Disclaimer

Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview for Request cder_mpl1r_wp019_nsdp_v01

Request ID: cder_mpl1r_wp019_nsdp_v01

Query Description: This report contains estimates of patients using four tyrosine kinase inhibitors (TKI): axitinib, pazopanib, sorafenib, and sunitinib.

Sentinel Modular Program Tool Used: Cohort Identification and Descriptive Analysis (CIDA) tool, version 3.0.2

Data Source: The query was run against the Sentinel Distributed Database (SDD) for the time period from January 1, 2006 - September 30, 2015. This request was distributed to 16 Data Partners on August 23, 2016. See Appendix A for a list of the latest dates of available data for each Data Partner.

Study Design: This request was designed to calculate background rates. The number of qualifying patients with the exposure of interest were calculated overall and stratified by age group, sex, and year.

Exposure of Interest: The exposures of interest were TKIs, axitinib, pazopanib, sorafenib, and sunitinib, which were defined using National Drug Codes (NDCs). Please see Appendix B for generic and brand names used to define exposures in this request.

Cohort Eligibility Criteria: Patients were required to be continuously enrolled in plans with at least drug coverage for a minimum of 183 days before their index date, during which gaps in coverage of up to 45 days were allowed. Each scenario restricted same-day initiation of another specified TKI. The following age groups were included in the cohort: 18-44, 45-54, 55-64, 65-74 and 75+ years.

Limitations: Algorithms to define exposures are imperfect and, therefore, may be misclassified.

Please see the *Appendix C* for the specifications of parameters used in the analyses for this request.

Notes: Please contact the Sentinel Operations Center Query Fulfillment Team (qf@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document.

Table of Contents

Glossary of Terms for Analyses Using
Cohort Identification and Descriptive Analysis (CIDA) Tool*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing. This is equivalent to the "RxAmt" value in the MSCDM.

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or Missing (U). Along with the Principal Diagnosis Indicator, forms the Care Setting/PDX parameter.

Cohort Definition (drug/exposure) - indicates how the cohort will be defined: 1: Cohort includes only the first valid incident treatment episode during the query period; 2: Cohort includes all valid incident treatment episodes during the query period; 3: Cohort includes all valid incident treatment episodes during the query period until an event occurs.

Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes.

Episodes - treatment episodes; length of episode is determined by days supplied in one dispensing or consecutive dispensings bridged by the

Eligible Members - number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.

Years at Risk - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.25.

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a "continuously enrolled"

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same treatment episode.

Event Deduplication - specifies how events are counted by the MP algorithm: 0: Counts all occurrences of an HOI during an exposure episode; 1: de-duplicates occurrences of the same HOI code and code type on the same day; 2: de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode.

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time."

Lookback Period (pre-existing condition) - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing).

Member-Years - sum of all days of enrollment with medical and drug coverage** in the query period preceded by an exposure washout

Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be considered.

Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered.

Principal Diagnosis (PDX) - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. 'P' = principal diagnosis, 'S' = secondary diagnosis, 'X' = unspecified diagnosis, '.' = blank. Along with the Care Setting values, forms the

Treatment Episode Truncation Indicator - indicates whether observation of the incident query code during follow-up requires truncation of valid treatment episodes. A value of Y indicates that the treatment episodes should be truncated at the first occurrence of an incident query code. A value of N indicates that the treatment episodes should not be truncated at the occurrence of the incident query code.

Users - number of members with exposure during the query period. Member must have no evidence of exposure(s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.

Washout Period (drug/exposure) - number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.

Washout Period (event/outcome) - number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

*all terms may not be used in this report
**incident treatment episodes must be incident to both the exposure and the event

Table 1: Summary of Incident Tyrosine Kinase Inhibitor Use in the Sentinel Distributed Database (SDD) between January 1, 2006 and September 30, 2015, by Drug

	New Users	Dispensings	Days Supplied	Amount Supplied	Years at Risk	Eligible Members	Member- Years	New Users / 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing
Axitinib											
	503	2,721	84,601	243,749	249.5	97,865,905	250,915,572.4	0.01	168.19	5.41	31.09
Pazopanib											
	3,420	14,979	434,533	1,591,676	1,323.8	97,865,907	250,914,993.9	0.03	127.06	4.38	29.01
Sorafenib											
	8,333	30,578	892,388	3,023,921	2,767.3	97,865,912	250,913,350.0	0.09	107.09	3.67	29.18
Sunitinib											
	7,224	34,279	1,078,837	1,394,038	3,668.0	97,865,910	250,913,022.7	0.07	149.34	4.75	31.47

