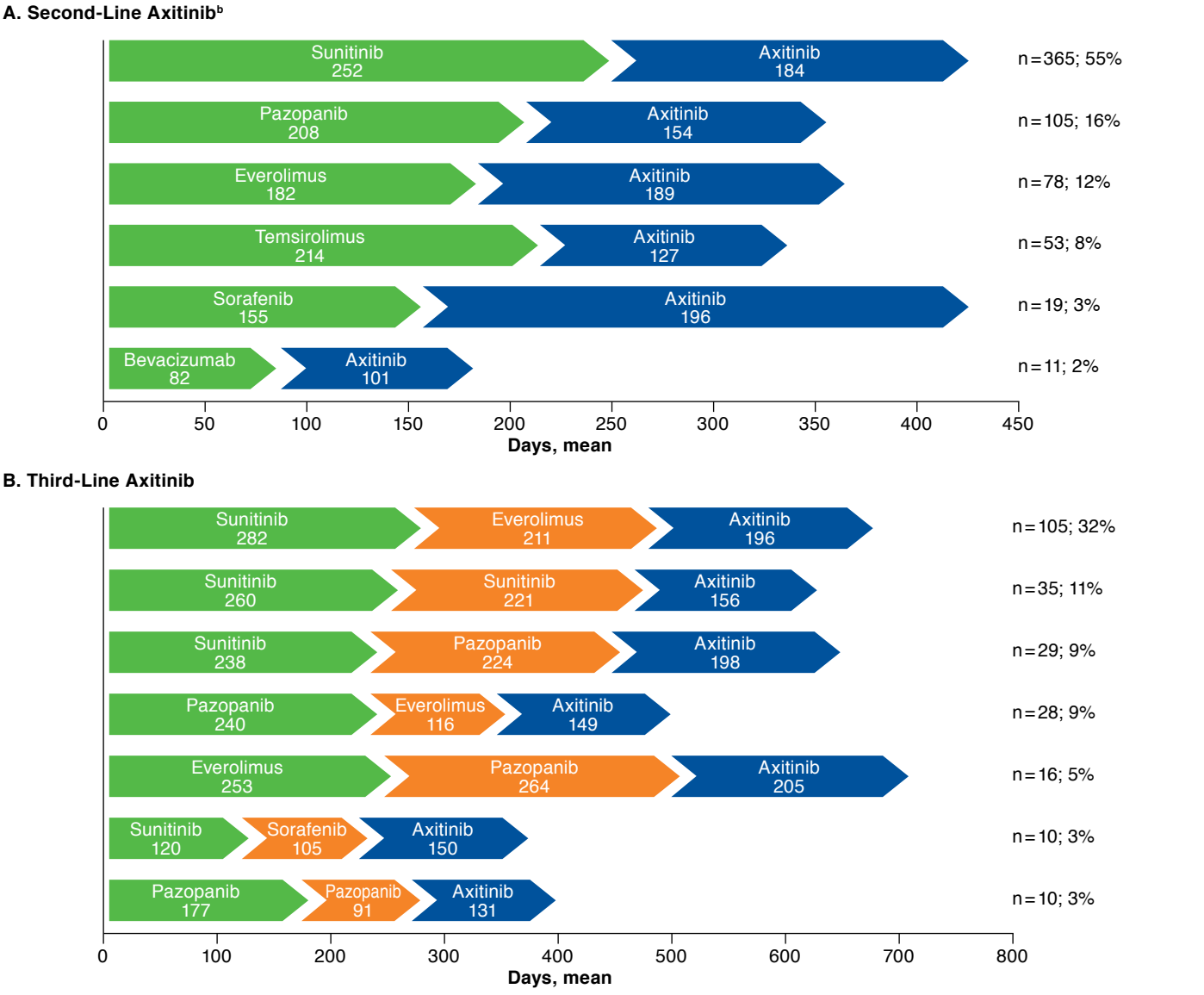
Results of multivariate logistic regression (Table 4) indicated that younger age (OR = 0.958, 95% CI = 0.941-0.975); male gender (OR = 0.573, 95% CI = 0.364-0.903); and lack of concomitant medication as described by Rx Risk V (OR = 0.468, 95% CI = 0.314-0.697) were associated with an increase in dose.

Discussion

The benefits of targeted agents in patients with mRCC have been demonstrated in numerous clinical studies. However, development of drug resistance and/or refractory disease in patients receiving these treatments necessitates administration of subsequent therapies. Although current guidelines from NCCN recommend use of consecutive targeted agents,[2] an optimal sequencing strategy has not yet been determined from prospective clinical trial data. Observational studies in patients with mRCC treated with targeted therapies, including the present analysis, provide insight into real-world sequencing patterns, as well as patient, provider, and reimbursement characteristics.

Coincident with the shift from cytokine-based therapies to targeted agents to treat mRCC has been an expansion of oncology drug distribution via specialty pharmacies.[15] However,

FIGURE 2 Treatment Sequences and Duration in Patients Receiving Second-Line Axitinib or Third-Line Axitinib[a]



[a]*Previous therapies (A) or sequences (B) and axitinib regimens received by ≥10 patients are shown.*
[b]*Figure 2A is based on monotherapy.*

pharmacy records provide limited information with regard to patient and provider characteristics. Linking independent databases in a HIPAA-compliant manner is a growing method to enrich these datasets. This retrospective, observational study demonstrates the feasibility of matching de-identified specialty pharmacy data to other longitudinal databases, as is evidenced by 94% of patients with their first axitinib prescriptions dispensed by specialty pharmacies from May 2012 to April 2013 also having information in the medical and pharmacy claims databases (Figure 1). With a study population of 1,175 patients, this methodology yields one of the largest sample sizes in observational studies examining mRCC treatment patterns in the United States.[16-27]

Baseline demographics of the patient population evaluated here were consistent with the known epidemiology of kidney cancer in the United States, including a higher prevalence in

TABLE 4 Logistic Regression of Key Patient Characteristics on Axitinib Dose Modifications

Variable	Odds Ratio	95% CI
Dose decrease		
Age	1.015	0.998-1.033
Gender (female vs. male)	0.695	0.462-1.047
Baseline hypothyroidism treatment (yes vs. no)	1.662	1.088-2.539
Other baseline treatment (yes vs. no)	0.913	0.639-1.306
Dose increase only		
Age	0.958	0.941-0.975
Gender (female vs. male)	0.573	0.364-0.903
Baseline hypothyroidism treatment (yes vs. no)	2.149	1.353-3.413
Other baseline treatment (yes vs. no)	0.468	0.314-0.697
Dose increase then decrease		
Age	0.989	0.967-1.012
Gender (female vs. male)	1.033	0.627-1.702
Baseline hypothyroidism treatment (yes vs. no)	2.381	1.396-4.060
Other baseline treatment (yes vs. no)	0.762	0.469-1.237

CI = confidence interval.

males versus females and in patients aged 55-74 years versus other age groups, and with hypertension as a comorbidity.[1,4,28] Patient characteristics in this analysis were also generally consistent with other retrospective studies in patients with mRCC treated with targeted agents.[16-27] Whereas the majority of previous observational studies used data from community or tertiary oncology practices in the United States,[16-18,21,23] the present study evaluated patients treated by physicians affiliated with both academic centers and community practices, of which the proportions of prescribers were similar to those reported in a retrospective study of patients receiving first-line targeted therapy for mRCC.[22] Although we found that patient characteristics, including comorbidity profiles, were similar regardless of prescriber affiliation (data not shown), patients seeking care in community settings have characteristics that might restrict their ability to travel to academic centers (e.g., advanced age and/or a greater degree of comorbidity). The present analysis may be limited by classification of physicians associated with both academic centers and community practices as affiliated with academic centers only. The affiliation describes provider characteristics but does not necessarily describe where patient treatments took place.

