## Disclaimer

The following report(s) provides findings from an FDA-initiated query using Sentinel. While Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Sentinel, and seeking to better understand Sentinel capabilities.

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_mpl1p_wp023**

**Request ID:** cder_mpl1p_wp023_nsdp_v01

**Request Description:** This report contains estimates of hydrochlorothiazide (HCTZ), angiotensin-converting enzyme inhibitor (ACEI), and angiotensin II receptor blocker (ARB) utilization in the Sentinel Distributed Database (SDD).

**Sentinel Modular Program Tool Used:** Cohort Identification and Descriptive Analysis (CIDA) tool, version 5.4.3 with additional ad hoc programming.

**Data Source:** Data from January 1, 2000 to June 30, 2018 from 17 Data Partners contributing to the SDD were included in this report. This request was distributed to Data Partners on August 20, 2018. Please see Appendix A for dates of available data for each Data Partner.

**Study Design:** The request was designed to calculate length and dose of cumulative treatment episodes and enrolled time. Results were stratified by race and enrolled follow-up time.

**Exposures of Interest:** The exposures of interest were any HCTZ-containing product (including HCTZ monotherapy, HCTZ-ACEI combination products, HCTZ-ARB combination products, and HCTZ-amiloride combination products), ACEI monotherapy, non-HCTZ ACEI combination products, ARB monotherapy, and non-HCTZ ARB combination products. These exposures were identified using National Drug Codes (NDC). See Appendix B for generic drug names used to define the exposures of interest.

**Cohort Eligibility Criteria:** Members included in the cohort were required to be enrolled in health plans with medical and drug coverage for 183 days prior to the dispensing date of the exposure of interest, during which gaps in enrollment coverage of up to 45 days were allowed. Incidence was assessed in the 183 days prior to the dispensing of interest (index), with respect to the index-defining drugs of interest. The following age groups were analyzed in the cohort: 0-19, 20-44, 45-64, 65+ years.

**Dose Calculation**: Cumulative exposed time and cumulative dose of a member's exposure to any HCTZ-containing product were calculated from the date of a member's index dispensing to the first occurrence of any of the following: (1) death; (2) end of exposure episode; (3) end of Data Partner data availability; or (4) disenrollment. Only exposure episodes during the first continuous enrollment span contributed to the calculation of cumulative exposure.

All NDC dispensings were stockpiled to sum the days' and amount supply of overlapping dispensings. Additionally, same-day dispensings were summed together. When calculating the length of treatment episodes, a zero-day gap was used. When calculating cumulative dose of HCTZ use, gaps between exposure episodes within a continuous enrollment were allowed.

Dose of each dispensing was calculated by multiplying the amount supplied and the HCTZ strength unique to each NDC. Cumulative dose represented the sum of doses associated with all HCTZ-containing dispensings, including and following the initial index-defining dispensing. For dispensings with amount supplied values outside of the expected range of 1-365 days, the amount supplied value was replaced with the days supplied. Exceptions to this replacement applied to the following custom values: 600, 900, 1800, 6000, 9000, 18000; these raw amount supplied values were replaced with the custom amount supplied values of 60, 90, 180, 60, 90, and 180, respectively.

**Please refer to Appendices C and D for detailed specifications of parameters used in this request.**

**Limitations:** Algorithms used to define exposures and dose are imperfect; thus, it is possible that there may be misclassification. Therefore, data should be interpreted with this limitation in mind.

**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.

Sentinel

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**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.

**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.

- **Ambulatory Visit (AV) -** includes visits at outpatient clinics, same-day surgeries, urgent care visits, and other same-day ambulatory hospital encounters, but excludes emergency department encounters.
- **Emergency Department (ED) -** includes ED encounters that become inpatient stays (in which case inpatient stays would be a separate encounter). Excludes urgent care visits.
- **Inpatient Hospital Stay (IP) -** includes all inpatient stays, same-day hospital discharges, hospital transfers, and acute hospital care where the discharge is after the admission date.
- **Non-Acute Institutional Stay (IS) -** includes hospice, skilled nursing facility (SNF), rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays.
- **Other Ambulatory Visit (OA) -** includes other non overnight AV encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone and email consultations.