Table 2: Summary of Incident Tyrosine Kinase Inhibitor Use in the Sentinel Distributed Database (SDD) between January 1, 2006 and September 30, 2015, by Drug and Age Group

	New Users	Dispensings	Days Supplied	Amount Supplied	Years at Risk	Eligible Members	Member-Years	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing
Axitinib											
18-44 Years	15	72	2,881	9,569	8.2	53,760,776	109,291,400.9	0.00	192.07	4.80	40.01
45-54 Years	60	303	9,645	31,808	28.3	22,781,214	49,552,740.0	0.00	160.75	5.05	31.83
55-64 Years	168	1,018	31,495	88,431	92.9	17,503,707	40,862,024.0	0.01	187.47	6.06	30.94
65-74 Years	176	927	28,504	77,449	84.0	11,955,079	28,697,166.4	0.01	161.95	5.27	30.75
75+ Years	84	401	12,076	36,493	36.1	7,344,336	22,512,241.1	0.01	143.76	4.77	30.11
Pazopanib											
18-44 Years	322	1,226	35,422	128,215	112.5	53,760,777	109,291,356.1	0.01	110.01	3.81	28.89
45-54 Years	556	2,483	72,674	275,287	224.4	22,781,201	49,552,686.7	0.02	130.71	4.47	29.27
55-64 Years	995	4,750	139,946	518,632	424.8	17,503,678	40,861,906.6	0.06	140.65	4.77	29.46
65-74 Years	983	4,361	125,770	456,191	378.2	11,955,045	28,696,960.0	0.08	127.95	4.44	28.84
75+ Years	564	2,159	60,721	213,351	184.0	7,344,300	22,512,084.6	0.08	107.66	3.83	28.12
Sorafenib											
18-44 Years	468	1,560	45,812	149,014	145.5	53,760,776	109,291,232.3	0.01	97.89	3.33	29.37
45-54 Years	1,179	4,048	118,014	408,898	365.6	22,781,189	49,552,478.2	0.05	100.10	3.43	29.15
55-64 Years	2,814	10,397	301,653	1,044,252	934.6	17,503,606	40,861,358.6	0.16	107.20	3.69	29.01
65-74 Years	2,348	9,170	269,341	909,298	832.4	11,954,962	28,696,557.5	0.20	114.71	3.91	29.37
75+ Years	1,524	5,403	157,568	512,460	489.1	7,344,232	22,511,723.4	0.21	103.39	3.55	29.16
Sunitinib											
18-44 Years	452	1,883	60,415	85,954	203.2	53,760,776	109,291,278.2	0.01	133.66	4.17	32.08
45-54 Years	1,215	5,978	192,816	246,076	650.0	22,781,175	49,552,433.8	0.05	158.70	4.92	32.25
55-64 Years	2,361	12,193	380,828	516,499	1,319.0	17,503,592	40,861,410.1	0.13	161.30	5.16	31.23
65-74 Years	1,999	9,597	300,784	376,874	1,013.9	11,954,937	28,696,365.2	0.17	150.47	4.80	31.34
75+ Years	1,197	4,628	143,994	168,635	481.9	7,344,170	22,511,535.4	0.16	120.30	3.87	31.11

Table 3: Summary of Incident Tyrosine Kinase Inhibitor Use in the Sentinel Distributed Database (SDD) between January 1, 2006 and September 30, 2015, by Drug and Sex

	New Users	Dispensings	Days Supplied	Amount Supplied	Years at Risk	Eligible Members	Member- Years	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing
Axitinib											
Female	146	804	25,904	77,755	76.4	50,619,177	132,051,612.6	0.00	177.42	5.51	32.22
Male	357	1,917	58,697	165,995	173.1	47,242,451	118,853,310.8	0.01	164.42	5.37	30.62
Unknown	0	0	0	0	0.0	4,277	10,649.1	0.00	---	---	---
Pazopanib											
Female	1,379	5,636	163,030	589,917	497.5	50,619,179	132,051,359.9	0.03	118.22	4.09	28.93
Male	2,041	9,343	271,503	1,001,759	826.3	47,242,451	118,852,985.0	0.04	133.02	4.58	29.06
Unknown	0	0	0	0	0.0	4,277	10,649.1	0.00	---	---	---
Sorafenib											
Female	2,324	8,743	256,367	821,533	794.8	50,619,180	132,050,869.7	0.05	110.31	3.76	29.32
Male	6,009	21,835	636,021	2,202,388	1,972.5	47,242,455	118,851,831.3	0.13	105.84	3.63	29.13
Unknown	0	0	0	0	0.0	4,277	10,649.1	0.00	---	---	---
Sunitinib											
Female	2,512	11,165	353,456	452,018	1,184.4	50,619,178	132,050,658.6	0.05	140.71	4.44	31.66
Male	4,712	23,114	725,381	942,020	2,483.6	47,242,455	118,851,715.1	0.10	153.94	4.91	31.38
Unknown	0	0	0	0	0.0	4,277	10,649.1	0.00	---	---	---