In this study, the majority of patients (56%) were treated with axitinib in the second line of therapy. Evaluation of real-world treatment patterns in patients receiving axitinib as second-line therapy revealed that sunitinib was the most common first-line therapy, but other targeted agents, including pazopanib (16%) and everolimus (12%), were also prescribed. Prior retrospective analyses in previously treated patients with mRCC also reported sunitinib as the most commonly administered first-line therapy.[16,19,21,24,27] Similar proportions of patients received first-line sunitinib in the present analysis versus the AXIS trial (56% vs. 54%), whereas proportions of patients who received first-line temsirolimus (8% vs. 3%) or bevacizumab (2% vs. 8%) varied slightly.[9] There were very few patients treated with cytokines in the current study, whereas 35% of patients in the AXIS trial were cytokine-refractory.[9] The AXIS trial did not restrict the number of patients enrolled for each first-line therapy; therefore, the population was expected to parallel real-world treatment trends for mRCC at the time of trial initiation—these trends may have evolved since 2008 when enrollment began.

Few retrospective studies have evaluated treatment for mRCC beyond second-line therapy. Harrison et al. (2013, 2014) assessed up to 3 lines of treatment for mRCC from a joint community-academic registry.[19,20] For patients receiving 3 subsequent targeted agents, TKI to mTOR inhibitor to another TKI was a more common treatment sequence than switching from one TKI to another TKI followed by an mTOR inhibitor.[20] Likewise, in a review of medical records from oncology practices in the United States, Jonasch et al. (2014) found that the most common 3-line targeted therapy sequence was a VEGF inhibitor to an mTOR inhibitor to another VEGF inhibitor, with sunitinib, everolimus, and bevacizumab, respectively, the most frequently used treatments in this sequence.[21] In the present analysis, the most common previous therapy sequence in patients prescribed third-line axitinib was also first-line sunitinib followed by second-line everolimus. Because axitinib was not approved in the United States until 2012 (sorafenib and sunitinib were approved in 2005 and 2006, respectively), axitinib was not frequently reported as second- or third-line therapy in earlier retrospective studies.

For patients receiving second-line axitinib in this study, mean duration of first-line therapy ranged from 82 days to 252 days and was longest in patients who previously received sunitinib. Mean duration of second-line axitinib varied somewhat by first-line therapy, ranging from 127 days to 196 days for therapies received by ≥ 10 patients. However, it cannot be determined if duration of first-line therapy influenced duration of second-line axitinib. Moreover, because reasons for treatment discontinuation (e.g., disease progression or adverse events) were not assessed, duration of treatment cannot be considered a surrogate for efficacy.

Our results indicate that duration of axitinib treatment was not affected by the affiliation of the prescriber (data not shown). In contrast, previous studies reported that median duration of sunitinib and sorafenib was shorter in patients with mRCC treated at community practices versus tertiary oncology centers.[17,18] These authors speculated that community oncologists may have less experience in the use of targeted agents to

treat mRCC, which resulted in more frequent dose modifications and change in therapy.[17]

Analysis of dosing patterns indicated that most patients (87%) initiated axitinib at the recommended starting dose of 5 mg BID, and of these patients, the majority (70%) remained on that dose throughout treatment. This is consistent with previous analyses of axitinib-dispensing data from specialty pharmacies.[29,30] The frequency of axitinib dose modifications in the current analysis was lower (14% of patients in the overall population had a dose decrease; 12% had a dose increase; and 7% had a dose increase followed by a decrease) than in the AXIS trial (31% had dose decreases and 37% had dose increases).[9] This disparity may reflect differences in real-world management of patients with mRCC compared with management in the clinical trial setting, for instance, in terms of physician consideration of patient-specific factors such as performance status, comorbidities, and age. Although up titration in patients who tolerate the starting dose of axitinib is supported by results of a prospective, randomized phase II study,[11] drug exposure does not appear to be the sole determinant of clinical response. Identification of pharmacodynamic factors contributing to axitinib efficacy may help to personalize treatment.[31] Similarly, for other oncology drugs, efforts are underway to determine optimal dosing to balance safety and efficacy according to individual patient characteristics.[32]

The experience of patients and prescribers in clinical practice likely differs from the highly controlled setting of a clinical trial. Results from this analysis provide insight into routine clinical use of axitinib as subsequent therapy for mRCC in the United States in the period following FDA approval and complement information derived from clinical trials. The findings from this study also further expand the knowledge base of real-world treatment patterns of targeted agents for mRCC.

Limitations

This study used data from medical and pharmacy claims, which have inherent limitations. Because claims data are collected for billing and reimbursement purposes, rather than research objectives, causality (e.g., reason for change in therapy) cannot be inferred. In addition, data entry errors at sites of care cannot be detected or corrected in data analysis. There is potential for misclassification of treatment sequence because regimens may not be identified if a patient received treatment from a pharmacy/prescriber whose data are not included in the IMS database—for instance, the database may not include a patient's actual first line of therapy. Clinical outcomes (such as survival) were not addressed. In addition, the affiliation describes provider characteristics but does not necessarily describe where patient treatments took place. Although data used in this study were collected from all states, because of geographic biases, any unprojected geographic information may not be representative of the true distribution. Finally, the small number of patients in many subgroups evaluated (e.g., previous therapy or treatment sequence) preclude comparisons by statistical analysis, so results are descriptive in nature.

Conclusions

This retrospective, observational study, which linked data from specialty pharmacies with data from medical and pharmacy claims, evaluated patient, prescriber, and reimbursement characteristics associated with use of axitinib as subsequent therapy for mRCC in the United States. Of 1,175 patients analyzed, axitinib was prescribed as second-line therapy in 56% of patients and as third-line therapy in 28% of patients. The most common treatment before second-line axitinib was sunitinib, followed by pazopanib and everolimus. In contrast with results from the phase III AXIS trial,[9] real-world dosing patterns for axitinib in the current analysis found that 70% of patients who started at the standard 5 mg BID dose remained on that regimen. Further investigation of real-world axitinib use in patients with mRCC through review of medical records, which have greater detail regarding disease characteristics, is warranted.

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DISCLOSURES

This study was sponsored by Pfizer. MacLean and Cisar are employees of and hold stock in Pfizer. At the time of this analysis, Mehle, Eremina, and Quigley were employees of IMS Health who were paid consultants to Pfizer during the conduct of this study and in connection with the development of this manuscript.

MacLean and Cisar contributed to study design and manuscript development. Mehle, Eremina, and Quigley contributed to study design, analysis, and manuscript development.

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APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs

Comorbidities	ICD-9-CM Code
AIDS/HIV	042, 079.53, V08
Cancer	140.x, 141.x, 142.x, 143.x, 144.x, 145.x, 146.x, 147.x, 148.x, 149.x, 150.x, 151.x, 152.x, 153.x, 154.x, 155.x, 156.x, 158.x, 158.x, 159.x, 160.x, 161.x, 162.x, 163.x, 164.x, 165.x, 170.x, 171.x, 172.x, 174.x, 175.x, 176.x, 179, 180.x, 181, 182.x, 183.x, 184.x, 185, 186.x, 187.x, 188.x, 189.x, 190.x, 191.x, 192.x, 193, 194.x, 195.x, 200.x, 201.x, 202.x, 203.x, 204.x, 205.x, 206.x, 207.x, 208.x, 209.x, 235.x, 236.x, 237.x, 238.x, 239.x
Congestive heart failure	398.91, 404.x, 425.x, 428.x
Chronic pulmonary disease	490, 491.x, 492.x, 493.x, 494.x, 495.x, 496, 500, 501, 502, 503, 504, 505, 506.4
Cardiovascular disease	430, 431, 432.x, 433.x, 434.x, 435.x, 436, 437.x, 438.x
Dementia	290.x, 331.x
Diabetes with chronic complications	249.x, 250.x
Diabetes with or without acute complications	249.x, 250.x
Metastatic carcinoma	196.x, 197.x, 198.x, 199.x
Mild liver disease	571.x
Moderate to severe liver disease	456.x, 572.x
Myocardial infarction	410.x, 412
Paraplegia/hemiplegia	342.x, 344.1
Peptic ulcer disease	531.x, 532.x, 533.x, 534.x
Peripheral vascular disease	441.x, 443.9, 785.4, V434
Renal disease	582.x, 583.x, 585.x, 586, 588.xm
Rheumatologic disease	710.x, 714.x, 725
Rx-Risk-V Drugs	**GPI-14 Code**
Abacavir sulfate	1210500510*
Abacavir sulfate-lamivudine	1210990220*
Abacavir sulfate-lamivudine-zidovudine	1210990320*
Abciximab	8515301000*
Acarbose	2750001000*
Acebutolol HCl	3320001010*
Acetaminophen w/codeine	6599100205*
Acetaminophen-caffeine-dihydrocodeine	6599130305*
Acetaminophen-codeine & dietary management product	6599700310*
Acetaminophen-isometheptene-caffeine	6799000307*
Acetaminophen-isometheptene-dichloralphenazone	6799000310*
Acetohexamide	2720001000*
Acitretin	9025051000*
Acitretin w/moisturizer	9025051030*
Aclidinium bromide	44100007108020
Adalimumab	6627001500*
Adenosine	3550001000*
Albiglutide	2717001000*
Albuterol	4420101000*
Albuterol sulfate	4420101010*
Alclometasone dipropionate	9055000510*
Alefacept	9025051500*
Alendronate sodium	3004201010*
Alendronate sodium-cholecalciferol	3004201020*
Alfentanil	6510001500*
Alfuzosin HCl	5685201010*
Aliskiren fumarate	3617001010*
Aliskiren-amlodipine	3699670210*
Aliskiren-amlodipine-hydrochlorothiazide	3699680320*
Aliskiren-hydrochlorothiazide	3699600215*
Aliskiren-valsartan	3699650215*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Allopurinol	6800001000*
Allopurinol sodium	6800001010*
Almotriptan malate	6740601010*
Alogliptin benzoate	2755001010*
Alogliptin-metformin HCl	2799250210*
Alogliptin-pioglitazone	2799400210*
Alosetron HCl	5255401510
Alprazolam	5710001000*
Alprazolam-dietary management product	5799900210*
Amantadine HCl	7320001010*
Amcinonide	9055001000*
Amiloride HCl	3750001010*
Aminosalicylic acid	0900001000*
Amitriptyline HCl	5820001010*
Amitriptyline HCl & dietary management product	5899870210*
Amiodarone HCl	3540000500*
Amiodarone HCl in dextrose	3540000511*
Amlodipine besylate	3400000310*
Amlodipine besylate-benazepril HCl	3699150220*
Amlodipine besylate-olmesartan medoxomil	3699300205*
Amlodipine besylate-valsartan	3699300210*
Amlodipine-valsartan-hydrochlorothiazide	3699450320*
Ammoniated mercury-salicylic acid	90259902104110
Amobarbital sodium	6010001010*
Amoxapine	5820002000*
Amprenavir	1210451000*
Amyl nitrite	3210005000*
Amylase-lipase-protease	5199000320*
Amylase-lipase-protease w/ca carb	5199000420*
Anagrelide HCl	8515601010*
Anisindione	8330001000*
Anthralin	9025002000*
Acetaminophen w/butalbital & codeine	6599100310*
Apixaban	8337001000*
Apomorphine HCl	7320301010*
Apraclonidine HCl	8660201010*
Arformoterol tartrate	4420101210*
Argatroban	8333701500*
Argatroban in NaCl	8333701520*
Aripiprazole	5925001500*
Asenapine maleate	5915501510*
Aspirin buffered-pravastatin sodium	3940990215*
Aspirin w/codeine	6599100210*
Aspirin-acetaminophen-salicyl-caffeine w/codeine	6599100510*
Aspirin-caffeine-dihydrocodeine bitartrate	6599130310*
Aspirin-dipyridamole	8515990220*
Astemizole	4155001000*
Atazanavir sulfate	1210451520*
Atenolol	3320002000*
Atenolol & chlorthalidone	3699200210*
Atorvastatin calcium	3940001010*
Azatadine maleate	4150001015*
Azathioprine	9940601000*
Azathioprine sodium	9940601010*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Azelastine HCl-fluticasone propionate	4299550215*
Azilsartan medoxomil	3615001020*
Azilsartan medoxomil-chlorthalidone	3699400210*
Beclomethasone diprop monohyd	4220001032*
Beclomethasone dipropionate (nasal)	4220001030*
Bedaquiline fumarate	0900001510*
Belatacept	9940802000*
Benazepril HCl	3610000510*
Benazepril & hydrochlorothiazide	3699180215*
Bendroflumethiazide	3760001000*
Bendroflumethiazide/rauwolfia	3699100210*
Benzthiazide	3760001500*
Benztropine mesylate	7310001010*
Bepridil HCl	3400000510*
Betamethasone benzoate	9055002020*
Betamethasone dipropionate (topical)	9055002000*
Betamethasone dipropionate augmented	9055002005*
Betamethasone valerate	9055002010*
Betaxolol HCl	3320002110*
Betaxolol HCl (ophth)	8625001010*
Bimatoprost	8633001500*
Biperiden HCl	7310002010*
Bisoprolol & hydrochlorothiazide	3699200213*
Bisoprolol fumarate	3320002210*
Bitolterol mesylate	4420102010*
Bivalirudin	8333402000*
Bretylium tosylate	3540001010*
Brimonidine tartrate	8660202010*
Brimonidine tartrate-timolol maleate	8625990215*
Brinzolamide	8680232000*
Brinzolamide-brimonidine tartrate	8660990220*
Bromfenac sodium	6610000510*
Bromocriptine mesylate	7320002010*
Bromocriptine mesylate (diabetes)	2757402010*
Brompheniramine maleate	4110001015*
Brompheniramine tannate	4110001040*
Brompheniramine-diphenhydramine	4199100215*
Budesonide (nasal)	4220001500*
Budesonide-formoterol fumarate dihydrate	4420990241*
Bumetanide	3720001000*
Buprenorphine	6520001000*
Buprenorphine HCl	6520001010*
Buprenorphine HCl-naloxone HCl dihydrate	6520001020*
Bupropion HCl	5830004010*
Bupropion HCl (smoking deterrent)	6210000210*
Bupropion HCl-dietary management product	5899900220*
Bupropion hydrobromide	5830004020*
Butabarbital sodium	6010002510*
Butalbital-acetaminophen-caffeine w/codeine	6599100410*
Butalbital-aspirin-caffeine w/codeine	6599100430*
Butorphanol tartrate	6520002010*
Calcifediol	7720203400*
Calcipotriene	9025002500*
Calcipotriene-betamethasone dipropionate	9055990232*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Calcitriol	3090503000*
Calcitriol (topical)	9025002800*
Canagliflozin	2770002000*
Candesartan cilexetil	3615002010*
Candesartan cilexetil-hydrochlorothiazide	3699400220*
Capreomycin sulfate	0900002010*
Captopril	3610001000*
Captopril & hydrochlorothiazide	3699180225*
Carbachol (ophth)	8650102000*
Carbamazepine	7260002000*
Carbamazepine (antipsychotic)	5940001500*
Carbidopa	7340303000*
Carbidopa-levodopa	7320990210*
Carbidopa-levodopa-entacapone	7320990330*
Carbinoxamine maleate	4120001015*
Carbinoxamine maleate-carbinoxamine tannate	4199100230*
Carbinoxamine tannate	4120001025*
Carteolol HCl (ophth)	8625001210*
Celecoxib	6610052500*
Cerivastatin sodium	3940002010*
Cetirizine HCl	4155002010*
Chlordiazepoxide	5710002000*
Chlordiazepoxide HCl	5710002010*
Chlorpheniramine maleate	4110002015*
Chlorpheniramine maleate tannate	4110002017*
Chlorpheniramine tannate	4110002025*
Chlorpheniramine tannate-methscopolamine	4199200225*
Chlorpheniramine-methscopolamine	4199200220*
Chlorpropamide	2720002000*
Chlorpromazine	5920001500*
Chlorpromazine HCl	5920001510*
Chlorothiazide	3760002000*
Chlorothiazide sodium	3760002010*