**Charlson/Elixhauser Combined Comorbidity Score -** calculated based on comorbidities observed during a requester-defined window around the exposure episode start date (e.g., in the 183 days prior to index).

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

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

**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.

**Enrollment Gap -** number of days allowed between two consecutive enrollment periods without breaking a “continuously enrolled” sequence.

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

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

**Exposure Extension Period -** number of days post treatment period in which the outcomes/events are counted for a treatment episode. Extensions days are added after any episode gaps have been bridged

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

**Maximum Episode Duration -** truncates exposure episodes after a requester-specified number of exposed days. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

**Member-Years -** sum of all days of enrollment with medical and drug coverage in the query period preceded by an exposure washout period all divided by 365.25.

**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. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

**Monitoring Period -** used to define time periods of interest for both sequential analysis and simple cohort characterization requests.

**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 Caresetting/PDX parameter.

**Query Period -** period in which the modular program looks for exposures and outcomes of interest.

**Treatment Episode Truncation Indicator -** indicates whether the exposure episode will be truncated at the occurrence of a requester-specified code.

**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.

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

*not all terms may be used in this report

**Table 1. Summary of New Users of Hydrochlorothiazide (HCTZ), Angiotensin-Converting Enzyme Inhibitors (ACEIs), and Angiotensin II Receptor Blockers (ARBs) in the Sentinel Distributed Database (SDD) between January 1, 2000 to June 30, 2018, by Follow-up Time**

| | Number of New Users by Length of Enrollment From Index Date | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0-<1 year | 1-<2 years | 2-<3 years | 3-<4 years | 4-<5 years | 5-<6 years | 6-<7 years | 7+ years |
| **Hydrochlorothiazide** | | | | | | | | |
| Any HCTZ-Containing Product | 2,614,717 | 1,914,035 | 1,485,969 | 1,168,942 | 973,977 | 569,553 | 256,009 | 906,118 |
| HCTZ Monotherapy | 1,600,252 | 1,175,331 | 914,504 | 722,310 | 627,615 | 341,156 | 159,244 | 573,658 |
| HCTZ-ACEI Combination | 717,171 | 518,542 | 399,473 | 313,655 | 265,005 | 163,150 | 87,729 | 270,351 |
| HCTZ-ARB Combination | 593,507 | 448,077 | 353,026 | 274,521 | 226,777 | 127,746 | 51,851 | 105,806 |
| HCTZ-Amiloride Combination | 4,530 | 3,473 | 2,815 | 2,447 | 2,626 | 1,271 | 543 | 1,370 |
| **Angiotensin-Converting Enzyme Inhibitors (ACEIs)** | | | | | | | | |
| ACEI Monotherapy | 3,092,849 | 2,221,531 | 1,688,895 | 1,327,490 | 1,059,461 | 592,935 | 257,587 | 823,953 |
| ACEI Combinations (Non-HCTZ) | 117,253 | 90,521 | 68,962 | 53,022 | 46,193 | 26,706 | 12,136 | 34,122 |
| **Angiotensin II Receptor Blockers (ARBs)** | | | | | | | | |
| ARB Monotherapy | 1,629,999 | 1,180,196 | 904,491 | 702,924 | 560,359 | 290,235 | 118,761 | 292,879 |
| ARB Combinations (Non-HCTZ) | 94,403 | 67,411 | 55,202 | 42,694 | 38,345 | 22,599 | 9,190 | 22,049 |