Table 4: Summary of Incident Tyrosine Kinase Inhibitor Use in the Sentinel Distributed Database (SDD) between January 1, 2006 and September 30, 2015, by Drug and Year

	New Users	Dispensings	Days Supplied	Amount Supplied	Years at Risk	Eligible Members	Member- Years	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing
Axitinib											
2006	0	0	0	0	0.0	14,992,157	8,895,240.2	0.00	---	---	---
2007	0	0	0	0	0.0	21,811,313	13,692,190.1	0.00	---	---	---
2008	0	0	0	0	0.0	38,092,143	25,092,478.5	0.00	---	---	---
2009	0	0	0	0	0.0	38,293,581	30,277,474.4	0.00	---	---	---
2010	0	0	0	0	0.0	36,582,637	28,983,215.6	0.00	---	---	---
2011	0	0	0	0	0.0	36,668,588	28,948,186.9	0.00	---	---	---
2012	138	846	26,952	77,235	80.4	37,921,121	29,891,585.9	0.00	195.30	6.13	31.86
2013	128	839	27,047	75,994	79.0	38,423,085	30,705,121.5	0.00	211.30	6.55	32.24
2014	129	681	20,318	60,048	59.9	40,204,943	31,234,053.8	0.00	157.50	5.28	29.84
2015	108	355	10,284	30,473	30.3	38,278,497	23,196,025.6	0.00	95.22	3.29	28.97
Pazopanib											
2006	0	0	0	0	0.0	14,992,157	8,895,240.2	0.00	---	---	---
2007	0	0	0	0	0.0	21,811,313	13,692,190.1	0.00	---	---	---
2008	0	0	0	0	0.0	38,092,143	25,092,478.5	0.00	---	---	---
2009	19	95	2,978	11,485	8.6	38,293,581	30,277,474.5	0.00	156.74	5.00	31.35
2010	227	1,052	30,766	111,883	96.0	36,582,634	28,983,212.5	0.01	135.53	4.63	29.25
2011	318	1,582	47,338	169,748	143.6	36,668,528	28,948,159.3	0.01	148.86	4.97	29.92
2012	586	2,788	83,057	306,680	253.1	37,921,003	29,891,528.2	0.02	141.74	4.76	29.79
2013	785	3,748	111,514	407,208	339.9	38,422,888	30,705,009.2	0.02	142.06	4.77	29.75
2014	845	3,794	108,290	397,701	329.5	40,204,610	31,233,869.2	0.02	128.15	4.49	28.54
2015	640	1,920	50,590	186,971	153.2	38,278,066	23,195,832.2	0.02	79.05	3.00	26.35
Sorafenib											
2006	289	1,310	38,563	138,701	123.3	14,992,158	8,895,237.8	0.02	133.44	4.53	29.44
2007	407	1,730	47,629	178,393	147.2	21,811,253	13,692,158.4	0.02	117.02	4.25	27.53
2008	927	3,581	103,938	361,787	324.8	38,091,984	25,092,387.6	0.02	112.12	3.86	29.02
2009	1,009	3,659	106,890	369,563	333.4	38,293,243	30,277,294.1	0.03	105.94	3.63	29.21
2010	996	3,611	107,020	357,520	331.8	36,582,188	28,982,950.4	0.03	107.45	3.63	29.64

Table 4: Summary of Incident Tyrosine Kinase Inhibitor Use in the Sentinel Distributed Database (SDD) between January 1, 2006 and September 30, 2015, by Drug and Year