Chlorthalidone	3760002500*
Cholestyramine	3910001000*
Cholestyramine light	3910001010*
Choline fenofibrate	3920000600*
Ciclesonide (nasal)	4220001800*
Cilostazol	8515551600*
Cimetidine	4920001000*
Cimetidine HCl	4920001010*
Cimetidine in saline	4920001100*
Citalopram & dietary management product	5899850220*
Citalopram hydrobromide	5816002010*
Clemastine fumarate	4120002040*
Clevidipine butyrate	3400000710*
Clobazam	7210000700*
Clobetasol propionate	9055002510*
Clobetasol propionate & clobetasol propionate emulsion	9055002550*
Clobetasol propionate cream & coal tar solution	9055990235*
Clobetasol propionate emollient base	9055002515*
Clobetasol propionate emulsion	9055002520*
Clobetasol propionate ointment & coal tar solution	9055990236*
Clocortolone pivalate	9055003010*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Clofibrate	3920001000*
Clomipramine HCl	5820002510*
Clonazepam	7210001000*
Clonidine & chlorthalidone	3699500220*
Clonidine HCl	3620101010*
Clopidogrel bisulfate	8515802010*
Clorazepate dipotassium	5710003010*
Clozapine	5915202000*
Coal tar extract	9052001000*
Coal tar-amm mercury-methen sulfosalicylate	9052990340*
Coal tar-salicylic acid	9052990220*
Codeine phosphate	6510002010*
Codeine sulfate	6510002020*
Colchicine	6800002000*
Colchicine w/probenecid	6899000210*
Colesevelam HCl	3910001610*
Colestipol HCl	3910002010*
Cycloserine	0900003000*
Cyclosporine	9940202000*
Cyclosporine modified (for microemulsion)	9940202030*
Cyproheptadine HCl	4150002010*
Dabigatran etexilate mesylate	8333703020*
Dalteparin sodium	8310101010*
Danaparoid sodium	8310101410*
Dapagliflozin propanediol	2770004020*
Dapiprazole HCl	8650102510*
Darbepoetin alfa-albumin (human)	8240101512*
Darbepoetin alfa-polysorbate 80	8240101511*
Darunavir ethanolate	1210452010*
Delavirdine mesylate	1210902020*
Demecarium bromide	8650201010*
Deserpidine & hydrochlorothiazide	3699100222*
Deserpidine & methyclothiazide	3699100220*
Desipramine HCl	5820003010*
Desirudin	8333403000*
Desloratadine	4155002100*
Desonide	9055003500*
Desonide cream w/moisturizing lotion	9055003555*
Desonide cream w/wound dressing cream	9055003565*
Desonide lotion w/moisturizing cream	9055003550*
Desonide ointment w/moisturizing lotion	9055003560*
Desonide ointment w/wound dressing cream	9055003568*
Desoximetasone	9055004000*
Dexamethasone sodium phosphate	9055004510*
Desvenlafaxine	5818002000*
Desvenlafaxine fumarate	5818002010*
Desvenlafaxine succinate	5818002020*
Dexbrompheniramine tannate-pyrilamine maleate	4199100240*
Dexchlorpheniramine maleate	4110003015*
Dexlansoprazole	4927002000*
Dezocine	6520002500*
Diazepam	5710004000*
Diazepam (anticonvulsant)	7210003000*
Diazepam-dietary management product	5799900220*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Diazoxide	2730002000*
Diazoxide (antihypertensive)	3660001000*
Diclofenac	6610000700*
Diclofenac potassium	6610000710*
Diclofenac potassium (migraine)	6760004010*
Diclofenac sodium	6610000720*
Diclofenac w/misoprostol	6610990220*
Dicumarol	8320001000*
Didanosine	1210501500*
Diflorasone diacetate	9055005010*
Diflorasone diacetate emollient base	9055005015*
Digitoxin	3120002000*
Digoxin	3120001000*
Dihydroergotamine mesylate	6700003010*
Diltiazem HCl	3400001010*
Diltiazem HCl coated beads	3400001012*
Diltiazem HCl extended release beads	3400001011*
Diltiazem malate	3400001030*
Dipivefrin HCl	8660001000*
Dipyridamole	8515003000*
Disopyramide phosphate	3510001010*
Disulfiram	6280204000*, 6200002000*
Divalproex sodium	7250001010*
Dofetilide	3540002500*
Dolutegravir sodium	1210301510*
Donepezil HCl	6205102510*
Dorzolamide HCl	8680234010*
Dorzolamide HCl-timolol maleate	8625990220*
Doxazosin mesylate	3620200510*
Doxazosin mesylate (BPH)	5685202520*
Doxepin HCl	5820004010*
Doxylamine succinate	4120004010*
Doxylamine succinate tannate	4120004020*
Dronedarone HCl	3540002810*
Duloxetine HCl	5818002510*
Dutasteride-tamsulosin HCl	5685990225*
Echothiophate iodide	8650202010*
Efalizumab	9025052700*
Efavirenz	1210903000*
Efavirenz-emtricitabine-tenofovir disoproxil fumarate	1210990330*
Eletriptan hydrobromide	6740602510*
Elvitegravir-cobicistat-emtricitabine-tenofovir	1210990430*
Emtricitabine	1210603000*
Emtricitabine-rilpivirine-tenofovir disoproxil fumarate	1210990340*
Emtricitabine-tenofovir disoproxil fumarate	1210990230*
Enalapril maleate	3610002010*
Enalapril maleate & hydrochlorothiazide	3699180235*
Enalapril maleate-diltiazem malate	3699150226*
Enalapril maleate-felodipine	3699150230*
Enalaprilat	3610002510*
Encainide HCl	3530000510*
Enfuvirtide	1210253000*
Enoxaparin sodium	8310102010*
Entacapone	7315303000*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Epinephrine bitartrate (ophth)	8660002010*
Epinephrine HCl	4420202020*
Epinephrine HCl (ophth)	8660002020*
Epinephryl borate	8660002030*
Eplerenone	3625003000*
Epoetin alfa	8240102000*
Eprosartan mesylate	3615002420*
Eprosartan mesylate-hydrochlorothiazide	3699400225*
Eptifibatide	8515303000*
Ergot w/pentobarb-bella-caffeine	6799100420*
Ergotamine tartrate	6700002010*
Ergotamine w/caffeine	6799100210*
Ergotamine w/pb & belladonna	6799100320*
Escitalopram oxalate	5816003410*
Eslicarbazepine acetate	7260002410*
Esmolol HCl	3320002510*
Esmolol HCl-sodium chloride	3320002511*
Esomeprazole magnesium	4927002510*
Esomeprazole sodium	4927002520*
Esomeprazole strontium	4927002530*
Ethambutol HCl	0900004010*
Etanercept	6629003000*
Ethacrynate sodium	3720002010*
Ethacrynic acid	3720002000*
Ethionamide	0900005000*
Ethosuximide	7240001000*
Ethotoin	7220001000*
Etidronate disodium	3004204010*
Etodolac	6610000800*
Etravirine	1210903500*
Etretinate	9025003000*
Ezetimibe	3930003000*
Ezetimibe-atorvastatin	3999400220*
Ezetimibe-simvastatin	3999400230*
Ezogabine	7260002600*
Famotidine	4920003000*
Famotidine in NaCl	4920003011*
Febuxostat	6800003000*
Felbamate	7212002000*
Felodipine	3400001300*
Fenofibrate	3920002500*
Fenofibrate micronized	3920002510*
Fenofibric acid	3920002400*
Fenoldopam mesylate	3640203010*
Fenoprofen calcium	6610001010*
Fentanyl	6510002500*
Fentanyl citrate	6510002510*
Fentanyl citrate-bupivacaine HCl–NaCl	6599150330*
Fentanyl citrate-ropivacaine HCl–NaCl	6599150335*
Fentanyl citrate-NaCl	6510002512*
Fexofenadine HCl	4155002410*
Flecainide acetate	3530001010*
Fluocinolone acetonide	9055005510*
Fluocinolone acetonide & cleanser	9055990239*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Fluocinolone-emollient	9055990240*
Fluocinonide	9055006000*
Fluocinonide emulsified base	9055006010*
Fluoxetine HCl	5816004000*
Fluoxetine HCl-dietary management product	5899850245*
Fluphenazine decanoate	5920002530*
Fluphenazine enanthate	5920002520*
Fluphenazine HCl	5920002510*
Flurandrenolide	9055006500*
Flurbiprofen	6610001200*
Fluticasone furoate-vilanterol	4420990275*
Fluticasone propionate	9055006810*
Fluticasone-salmeterol	4420990270*
Fluvastatin sodium	3940003010*
Fluvoxamine maleate	5816004510*
Fondaparinux sodium	8310303010*
Formoterol fumarate	4420102710*
Fosamprenavir calcium	1210452510*
Fosinopril sodium	3610002710*
Fosinopril sodium & hydrochlorothiazide	3699180240*
Fosphenytoin sodium	7220001310*
Frovatriptan succinate	6740603010*
Furosemide	3720003000*
Gabapentin	7260003000*
Gabapentin-dietary management product	7299600230*
Gemfibrozil	3920003000*
Glimepiride	2720002700*
Glipizide	2720003000*
Glipizide-metformin HCl	2799700235*
Glyburide	2720004000*
Glyburide-metformin	2799700240*