**Table 2. Summary of New Users of Hydrochlorothiazide (HCTZ), Angiotensin-Converting Enzyme Inhibitors (ACEIs), and Angiotensin II Receptor Blockers (ARBs) in the Sentinel Distributed Database (SDD) between January 1, 2000 to June 30, 2018, by Race**

| | New Users | Eligible Members[1] | New Users per 10,000 Eligible Members | Eligible Member-Years[1] |
|---|---|---|---|---|
| **Hydrochlorothiazide** | | | | |
| Any HCTZ-Containing Product | | | | |
| Non-White | 1,267,994 | 9,934,393 | 1276.37 | 38,163,635.6 |
| White | 4,445,741 | 41,826,208 | 1062.91 | 145,961,988.7 |
| Unknown | 4,175,585 | 112,156,752 | 372.30 | 274,780,832 |
| HCTZ Monotherapy | | | | |
| Non-White | 852,134 | 10,523,935 | 809.71 | 42,093,025.4 |
| White | 2,955,515 | 44,390,066 | 665.81 | 162,269,790.7 |
| Unknown | 2,306,421 | 114,201,513 | 201.96 | 286,514,503 |
| HCTZ-ACEI Combination | | | | |
| Non-White | 370,864 | 10,683,609 | 347.13 | 44,857,829.5 |
| White | 1,133,700 | 45,024,665 | 251.80 | 171,756,461.3 |
| Unknown | 1,230,512 | 114,484,969 | 107.48 | 290,689,303 |
| HCTZ-ARB Combination | | | | |
| Non-White | 292,194 | 10,625,715 | 274.99 | 45,265,767.4 |
| White | 898,283 | 44,870,265 | 200.20 | 172,862,535.1 |
| Unknown | 990,834 | 114,302,602 | 86.69 | 290,562,423 |
| HCTZ-Amiloride Combination | | | | |
| Non-White | 1,981 | 10,844,613 | 1.83 | 46,877,011.0 |
| White | 9,386 | 45,749,847 | 2.05 | 178,852,089.6 |
| Unknown | 7,708 | 115,098,355 | 0.67 | 295,825,654 |
| **Angiotensin-Converting Enzyme Inhibitors (ACEIs)** | | | | |
| ACEI Monotherapy | | | | |
| Non-White | 1,280,785 | 10,074,494 | 1271.31 | 39,164,677.3 |
| White | 5,544,221 | 41,183,891 | 1346.21 | 142,924,712.6 |
| Unknown | 4,239,695 | 112,550,203 | 376.69 | 276,711,622 |
| ACEI Combinations (Non-HCTZ) | | | | |
| Non-White | 64,752 | 10,784,303 | 60.04 | 46,406,256.5 |
| White | 157,390 | 45,520,639 | 34.58 | 177,319,104.5 |
| Unknown | 226,773 | 114,850,312 | 19.75 | 294,282,012.7 |
| **Angiotensin II Receptor Blockers (ARBs)** | | | | |
| ARB Monotherapy | | | | |
| Non-White | 767,305 | 10,481,955 | 732.02 | 43,217,961.4 |
| White | 2,913,692 | 43,940,814 | 663.09 | 164,274,699.3 |
| Unknown | 1,998,847 | 113,971,849 | 175.38 | 287,364,233.1 |
| ARB Combinations (Non-HCTZ) | | | | |
| Non-White | 49,969 | 10,826,068 | 46.16 | 46,656,990.1 |
| White | 124,796 | 45,704,126 | 27.31 | 178,287,954.3 |
| Unknown | 177,128 | 115,053,762 | 15.40 | 295,211,189.8 |

[1]Eligible Members and Member-Years are reflective of the number of patients that met all cohort entry criteria on at least one day during the query period

**Table 3a. Summary of Cumulative Dose of Hydrochlorothiazide (HCTZ) Among New Users of Any HCTZ-Containing Products, in the Sentinel Distributed Database (SDD) between January 1, 2000 to June 30, 2018, by Follow-up Time**