	New Users	Dispensings	Days Supplied	Amount Supplied	Years at Risk	Eligible Members	Member- Years	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing
2011	993	3,721	111,570	365,262	345.6	36,668,054	28,947,859.2	0.03	112.36	3.75	29.98
2012	963	3,555	104,797	354,413	327.8	37,920,547	29,891,247.9	0.03	108.82	3.69	29.48
2013	1,005	3,838	112,571	365,405	344.7	38,422,517	30,704,769.1	0.03	112.01	3.82	29.33
2014	1,018	3,594	104,489	348,858	322.0	40,204,377	31,233,679.5	0.03	102.64	3.53	29.07
2015	726	1,979	54,921	184,019	166.7	38,277,997	23,195,766.1	0.02	75.65	2.73	27.75
Sunitinib											
2006	274	1,228	37,689	50,809	135.0	14,992,159	8,895,240.0	0.02	137.55	4.48	30.69
2007	433	2,203	68,210	86,918	247.0	21,811,252	13,692,166.4	0.02	157.53	5.09	30.96
2008	799	4,095	126,700	168,967	441.7	38,091,957	25,092,388.1	0.02	158.57	5.13	30.94
2009	907	4,270	129,559	182,720	456.2	38,293,232	30,277,287.3	0.02	142.84	4.71	30.34
2010	827	3,804	118,068	161,479	409.9	36,582,126	28,982,930.0	0.02	142.77	4.60	31.04
2011	879	4,300	142,124	189,357	477.6	36,667,980	28,947,845.6	0.02	161.69	4.89	33.05
2012	899	4,411	146,073	186,699	476.8	37,920,469	29,891,209.3	0.02	162.48	4.91	33.12
2013	872	4,693	151,861	187,049	505.7	38,422,400	30,704,711.0	0.02	174.15	5.38	32.36
2014	760	3,471	108,806	129,152	356.4	40,204,211	31,233,593.2	0.02	143.17	4.57	31.35
2015	574	1,804	49,747	50,888	161.8	38,277,769	23,195,651.9	0.01	86.67	3.14	27.58

Appendix A: Latest Date of Available Data for Each Data Partner up to Request End Date (September 30, 2015)

DP ID	End Date
DP0001	9/30/2015
DP0002	9/30/2015
DP0003	9/30/2015
DP0004	6/30/2015
DP0005	9/30/2015
DP0006	5/31/2015
DP0007	6/30/2012
DP0008	9/30/2015
DP0009	6/30/2015
DP0010	6/30/2015
DP0011	9/30/2015
DP0012	9/30/2015
DP0013	9/30/2015
DP0014	9/30/2015
DP0015	9/30/2015
DP0016	9/30/2015

Appendix B: Generic and Brand Names used to Define Exposures in this Request

Generic Name	Brand Name
AXITINIB	Inlyta
PAZOPANIB HCL	Votrient
SUNITINIB MALATE	Sutent
SORAFENIB TOSYLATE	Nexavar

Appendix C: Modular Program Specifications for cder_mpl1r_wp019_nsdp_v01

Sentinel's Cohort Identification and Descriptive Analysis (CIDA) tool, version 3.0.2, will be used to identify use of four tyrosine kinase inhibitors (TKIs) in the Sentinel Distributed Database (SDD): axitinib, pazopanib, sunitinib, and sorafenib. In total, 4 scenarios will be examined with four different exposures.

Enrollment Gap: 45 days
Age Groups: 18-44, 45-54, 55-64, 65-74, 75+ years
Query Period: January 1, 2006 - September 30, 2015
Enrollment Requirement: 183 days

							Drug/Exposure					Pre-Existing Condition				Event/Outcome
Scenario	Coverage Requirement	Incident exposure	Incident w/ respect to:	Washout (days)	Cohort Definition	Episode Gap	Exposure Extension Period	Min Episode Duration	Min Days Supplied	Additional censoring criteria	Pre-Existing Condition	Care Setting/ PDX	Include or Exclude	Lookback Start	Lookback End	Event/ Outcome
1	At least drug	Axitinib	Axitinib, Pazopanib, Sunitinib, Sorafenib	183	Retain first valid episode per person	60	0	0	1	None	Pazopanib, Sunitinib, Sorafenib	Any	Exclude	0	0	Dummy
2	At least drug	Pazopanib	Axitinib, Pazopanib, Sunitinib, Sorafenib	183	Retain first valid episode per person	60	0	0	1	None	Axitinib, Sunitinib, Sorafenib	Any	Exclude	0	0	Dummy
3	At least drug	Sunitinib	Axitinib, Pazopanib, Sunitinib, Sorafenib	183	Retain first valid episode per person	60	0	0	1	None	Axitinib, Pazopanib, Sorafenib	Any	Exclude	0	0	Dummy
4	At least drug	Sorafenib	Axitinib, Pazopanib, Sunitinib, Sorafenib	183	Retain first valid episode per person	60	0	0	1	None	Axitinib, Pazopanib, Sunitinib	Any	Exclude	0	0	Dummy

International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM), International Classification of Diseases, Tenth Edition, Clinical Modification (ICD-10-CM), Healthcare Common Procedure Coding System (HCPCS) , and Current Procedural Terminology, Fourth Revision (CPT-4) codes are provided by Optum360. NDC codes are checked against First Data Bank's "National Drug Data File (NDDF®) Plus."