Glyburide micronized	2720004010*
Golimumab	6627004000*
Guanabenz acetate	3620102010*
Guanadrel sulfate	3620201010*
Guanethidine & hydrochlorothiazide	3699550230*
Guanethidine monosulfate	3620202010*
Guanfacine HCl	3620102510*
Halazepam	5710005000*
Halcinonide	9055007000*
Halobetasol propionate	9055007310*
Halobetasol propionate & ammonium lactate	9055990247*
Halobetasol propionate & lactic acid	9055990249*
Haloperidol	5910001010*
Haloperidol decanoate	5910001030*
Haloperidol lactate	5910001020*
Heparin (porcine) in NaCl	8310002022*
Heparin sod (porcine) in d5w	8310002025*
Heparin sodium (bovine)	8310002021*
Heparin sodium (porcine)	8310002020*
Hydralazine & hydrochlorothiazide	3699900245*
Hydralazine & reserpine & hydrochlorothiazide	3699100320*
Hydralazine HCl	3640001010*
Hydrochlorothiazide	3760004000*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Hydrocodone bitartrate	6510003010*
Hydrocodone-acetaminophen	6599170210*
Hydrocodone-acetaminophen-dietary management product	6599170210*
Hydrocodone-aspirin	6599170220*
Hydrocodone-ibuprofen	6599170250*
Hydrocortisone (intrarectal)	8915001000*
Hydrocortisone & salicylic acid-sulfur & shampoo	9055990435*
Hydrocortisone acetate-aloe vera	9055990251*
Hydrocortisone-salicylic acid-sulfur	9055990330*
Hydromorphone HCl	6510003510*
Hydromorphone HCl-bupivacaine HCl-NaCl	6599180330*
Hydromorphone HCl-NaCl	6510003512*
Ibuprofen	6610002000*
Ibuprofen w/caffeine & vitamins	6610990328*
Ibuprofen w/liniment	6610002050*
Ibuprofen-famotidine	6610990232*
Ibutilide fumarate	3540005010*
Icosapent ethyl	3950003510*
Iloperidone	5907003500*
Imipramine HCl	5820005010*
Imipramine pamoate	5820005020*
Indacaterol maleate	4420104220*
Indapamide	3760005000*
Indinavir sulfate	1210453020*
Indomethacin	6610003000*
Indomethacin sodium	6610003010*
Infliximab	5250504000*
Insulin aspart	2710400200*
Insulin aspart protamine & aspart (human)	2710407000*
Insulin detemir	2710400600*
Insulin glargine	2710400300*
Insulin glulisine	2710400400*
Insulin lispro (human)	2710400500*
Insulin lispro protamine & lispro (human)	2710408000*
Insulin regular (human)	2710401000*
Insulin regular (pork)	2710301000*
Ipratropium bromide	4410003010*
Ipratropium bromide hfa	4410003012*
Ipratropium-albuterol	4420990201*
Irbesartan	3615003000*
Irbesartan-hydrochlorothiazide	3699400230*
Isocarboxazid	5810001000*
Isoetharine HCl	4420103010*
Isoetharine mesylate	4420103020*
Isoflurophate	8650203000*
Isometheptene mucate	6700005010*
Isoniazid	0900006000*
Isoniazid & rifampin	0999000210*
Isoniazid w/B6	0999000220*
Isoniazid-rifampin w/pyrazinamide	0999000320*
Isoproterenol & phenylephrine	4420990210*
Isoproterenol HCl	4420104010*
Isoproterenol sulfate	4420104020*
Isosorbide dinitrate	3210002000*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Isosorbide mononitrate	3210002500*
Isradipine	3400001500*
Ketoprofen	6610003500*
Ketorolac tromethamine	6610003710*
Labetalol & hydrochlorothiazide	6992002150*
Lacosamide	7260003600*
Lactulose	4660002000*
Lactulose (encephalopathy)	5240002000*
Lamivudine	1210606000*
Lamivudine-zidovudine	1210990250*
Lamotrigine	7260004000*
Lansoprazole	4927004000*
Lansoprazole-naproxen	6610990242*
Latanoprost	8633005000*
Lepirudin	8333405010*
Levalbuterol HCl	4420104510*
Levalbuterol tartrate	4420104550*
Levetiracetam	7260004300*
Levetiracetam in NaCl	7260004305*
Levobunolol HCl	8625002010*
Levocetirizine dihydrochloride	4155002710*
Levodopa	7320004000*
Levomethadyl acetate HCl	6510003710*
Levomilnacipran HCl	5818005010*
Levorphanol tartrate	6510004010*
Levothyroxine sodium	2810001010*
Lidocaine HCl (cardiac)	3520002010*
Lidocaine in d5w	3520002011*
Linaclotide	5255705000*
Linagliptin	2755005000*
Linagliptin-metformin HCl	2799250240*
Liothyronine sodium	2810002010*
Liotrix (t3-t4)	2810003000*
Lisinopril	3610003000*
Lisinopril & hydrochlorothiazide	3699180255*
Lisinopril-dietary management product	3699850250*
Lithium carbonate	5950001010*
Lithium citrate	5950001020*
Lomitapide mesylate	3948005020*
Lopinavir-ritonavir	1210990255*
Loratadine	4155003000*
Lorazepam	5710006000*
Losartan potassium	3615004020*
Losartan potassium & hydrochlorothiazide	3699400245*
Lovastatin	3940005000*
Loxapine	5915402000*
Loxapine HCl	5940002010*
Loxapine succinate	5940002020*
Lurasidone HCl	5940002310*
Maprotiline HCl	5830001010*
Maraviroc	1210206000*
Mecamylamine HCl	3660002010*
Meclofenamate sodium	6610004010*
Mefenamic acid	6610005000*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Meloxicam	6610005200*
Meloxicam w/liniment	6610005260*
Meperidine HCl	6510004510*
Meperidine HCl-NaCl	6510004512*
Meperidine w/promethazine	6599300220*
Mephenytoin	7220002000*
Mephobarbital	6010004000*
Mesoridazine besylate	5920003010*
Metaproterenol sulfate	4420105020*
Metformin HCl	2725005000*
Metformin HCl-dietary management product	2799900250*
Methadone HCl	6510005010*
Methotrexate	2130005000*
Methotrexate (antirheumatic)	6625005000*
Methotrexate sodium	2130005010*
Methotrexate sodium (antirheumatic)	6625005010*
Methoxsalen rapid	9025056010*
Methsuximide	7240002000*
Methyclothiazide	3760005500*
Methyldopa	3620103000*
Methyldopa & chlorothiazide	3699500260*
Methyldopa & hydrochlorothiazide	3699500270*
Methyldopate HCl	3620103010*
Methysergide maleate	6700001010*
Metipranolol	8625001510*
Metolazone	3760006000*
Metoprolol & hydrochlorothiazide	3699200220*
Metoprolol succinate	3320003005*
Metoprolol tartrate	3320003010*
Metoprolol tartrate-dietary management product	3699880260*
Metyrosine	3630002500*
Mexiletine HCl	3520002510*
Mibefradil dihydrochloride	3400001710*
Mifepristone (hyperglycemia)	2730405000*
Miglitol	2750005000*
Minoxidil	3640002000*
Mipomersen sodium	3950004010*
Mirtazapine	5803005000*
Moexipril HCl	3610003310*
Moexipril-hydrochlorothiazide	3699180260*
Molindone HCl	5916005010*
Mometasone furoate	9055008210*
Mometasone furoate-ammonium lactate	9055990254*
Mometasone furoate-formoterol fumarate dihydrate	4420990290*
Montelukast sodium	4450505010*
Moricizine HCl	3505003010*
Morphine sulfate	6510005510*
Morphine sulfate beads	6510005520*
Morphine sulfate for continuous microinfusion	6510005530*
Morphine sulfate in dextrose	6510005511*
Morphine sulfate liposome	6510005540*
Morphine sulfate-NaCl	6510005515*
Morphine-naltrexone	6510005570*
Mycophenolate mofetil	9940303010*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Mycophenolate mofetil HCl	9940303020*
Mycophenolate sodium	9940303030*
Nabumetone	6610005500*
Nadolol & bendroflumethiazide	3699200230*
Nalbuphine HCl	6520003010*
Naltrexone	9340003000*
Naltrexone HCl	9340003010*, 6540003010*
Naproxen	6610006000*
Naproxen sodium	6610006010*
Naproxen w/liniment	6610006050*
Naproxen-esomeprazole magnesium	6610990244*
Naratriptan HCl	6740605010*
Nateglinide	2728004000*
Nebivolol HCl	3320004010*
Nefazodone HCl	5812005010*
Nelfinavir mesylate	1210454520*
Nevirapine	1210905000*
Niacin (antihyperlipidemic)	3945005000*
Niacin-lovastatin	3940990245*
Niacin-simvastatin	3940990270*
Nicardipine HCl	3400001810*
Nicardipine HCl in dextrose	3400001812*
Nicardipine HCl in NaCl	3400001814*
Nicotine	6210000500*
Nicotine polacrilex	6210001000*
Nifedipine	3400002000*
Nimodipine	3400002200*
Nisoldipine	3400002400*
Nitroglycerin	3210003000*
Nitroglycerin in d5w	3210003010*
Nitroprusside sodium	3640004010*
Nizatidine	4920004000*
Nortriptyline HCl	5820006010*
Olanzapine	5915706000*
Olanzapine pamoate	5915706010*
Olmesartan medoxomil	3615005520*