| | Length of Enrollment from Index Date (after establishing new use) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cumulative Dose** | **0-<1 year** | **1-<2 years** | **2-<3 years** | **3-<4 years** | **4-<5 years** | **5-<6 years** | **6-<7 years** | **7+ years** |
| <10,000mg | 2,612,217 | 1,866,533 | 1,341,599 | 967,891 | 744,524 | 403,618 | 167,930 | 489,574 |
| 10,000 - 24,999mg | 2,486 | 46,980 | 140,333 | 190,536 | 205,223 | 138,588 | 66,637 | 232,031 |
| 25,000 - 49,999mg | ***** | ***** | 3,989 | 10,222 | 23,271 | 26,016 | 20,039 | 135,075 |
| 50,000 - 74,999mg | ***** | ***** | ***** | 271 | 913 | 1,218 | 1,184 | 34,857 |
| 75,000 - 99,999mg | 0 | 0 | ***** | ***** | ***** | ***** | 208 | 9,843 |
| >100,000mg | 0 | 0 | 0 | ***** | ***** | ***** | 11 | 4,738 |

*****Data are not presented in these cells due to a small sample size or to assure a small cell cannot be recalculated through the cells presented.

**Table 3b. Summary of Cumulative Dose of Hydrochlorothiazide (HCTZ) Among New Users of Any HCTZ-Containing Products, in the Sentinel Distributed Database (SDD) between January 1, 2000 to June 30, 2018, by Follow-up Time and Race**

| | Length of Enrollment from Index Date (after establishing new use) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cumulative Dose** | **0-<1 year** | **1-<2 years** | **2-<3 years** | **3-<4 years** | **4-<5 years** | **5-<6 years** | **6-<7 years** | **7+ years** |
| **<10,000mg** | | | | | | | | |
| Non-White | 290,158 | 223,970 | 168,481 | 125,477 | 99,224 | 51,191 | 18,819 | 77,516 |
| White | 958,645 | 788,824 | 644,227 | 502,207 | 424,587 | 216,766 | 61,247 | 231,866 |
| Unknown | 1,363,414 | 853,739 | 528,891 | 340,207 | 220,713 | 135,661 | 87,864 | 180,192 |
| **10,000 - 24,999mg** | | | | | | | | |
| Non-White | 290 | 6,023 | 19,890 | 27,932 | 31,246 | 20,349 | 8,968 | 41,519 |
| White | 1,098 | 20,440 | 63,219 | 92,189 | 109,849 | 69,974 | 22,047 | 102,940 |
| Unknown | 1,098 | 20,517 | 57,224 | 70,415 | 64,128 | 48,265 | 35,622 | 87,572 |
| **25,000 - 49,999mg** | | | | | | | | |
| Non-White | ***** | ***** | 528 | 1,383 | 3,193 | 3,821 | 3,221 | 30,389 |
| White | ***** | ***** | 2,069 | 5,483 | 13,053 | 13,042 | 6,780 | 65,107 |
| Unknown | ***** | ***** | 1,392 | 3,356 | 7,025 | 9,153 | 10,038 | 39,579 |
| **50,000 - 74,999mg** | | | | | | | | |
| Non-White | ***** | ***** | ***** | 40 | 129 | 170 | 186 | 9,630 |
| White | ***** | ***** | ***** | 164 | 553 | 643 | 482 | 19,052 |
| Unknown | ***** | ***** | ***** | 67 | 231 | 405 | 516 | 6,175 |
| **75,000 - 99,999mg** | | | | | | | | |
| Non-White | 0 | 0 | ***** | ***** | ***** | ***** | 39 | 2,806 |
| White | 0 | 0 | ***** | ***** | **** | ***** | 86 | 5,760 |
| Unknown | 0 | 0 | ***** | ***** | ***** | ***** | 83 | 1,277 |
| **>100,000mg** | | | | | | | | |
| Non-White | 0 | 0 | 0 | ***** | ***** | ***** | ***** | 1,325 |
| White | 0 | 0 | 0 | ***** | ***** | ***** | ***** | 2,926 |
| Unknown | 0 | 0 | 0 | ***** | ***** | ***** | ***** | 487 |

*****Data are not presented in these cells due to a small sample size or to assure a small cell cannot be recalculated through the cells presented.

**Table 4a. Summary of Cumulative Duration of Use of Hydrochlorothiazide (HCTZ) Among New Users of Any HCTZ-Containing Products, in the Sentinel Distributed Database (SDD) between January 1, 2000 to June 30, 2018, by Enrolled Follow-up Time**

| | Length of Enrollment from Index Date (after establishing new use) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cumulative Duration of Use** | **0-<1 year** | **1-<2 years** | **2-<3 years** | **3-<4 years** | **4-<5 years** | **5-<6 years** | **6-<7 years** | **7+ years** |
| 0-<1 year | 2,614,717 | 1,203,621 | 701,468 | 487,485 | 373,737 | 202,512 | 85,016 | 240,999 |
| 1-<2 years | 0 | 710,414 | 392,567 | 209,573 | 148,918 | 80,162 | 32,694 | 93,933 |
| 2-<3 years | 0 | 0 | 391,934 | 233,071 | 131,168 | 66,153 | 26,057 | 70,370 |
| 3-<4 years | 0 | 0 | 0 | 238,813 | 159,918 | 65,487 | 24,715 | 66,828 |
| 4-<5 years | 0 | 0 | 0 | 0 | 160,236 | 87,459 | 24,863 | 63,019 |
| 5-<6 years | 0 | 0 | 0 | 0 | 0 | 67,780 | 32,131 | 59,918 |
| 6-<7 years | 0 | 0 | 0 | 0 | 0 | 0 | 30,533 | 69,632 |
| 7+ years | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 241,419 |

**Table 4b. Summary of Cumulative Duration of Use of Hydrochlorothiazide (HCTZ) Among New Users of Any HCTZ-Containing Products, in the Sentinel Distributed Database (SDD) between January 1, 2000 to June 30, 2018, by Enrolled Follow-up Time and Race**

| | Length of Enrollment from Index Date (after establishing new use) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Cumulative Duration of Use** | **0-<1 year** | **1-<2 years** | **2-<3 years** | **3-<4 years** | **4-<5 years** | **5-<6 years** | **6-<7 years** | **7+ years** |
| **0-<1 year** | | | | | | | | |
| Non-White | 290,448 | 154,037 | 95,112 | 67,609 | 53,268 | 27,515 | 10,129 | 40,177 |
| White | 959,748 | 478,762 | 320,237 | 243,581 | 206,493 | 103,861 | 28,605 | 105,305 |
| Unknown | 1,364,521 | 570,822 | 286,119 | 176,295 | 113,976 | 71,136 | 46,282 | 95,517 |
| **1-<2 years** | | | | | | | | |
| Non-White | 0 | 76,016 | 53,586 | 32,348 | 23,933 | 12,317 | 4,470 | 17,891 |
| White | 0 | 330,772 | 177,999 | 100,469 | 78,880 | 40,681 | 10,877 | 40,445 |
| Unknown | 0 | 303,626 | 160,982 | 76,756 | 46,105 | 27,164 | 17,347 | 35,597 |
| **2-<3 years** | | | | | | | | |
| Non-White | 0 | 0 | 40,203 | 30,325 | 19,777 | 9,812 | 3,359 | 12,935 |
| White | 0 | 0 | 211,306 | 117,346 | 70,749 | 33,461 | 8,583 | 29,730 |
| Unknown | 0 | 0 | 140,425 | 85,400 | 40,642 | 22,880 | 14,115 | 27,705 |
| **3-<4 years** | | | | | | | | |
| Non-White | 0 | 0 | 0 | 24,552 | 20,350 | 8,980 | 3,336 | 12,564 |
| White | 0 | 0 | 0 | 138,665 | 90,747 | 34,456 | 8,125 | 29,036 |
| Unknown | 0 | 0 | 0 | 75,596 | 48,821 | 22,051 | 13,254 | 25,228 |
| **4-<5 years** | | | | | | | | |
| Non-White | 0 | 0 | 0 | 0 | 16,466 | 10,171 | 3,108 | 11,730 |
| White | 0 | 0 | 0 | 0 | 101,203 | 49,420 | 8,637 | 27,686 |
| Unknown | 0 | 0 | 0 | 0 | 42,567 | 27,868 | 13,118 | 23,603 |
| **5-<6 years** | | | | | | | | |
| Non-White | 0 | 0 | 0 | 0 | 0 | 6,751 | 3,672 | 10,643 |
| White | 0 | 0 | 0 | 0 | 0 | 38,608 | 11,962 | 26,022 |
| Unknown | 0 | 0 | 0 | 0 | 0 | 22,421 | 16,497 | 23,253 |
| **6-<7 years** | | | | | | | | |
| Non-White | 0 | 0 | 0 | 0 | 0 | 0 | 3,159 | 11,776 |
| White | 0 | 0 | 0 | 0 | 0 | 0 | 13,857 | 31,759 |
| Unknown | 0 | 0 | 0 | 0 | 0 | 0 | 13,517 | 26,097 |
| **7+ years** | | | | | | | | |
| Non-White | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 45,469 |
| White | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 137,668 |
| Unknown | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 58,282 |