Olmesartan medoxomil-amlodipine-hydrochlorothiazide	3699450345*
Olmesartan medoxomil-hydrochlorothiazide	3699400250*
Omega-3-acid ethyl esters	3950004520*
Omeprazole	4927006000*
Omeprazole magnesium	4927006010*
Oxaprozin	6610006500*
Oxazepam	5710007000*
Oxcarbazepine	7260004600*
Oxycodone HCl	6510007510*
Oxycodone w/acetaminophen	6599000220*
Oxycodone-aspirin	6599000222*
Oxycodone-ibuprofen	6599000226*
Oxymorphone HCl	6510008010*
Paliperidone	5907005000*
Paliperidone palmitate	5907005010*
Pancreatin	5120001000*
Pancrelipase	5120002000*
Pancrelipase (lipase-protease-amylase)	5120002400*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Pantoprazole sodium	4927007010*
Paramethadione	7230001000*
Paroxetine HCl	5816006000*
Paroxetine mesylate	5816006030*
Pegloticase	6800005000*
Pentaerythritol tetranitrate	3210004000*
Pentazocine lactate	6520004020*
Pentazocine w/aspirin	6599400220*
Pentazocine w/naloxone	6520004030*
Pentazocine-acetaminophen	6599400210*
Pentobarbital	6010005500*
Pentobarbital sodium	6010005510*
Perampanel	7255006000*
Pergolide mesylate	7320005000*
Perindopril erbumine	3610003510*
Perphenazine	5920004500*
Phenacemide	7260005000*
Phenelzine sulfate	5810002010*
Pheniramine-phenyltoloxamine-pyrilamine	4199100310*
Phenobarbital	
Phenobarbital sodium	6010006010*
Phenoxybenzamine HCl	3630001010*
Phentolamine mesylate	3630002010*
Phenylbutazone	6610101000*
Phenytoin	7220003000*
Phenytoin sodium	7220003005*
Phenytoin sodium extended	7220003020*
Phenytoin sodium prompt	7220003010*
Phenytoin w/phenobarbital	7260990210*
Physostigmine sulfate	8650204020*
Pilocarpine & epinephrine	8650990210*
Pilocarpine HCl	8650103010*
Pilocarpine nitrate	8650103020*
Pioglitazone HCl	2760705010*
Pioglitazone HCl-glimepiride	2799780240*
Pioglitazone HCl-metformin HCl	2799800240*
Pirbuterol acetate	4420105500*
Piroxicam	6610007000*
Pitavastatin calcium	3940005810*
Polythiazide	3760006500*
Pramipexole dihydrochloride	73203060100305
Prasugrel HCl	8515806010*
Pravastatin sodium	3940006510*
Prazepam	5710008000*
Prazosin HCl	3620203010*
Prazosin & polythiazide	3699550270*
Prednicarbate	9055008300*
Pregabalin	7260005700*
Primidone	7260006000*
Probenecid	6810001000*
Probucol	3950005500*
Procainamide HCl	3510002010*
Prochlorperazine	5920005500*
Prochlorperazine edisylate	5920005520*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Prochlorperazine maleate	5920005510*
Procyclidine HCl	7310006000*
Promazine HCl	5920006010*
Promethazine HCl	4140002010*
Propafenone HCl	3530005000*
Propoxyphene compound	6599200210*
Propoxyphene HCl	6510008510*
Propoxyphene HCl w/acetaminophen	6599200220*
Propoxyphene napsylate	6510008520*
Propoxyphene w/aspirin	6599200230*
Propoxyphene-n w/acetaminophen	6599200240*
Propoxyphene-n w/acetaminophen & dietary management product	6599800250*
Propranolol & hydrochlorothiazide	3699200240*
Protriptyline HCl	5820007010*
Pyrazinamide	0900007000*
Pyrilamine tannate	4130001040*
Quetiapine fumarate	5915307010*
Quinapril HCl	3610004010*
Quinapril-hydrochlorothiazide	3699180265*
Quinidine gluconate	3510003010*
Quinidine polygalacturonate	3510003020*
Quinidine sulfate	3510003030*
Rabeprazole sodium	4927007610*
Raltegravir potassium	1210306010*
Ramipril	3610005000*
Ranitidine bismuth citrate	4920002005*
Ranitidine HCl	4920002010*
Ranitidine HCl in NaCl	4920002011*
Rasagiline mesylate	7330002520*
Remifentanil HCl	6510008710*
Repaglinide	2728006000*
Repaglinide-metformin HCl	2799500270*
Reserpine	3620304000*
Reserpine & chlorothiazide	3699100232*
Reserpine & hydrochlorothiazide	3699100234*
Reserpine & hydroflumethiazide	3699100235*
Reserpine & methyclothiazide	3699100236*
Reserpine & polythiazide	3699100237*
Reserpine & trichlormethiazide	3699100239*
Ribavirin-interferon alfa-2b	1299500260*
Rifabutin	0900007500*
Rifampin	0900008000*
Rifapentine	0900008500*
Rilpivirine HCl	1210908010*
Risperidone	5907007000*
Risperidone microspheres	5907007010*
Ritonavir	1210456000*
Rivaroxaban	8337006000*
Rizatriptan benzoate	6740606010*
Rofecoxib	6610056500*
Ropinirole HCl	7320307010*
Rosiglitazone maleate	2760706010*
Rosiglitazone maleate-glimepiride	2799780260*
Rosiglitazone maleate-metformin HCl	2799800260*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Rosuvastatin calcium	3940006010*
Rotigotine	7320307500*
Rufinamide	7260006500*
Saquinavir	1210458000*
Saquinavir mesylate	1210458020*
Sacrosidase	5120006000*
Salmeterol xinafoate	4420105810*
Saxagliptin HCl	2755006510*
Saxagliptin-metformin HCl	2799250260*
Secobarbital sodium	6010007010*
Selegiline	5810002700*
Selegiline HCl	7330003010*
Sertraline HCl	5816007010*
Sevelamer carbonate	5280007005*
Sevelamer HCl	5280007010*
Silodosin	5685206000*
Simvastatin	3940007500*
Sirolimus	9940407000*
Sitagliptin phosphate	2755007010*
Sitagliptin-metformin HCl	2799250270*
Sitagliptin-simvastatin	2799300270*
Sodium polystyrene sulfonate	9945001000*
Spironolactone	3750002000*
Stavudine	1210807000*
Sufentanil citrate	6510009010*
Sulfinpyrazone	6810002000*
Sulindac	6610008000*
Sumatriptan	6740607000*
Sumatriptan succinate	6740607010*
Sumatriptan-naproxen sodium	6799200260*
Tacrine HCl	6205105010*
Tacrolimus	9940408000*
Tafluprost	8633006500*
Tamsulosin HCl	5685207010*
Tapentadol HCl	6510009110*
Tazarotene	9025007000*
Tegaserod maleate	5255506020*
Telmisartan	3615007000*
Telmisartan-amlodipine	3699300270*
Telmisartan-hydrochlorothiazide	3699400260*
Tenofovir disoproxil fumarate	1210857010*
Terazosin HCl	3620204010*
Terbutaline sulfate	4420106020*
Terfenadine	4155004000*
Thioridazine HCl	5920008010*
Thiothixene	5930002010*
Thiothixene HCl	5930002020*
Thyroglobulin	2810004000*
Thyroid	2810005000*
Thyroid (pork)	2810008000*
Thyroid strong	2810006000*
Tiagabine HCl	7217007010*
Ticagrelor	8515847000*
Ticlopidine HCl	8515808010*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Timolol	8625003000*
Timolol & hydrochlorothiazide	3699200250*
Timolol maleate (ophth)	8625003010*
Tinzaparin sodium	8310108010*
Tiotropium bromide monohydrate	4410008010*
Tipranavir	1210458500*
Tirofiban HCl	8515306010*
Tirofiban HCl in NaCl	8515306011*
Tocainide HCl	3520003010*
Tolazamide	2720005000*
Tolazoline HCl	3660003010*
Tolbutamide	2720006000*
Tolcapone	7315207000*
Tolmetin sodium	6610009010*
Topiramate	7260007500*
Torsemide	3720008000*
Tramadol HCl	6510009510*
Tramadol HCl-dietary management product	6599850250*
Tramadol-acetaminophen	6599500220*
Trandolapril	3610006000*
Trandolapril-verapamil HCl	3699150270*
Tranylcypromine sulfate	5810003010*
Travoprost	8633007000*
Trazodone HCl	5812008010*
Trazodone HCl-dietary management product	5899800275*
Triamterene	3750003000*
Trichlormethiazide	3760007500*
Trifluoperazine HCl	5920008510*
Trihexyphenidyl HCl	7310007010*
Trimeprazine tartrate	4140003010*
Trimethadione	7230002000*
Trimipramine maleate	5820008010*
Tripelennamine HCl	4130002010*
Triprolidine HCl	4110004010*
Triprolidine tannate	4110004030*
Troglitazone	2760707000*
Umeclidinium-vilanterol	4420990295*
Unoprostone isopropyl	8633008510*
Urea-hc acetate	9055990285*
Ustekinumab	9025058500*
Valdecoxib	6610057500*
Valproate sodium	7250002010*
Valproic acid	7250003000*
Valsartan	3615008000*
Valsartan-hydrochlorothiazide	3699400270*
Varenicline tartrate	6210008020*
Venlafaxine HCl	5818009010*
Verapamil HCl	3400003010*
Vigabatrin	7217008500*
Vilazodone HCl	5812008810*
Vorapaxar sulfate	8515578030*
Vortioxetine HBr	5812009310*
Warfarin sodium	8320003020*
Zafirlukast	4450508000*

APPENDIX A ICD-9-CM Codes Used to Identify Comorbidities and GPI-14 Codes Used to Identify Rx-Risk-V Drugs *(continued)*

Rx-Risk-V Drugs	GPI-14 Code
Zalcitabine	1210608500*
Zidovudine	1210808500*
Ziprasidone HCl	5940008510*
Ziprasidone mesylate	5940008520*
Zolmitriptan	6740608000*
Zonisamide	7260009000*

*Note: The asterisk * represents a wild card. The first 10 digits of the GPI define the therapeutic class code (Drug Group, Drug Class, Drug sub-class, Drug name, Drug name extension), and the last 4 digits define route, dosage, or strength. Use of the wild card is a shorthand for reporting a large number of unique GPI codes belonging to the same category.*

D5W = 5% dextrose in water; GPI = Generic Product Identifier; HCl = hydrochloride; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; NaCl = sodium chloride; ophth = ophthalmic solution.

APPENDIX B NDC Numbers and HCPCS/J Codes Used to Identify Treatments

Drug	NDC Number[a]	HCPCS/J Code
Ado-trastuzumab		C9131, J9354
Ado-trastuzumab emtansine	5024200	
Alemtuzumab	5846803, 5041903	S0087, J9010, C9110
Afatinib dimaleate	0059701	
Aldesleukin	6548301, 5390509, 0007804, 5486855	J9015
Alitretinoin	6436505, 6285606	
Arsenic trioxide	6055301, 6345906	J9017, C9012
Asparaginase	6738604, 0000646, 0024712	C9289, J9020
Asparaginase erwinia chrysanthemi	5790202	
Axitinib	0006901	
Azacitidine	4359803, 0078132, 0078192, 5957201, 6721101	J9025, C9218, S0168
BCG vaccine	1179308	
Bevacizumab	5024200	C9214, S0116, J9035
Bexarotene oral	6285606, 0018755, 6436505	
Bexarotene topical	6436505, 6285606	
Bosutinib	0006901	
Brentuximab	5114400	C9287, J9042
Busulfan	0017307, 6728600, 5914800, 7638807, 6216100, 0008107	C1178, J8510, J0594
Cabazitaxel	0002458	J9043, C9276
Cabozantinib	4238800	
Carboplatin	0001532, 2502102, 6170303, 6675800, 1013900, 1521000, 0059134, 0070332, 0070342, 5539001, 6781700, 6686001, 5539002, 6332301, 5011109, 1001909, 0059136, 0059133, 0040911, 0059122	J9045
Carfilzomib	7607501	C9295, J9047
Carmustine	0001530, 2315502	C9437, J9050
Carmustine in polifeprosan intracranial implant	6285601, 6137901, 5806301	
Cetuximab	6673309	C9215, J9055
Chlorambucil	5486811, 0017306, 0008106, 7638806	S0172
Cisplatin	5539004, 0070357, 0001532, 6332301, 5539001, 4456705, 1001909, 0001530, 0006900, 5539000	J9062, C9418, J9060
Cladribine	6332301, 5539001, 5967602, 0006900, 0006902	C9419, J9065
Clofarabine	5846801	J9027, C9129
Crizotinib	0006981	
Cyclophosphamide	1001909, 5456903, 0005441, 0001505, 0001356, 0008705, 5486850, 5486852, 5456957, 0005481, 0064122, 0005480	C9420, J9096, J9092, J9070, J9080, J9093, J9097, C9421, J9090, J9094, J8530, J9091, J9095
Cytarabine	0000903, 0006901, 0036424, 6332301, 5539001, 5539008, 6170303, 0000904, 0000930, 0070351, 6745704, 0000932, 5390501	J9098, C9422, J9110, J9100
Cytarabine liposome	5766503, 5390503	C1166
Dabrafenib	0017308	
Dactinomycin	0000632, 5529208, 6738608, 5539003	J9120
Dasatinib	0000308, 0000305, 5486857	
Daunorubicin citrate liposome	5614603, 6195803, 1088500	J9151
Daunorubicin HCl	6332301, 0070352, 5539001, 5539008, 5539002, 0070350	C9424, J9150
Decitabine	5511105, 4359803, 6285606, 5806306	C9231, J0894
Denileukin diftitox	6436505, 6285606	C1084, J9160
Docetaxel	0007580, 0040902, 0095510, 1672902, 6050560, 2502102, 4733502, 6675800, 1672901	J9170, J9171
Doxorubicin HCl	0001311, 0001533, 0018615, 0046988, 1001909, 5390502, 5390508, 5539002, 0001312, 0001310, 0007450, 0006930, 0006901, 0070350, 0006940, 5315003, 2502102, 6745703, 6332308, 6275608, 6332301, 6745704, 0070202	Q2048, J9000, C9415