**Appendix A. Dates of Available Data for Each Data Partner (DP) as of Request Distribution Date (August 20, 2018)**

| Data Partner ID | Start Date[1] | End Date[1] |
|---|---|---|
| DP01 | 06/01/2007 | 10/31/2017 |
| DP02 | 01/01/2000 | 10/31/2017 |
| DP03 | 01/01/2000 | 06/30/2018 |
| DP04 | 01/01/2008 | 03/31/2018 |
| DP05 | 01/01/2006 | 12/31/2017 |
| DP06 | 01/01/2000 | 12/31/2016 |
| DP07 | 01/01/2008 | 06/30/2017 |
| DP08 | 01/01/2010 | 12/31/2015 |
| DP09 | 01/01/2005 | 09/30/2017 |
| DP10 | 01/01/2000 | 03/31/2016 |
| DP11 | 01/01/2000 | 05/31/2015 |
| DP12 | 01/01/2000 | 03/31/2018 |
| DP13 | 01/01/2000 | 12/31/2017 |
| DP14 | 01/01/2000 | 06/30/2017 |
| DP15 | 01/01/2004 | 01/31/2018 |
| DP16 | 01/01/2000 | 03/31/2018 |
| DP17 | 01/01/2012 | 06/30/2017 |

[1]The start and end dates are based on the minimum and maximum dates within each DP. The month with the maximum date must have at least 80% of the number of records in the previous month.

**Appendix B. List of Generic Drug Names Used to Define Exposures in this Request**

| Generic Name |
|---|
| **Any Hydrochlorothiaizde (HCTZ)-Containing Product** |
| benazepril HCl/hydrochlorothiazide |
| captopril/hydrochlorothiazide |
| enalapril maleate/hydrochlorothiazide |
| fosinopril sodium/hydrochlorothiazide |
| lisinopril/hydrochlorothiazide |
| moexipril HCl/hydrochlorothiazide |
| quinapril HCl/hydrochlorothiazide |
| amiloride HCl/hydrochlorothiazide |
| amlodipine besylate/valsartan/hydrochlorothiazide |
| candesartan cilexetil/hydrochlorothiazide |
| eprosartan mesylate/hydrochlorothiazide |
| irbesartan/hydrochlorothiazide |
| losartan potassium/hydrochlorothiazide |
| olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide |
| olmesartan medoxomil/hydrochlorothiazide |
| telmisartan/hydrochlorothiazide |
| valsartan/hydrochlorothiazide |
| hydrochlorothiazide |
| aliskiren hemifumarate/amlodipine/hydrochlorothiazide |
| aliskiren hemifumarate/hydrochlorothiazide |
| bisoprolol fumarate/hydrochlorothiazide |
| guanethidine sulfate/hydrochlorothiazide |
| hydralazine HCl/hydrochlorothiazide |
| hydralazine HCl/reserpine/hydrochlorothiazide |
| methyldopa/hydrochlorothiazide |
| metoprolol succinate/hydrochlorothiazide |
| metoprolol tartrate/hydrochlorothiazide |
| propranolol HCl/hydrochlorothiazide |
| reserpine/hydrochlorothiazide |
| spironolactone/hydrochlorothiazide |
| timolol maleate/hydrochlorothiazide |
| triamterene/hydrochlorothiazide |
| **HCTZ Monotherapy** |
| hydrochlorothiazide |
| **Angiotensin-Converting Enzyme Inhibitors (ACEI) - HCTZ Combination Products** |
| benazepril HCl/hydrochlorothiazide |
| captopril/hydrochlorothiazide |
| enalapril maleate/hydrochlorothiazide |
| fosinopril sodium/hydrochlorothiazide |
| lisinopril/hydrochlorothiazide |
| moexipril HCl/hydrochlorothiazide |
| quinapril HCl/hydrochlorothiazide |
| **Angiotensin II Receptor Blockers (ARB) - HCTZ Combination Products** |
| amlodipine besylate/valsartan/hydrochlorothiazide |
| candesartan cilexetil/hydrochlorothiazide |
| eprosartan mesylate/hydrochlorothiazide |

**Appendix B. List of Generic Drug Names Used to Define Exposures in this Request**

| Generic Name |
|---|
| irbesartan/hydrochlorothiazide |
| losartan potassium/hydrochlorothiazide |
| olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide |
| olmesartan medoxomil/hydrochlorothiazide |
| telmisartan/hydrochlorothiazide |
| valsartan/hydrochlorothiazide |
| **Amiloride - HCTZ Combination Products** |
| amiloride HCl/hydrochlorothiazide |
| **ACEI Monotherapy** |
| benazepril HCl |
| captopril |
| enalapril maleate |
| fosinopril sodium |
| lisinopril |
| moexipril HCl |
| perindopril erbumine |
| quinapril HCl |
| ramipril |
| trandolapril |
| **Non-HCTZ ACEI Combination Products** |
| amlodipine besylate/benazepril HCl |
| enalapril maleate/diltiazem malate |
| enalapril maleate/felodipine |
| lisinopril/dietary supplement,comb.10 |
| perindopril arginine/amlodipine besylate |
| trandolapril/verapamil HCl |
| **ARB Monotherapy** |
| azilsartan medoxomil |
| candesartan cilexetil |
| eprosartan mesylate |
| irbesartan |
| losartan potassium |
| olmesartan medoxomil |
| telmisartan |
| valsartan |
| **Non-HCTZ ARB Combination Products** |
| amlodipine besylate/olmesartan medoxomil |
| amlodipine besylate/valsartan |
| azilsartan medoxomil/chlorthalidone |
| nebivolol HCl/valsartan |
| sacubitril/valsartan |
| telmisartan/amlodipine besylate |

**Appendix C. Specifications for Parameters for Request cder_mpl1p_wp023**

This request uses the Cohort Identification and Descriptive Analysis (CIDA) tool, version 5.4.3, to calculate utilization hydrochlorothiaizde (HCTZ), chlorothiazide (CTZ), bendroflumethiazide (BFMTZ), angiotensin-converting enzyme inhibitors (ACEI), beta blockers, or calcium channel blockers (CaChannel) in the Sentinel Distributed Database (SDD).

**Query Period:** January 1, 2000 - August 20, 2018
**Enrollment Requirement:** 183 days
**Enrollment Gap:** 45 days
**Coverage Requirement:** Medical and Drug
**Age Stratifications:** 0-19, 20-44, 45-64, 65+ years
**Results Stratified by:** Race