APPENDIX B NDC Numbers and HCPCS/J Codes Used to Identify Treatments *(continued)*

Drug	NDC Number[a]	HCPCS/J Code
Epirubicin HCl	6170303, 5992307, 6332301, 1051801, 5315002, 6675800, 5539002, 0059134, 1013900, 2502102, 0000950, 5976250, 0070330	J9178, J9180, C1167
Eribulin	6285603	C9280, J9179
Erlotinib	5024200, 5456958, 5486854, 5486852	
Etoposide	0001530, 0007414, 0020930, 0070356, 1001909, 5539002, 5840607, 6332301, 0007456, 0001373, 0036430, 5107909, 5539004, 0018615, 0037832, 5390502, 5456957, 5486853, 1672901, 0001534	C9414, J9182, C9425, J8560, J9181
Everolimus	0007805, 0007806	J7527
Floxuridine	5539004, 6170303, 0000419, 6332301, 5539001	C9426, J9200
Fludarabine		Q2025, J9185, C9262
Fludarabine phosphate	0006993, 5041905, 5846801, 6332301, 0070348, 0070358, 6170303, 0002458, 6745702, 2502102, 6675800	
Fluorouracil	1672902, 0001310, 0070330, 3976900, 6332301, 6170304, 1013900, 0046917, 0006901, 0070217, 1001909, 6675800, 0000419, 0018739, 0018230	J9190
Gefitinib	0031004	J8565
Gemcitabine	6332301, 5511106, 0006938, 0040901, 1672901, 2315502, 0000275, 0078132, 0070357, 4733501, 0059135, 2502102, 5539003, 1672900	J9201
Ibrutinib	5796201	
Idarubicin HCl	0001325, 0070341, 5539002, 6332301, 5976225	C9429, J9211
Ifosfamide & mesna	0001535, 0070341	
Imatinib mesylate	5486852, 5486854, 0007804, 6825890, 0007803, 5456958	S0088
Interferon alfa-2a	0000419, 0000420, 0000469	J9213
Interferon alfa-2b	0033965, 0008501, 5486830, 0008505, 0008506, 0008509, 0008511, 0008512, 0008507, 5486833, 0008502	J9214
Interferon alfa-n3	5474600, 0003410	J9215
Ipilimumab	0000323	C9284, J9228
Ixabepilone	0001519	C9240, J9207
Lapatinib ditosylate	0017307	
Lenalidomide	5957204	
Levamisole HCl	5045802	S0177
Lomustine	0001530, 5818130	C9017, S0178
Mechlorethamine	0000677, 6738609, 5529209	J9230
Melphalan	5260930, 6745701, 5486843, 0017300, 5957203, 5456903, 0017301, 0008100, 5260900, 6745702	J8600, J9245
Mercaptopurine	0037835, 6808403, 0008108, 5784405, 0005445, 5486852, 6825891, 0017308, 4988409, 0009355	S0108
Mesna	0001535, 2502102, 6710835, 0033813, 6745701, 6332307, 5539000, 5539002, 1001909, 0070348, 5539003	
Methotrexate		J9250, J8610, J9260
Mitomycin	1672901, 0001530, 5390502, 1672902, 5539002, 5539004, 6332301, 6270100, 6170303	J9290, J9280, C9432, J9291
Mitoxantrone HCl	0020593, 1051801, 4408715, 5539000, 6170303, 6332301, 1521004, 0070346, 5840606	J9293
Nelarabine	0000744	J9261
Nilotinib	0007805	
Obinutuzumab	5024200	
Ofatumumab	0017308	C9260, J9302
Omacetaxine mepesuccinate	6345901	
Paclitaxel	5107909, 0007443, 5539003, 1051801, 6675800, 0070347, 0001534, 6332307, 2502102, 0006900, 0017237, 5539001, 6170303, 5539005, 0055519	C9431, J9265

APPENDIX B NDC Numbers and HCPCS/J Codes Used to Identify Treatments *(continued)*

Drug	NDC Number[a]	HCPCS/J Code
Pazopanib	0017308	
Pegaspargase	0007506, 5448203, 5766500	J9266
Peginterferon alfa-2a	0000403, 5486848	S0145
Peginterferon alfa-2b	0008512, 0008513, 5486850	S0146
Pentostatin	5539002, 0040908, 6270108	J9268
Pertuzumab	5024201	C9292, J9306
Plicamycin		J9270
Pomalidomide	5957205	
Ponatinib	7618905	
Porfimer sodium	5891415, 0002415, 7612801, 5891401	J9600
Pralatrexate	4881800	C9259, J9307
Procarbazine		S0182
Procarbazine HCl	5486813, 5448200, 0000400	
Regorafenib	5041901	
Rituximab	5024200	J9310
Romidepsin	5957209, 4602609	J9315, C9265
Ruxolitinib	5088100	
Sipuleucel-t	3023789	C9273, Q2043
Sorafenib tosylate	0002684, 5041904	
Streptozocin	0000908, 0024713, 0070346	J9320
Sunitinib malate	0006907, 0006909, 5456959, 0006905, 5486855	
Temozolomide	0078126, 0008513, 0008530, 0008515, 5486853, 0008514, 0008512, 5456958, 5486841, 4733509, 4733508, 0009376, 6726305, 5486859, 0009375	C1086, C9253, J8700, J9328
Temsirolimus	0000811	J9330, C9239
Teniposide	0001530, 4456705	Q2017
Thalidomide	5957202, 5957201	
Thioguanine	0008108, 7638808, 0017308	
Thiotepa	5840606, 0000546, 0070343, 5539000	J9340, C9433
Topotecan		J9351, J8705, J9350
Tositumomab	6780001, 0000732	G3001
Trametinib	0985008, 0017308	
Tretinoin	6808400, 0000402, 0055508, 1037002	S0117
Uracil mustard	0000909	
Valrubicin	5301402, 6797900	J9357
Vandetanib	0031078	
Vemurafenib	5024200	
Vincristine sulfate	0001374, 0070344, 0036424, 0000271, 6170303, 0030421, 0046935, 5130902, 0040210	J9380, J9370, J9375
Vincristine sulfate liposome	2053603	
Vismodegib	5024201	
Vorinostat	0000605	
Ziv-aflibercept	0002458	C9296, J9400

[a]*Concatenated NDC number to numbers 1-7 to include multiple subcodes at NDC11 level.*

BCG = Bacillus Calmette–Guérin; HCl = hydrochloride; HCPCS = Healthcare Common Procedure Coding System; NDC = National Drug Code.

APPENDIX C Multivariate Regression of Key Patient Characteristics on Duration of Axitinib Therapy

Variable	Estimate	Standard Error	T Value	*P* Value
Intercept	164.054	9.316	17.61	<0.0001
Gender (female vs. male)	-20.628	8.251	-2.500	0.013
Geography				
Midwest vs. Northeast	-27.978	10.763	-2.60	0.010
West vs. Northeast	-27.710	11.456	-2.42	0.016
South vs. Northeast	-10.709	9.959	-1.08	0.282
Unknown vs. Northeast	156.946	122.997	1.28	0.202
Prior regimen				
Everolimus vs. sunitinib	18.188	9.619	1.890	0.059
Pazopanib vs. sunitinib	-2.983	9.865	-0.300	0.762
Temsirolimus vs. sunitinib	-31.320	14.791	-2.120	0.034
Other vs. sunitinib	-46.400	16.075	-2.890	0.004
Sorafenib vs. sunitinib	-3.385	19.412	-0.170	0.862
Bevacizumab vs. sunitinib	-50.226	22.874	-2.200	0.028
Baseline hypothyroidism treatment (yes vs. no)	25.538	8.927	2.860	0.004