| | Exposure | | | | | |
|---|---|---|---|---|---|---|
| **Scenario** | **Exposure** | **Incident with Respect to:** | **Washout (days)** | **Censor** | **Censor Categories (years)** | **Cohort Definition** |
| **1** | Any HCTZ products, all product stockpiling | Any HCTZ products | 183 | Death, Data Partner (DP) End Date | 0<1, 1<2, 2<3, 3<4, 4<5, 5<6, 6<7, and 7+ | 01: First valid incident exposures |
| **2** | HCTZ monotherapy | HCTZ monotherapy | 183 | Death, DP End Date | 0<1, 1<2, 2<3, 3<4, 4<5, 5<6, 6<7, and 7+ | 01: First valid incident exposures |
| **3** | HCTZ-ACEI combination | HCTZ-ACEI combination | 183 | Death, DP End Date | 0<1, 1<2, 2<3, 3<4, 4<5, 5<6, 6<7, and 7+ | 01: First valid incident exposures |
| **4** | HCTZ-ARBs combination | HCTZ-ARBs combination | 183 | Death, DP End Date | 0<1, 1<2, 2<3, 3<4, 4<5, 5<6, 6<7, and 7+ | 01: First valid incident exposures |
| **5** | HCTZ-amiloride combination | HCTZ-amiloride combination | 183 | Death, DP End Date | 0<1, 1<2, 2<3, 3<4, 4<5, 5<6, 6<7, and 7+ | 01: First valid incident exposures |
| **6** | ACEI monotherapy | ACEI monotherapy | 183 | Death, DP End Date | 0<1, 1<2, 2<3, 3<4, 4<5, 5<6, 6<7, and 7+ | 01: First valid incident exposures |
| **7** | ACEI combinations (non-HCTZ combinations) | ACEI combinations (non-HCTZ combinations) | 183 | Death, DP End Date | 0<1, 1<2, 2<3, 3<4, 4<5, 5<6, 6<7, and 7+ | 01: First valid incident exposures |
| **8** | ARB monotherapy | ARB monotherapy | 183 | Death, DP End Date | 0<1, 1<2, 2<3, 3<4, 4<5, 5<6, 6<7, and 7+ | 01: First valid incident exposures |
| **9** | ARB combinations (non-HCTZ combinations) | ARB combinations (non-HCTZ combinations) | 183 | Death, DP End Date | 0<1, 1<2, 2<3, 3<4, 4<5, 5<6, 6<7, and 7+ | 01: First valid incident exposures |

National Drug Codes (NDCs) are checked against First Data Bank's "National Drug Data File (NDDF®) Plus."

**Appendix D. Specifications for Parameters for Request cder_mpl1p_wp023, Dose Calculation**

This request uses the Cohort Identification and Descriptive Analysis (CIDA) tool, version 5.4.4 to calculate rates of non-melanoma skin cancer (NMSC) events after exposure to hydrochlorothiaizde (HCTZ), chlorothiazide (CTZ), bendroflumethiazide (BFMTZ), angiotensin-converting enzyme inhibitors (ACEI), beta blockers, or calcium channel blockers (CaChannel) in the Sentinel Distributed Database (SDD).

**Query Period:** January 1, 2000 - August 20, 2018
**Enrollment Requirement:** 183 days
**Enrollment Gap:** 45 days
**Coverage Requirement:** Medical and Drug
**Age Stratifications:** 0-19, 20-44, 45-64, 65+ years

| | Exposure | | | | Episode Creation | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Scenario** | **Exposure** | **Incident with Respect to:** | **Washout (days) - For first Dispensings** | **Censor** | **Episode Gap** | **Stockgroup Criteria** | **Same-Day Dispensings** | **Days Supplied Range** | **Amount Supplied Range *** |
| **10** | Any HCTZ products, all product stockpiling | Any HCTZ products, all product stockpiling | 183 | Death, Data Partner End Date | Fixed, 0 days | All NDCs same stockgroup | Sum (keep all) | Any | 1-365 |

National Drug Codes (NDCs) are checked against First Data Bank's "National Drug Data File (NDDF®) Plus."

*For amount supply outside of the expected range of 1-365, amount supplied will be replaced with days supply of the claim - except for the following values:

| Raw Amount Supplied | Custom Amount Supplied |
|---|---|
| 600 | 60 |
| 900 | 90 |
| 1800 | 180 |
| 6000 | 60 |
| 9000 | 90 |
| 18000 | 180 |